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Hypertensive Disorders of Pregnancy: Diagnosis, Management and Timing of Birth

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Hypertensive disorders of pregnancy are significant contributors to maternal and perinatal morbidity and mortality. The definition, classification, and management of these disorders have evolved over time. Notably, the disease classification enables caretakers to manage the disease as well as safeguard maternal and fetal health. The approach and management for pregnancies with gestational and chronic hypertension or pre-eclampsia with or without severe features should be adequately elucidated to mitigate adverse perinatal outcomes. This review aimed to present the most recent definition and classification of hypertensive disorders of pregnancy to address their management, determine the optimal timing of birth, and establish short- and long-term follow-up protocols following parturition.

THE CLASSIFICATION OF HYPERTENSION IN PREGNANCY. DEFINITION OF HYPERTENSION AND PROTEINURIA

The diagnosis of hypertension (HT) was made if the average of at least two measurements of systolic blood pressure (sBP) and/or diastolic blood pressure (dBP) ≥ 140 mmHg and/or ≥ 90 mmHg, respectively. The blood pressure (BP) must be measured in both arms, and then the arm with the higher BP should be selected, and the BP measurement be repeated to verify the diagnosis of HT. If sBP is ≥ 160 and/or dBP is ≥ 110 mmHg (severe HT), it is recommended to repeat the measurement within 15 minutes. The measurement should be repeated within a minimum of four hours or in two consecutive outpatient clinic visits.[1] The American College of Obstetricians and Gynecologists (ACOG) defines HT in pregnant women as sBP ≥ 140 mmHg or dBP ≥ 90 mmHg in two measurements obtained four hours apart.[2]

In the statement published by the "International Society for the Study of Hypertension in Pregnancy (ISSHP)", proteinuria is defined as urinary albumin/creatinine ratio (ACR) ≥ 8 mg/mmol or protein/creatinine ratio (PrCr) ≥ 30 mg/mmol in a spot urine sample; or ≥ 0.3 g/day in 24-hour urine; or ≥ 0.3 g/day protein in 24-hour urine; or ≥ +2 protein by urinary dipstick method if there is no confirmatory test.[1] "The National Institute for Health and Care Excellence (NICE)" endorses these threshold values for PrCr and ACR; however, it does not recommend routine 24-hour urine collection or obtaining first morning urine to diagnose proteinuria.[3] Proteinuria is defined by the ACOG as the presence of ≥ 300 mg of protein in a 24-hour urine collection, a PrCr of 30 mg/mmol, or ≥ +2 protein as detected using the dipstick method.[2] The dipstick method has low diagnostic accuracy, particularly at the 1+ level, due to its low sensitivity and specificity for proteinuria.[4]

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Proteinuria during pregnancy may also be crucial in identifying an underlying chronic kidney disease. Urinary sediment microscopic analysis and the detection of white and red blood cells are essential in the monitoring of chronic kidney disease.[1,5] The ISSHP suggests that quantitative proteinuria assays (urinary PrCr, ACR, or 24-hour urine analysis) be conducted when PE is suspected, in pregnancies with HT, or in pregnant women with normal blood pressure and PE findings when ≥ +1 protein is detected by the dipstick method.[1]

The etiopathogenesis of pre-eclampsia (PE) remains unclear. Research reveals that placental mosaicism coexists with pregnancy-induced HT, including PE, gestational HT, and small for gestational age (SGA).[6,7] This is significant as it illustrates the critical role of the placenta in the pathophysiology of pregnancy-induced HT.

HT during pregnancy has been evaluated under two primary headings (Figure 1):

1. HT < 20 weeks of gestation or prepregnancy HT;

a. Chronic HT (essential/primary and secondary HT),

b. White coat HT,

c. Masked HT.

2. HT that occurs after a minimum of 20 weeks;

a. Gestational HT,

b. Transient gestational HT,

c. PE (newly developed PE and superimposed PE).

Chronic HT is diagnosed when HT is detected prior to the 20th weeks of pregnancy or in the prepregnancy period and persists during pregnancy. Essential or primary HT constitutes the majority of chronic HT. In secondary HT, a secondary etiology, such as an underlying renal disease, is present. In pregnant women with HT, it is typically accompanied by obesity/overweight or a family history of HT.[1,8]

White coat HT is defined as sBP > 140 mmHg and/or dBP > 90 mmHg measured in a clinical setting, while exhibiting a sBP < 135 mmHg and/or dBP < 85 mmHg during 24-hour ambulatory BP monitoring or home BP monitoring. Masked HT is characterized by a BP < 140/90 mmHg in the clinic, but BP is ≥ 135/85 mmHg when measured outside the clinic or hospital.[1]

Gestational HT is defined as HT that develops at or after the 20th weeks of pregnancy without proteinuria or other signs of PE. If this HT resolves through repeated BP measurements, it is classified as "transient gestational HT." In such cases the risk of developing true gestational HT or PE is approximately 40%.[1,9]

In the absence of proteinuria, pregnant women with new-onset HT are diagnosed with PE if they develop any of the following clinical features: thrombocytopenia (platelet count <100 x 10^9/l); impaired hepatic function, defined as elevated blood concentrations of liver transaminases to twice the normal concentration; severe persistent pain in the right upper quadrant of the abdomen or epigastrium

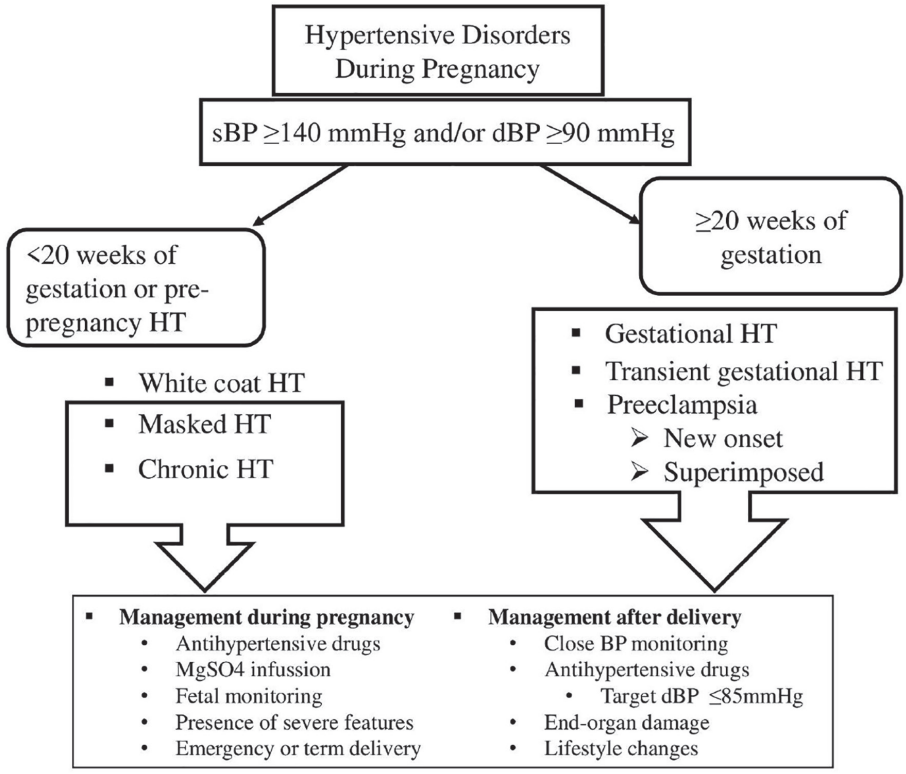

FIG. 1. Classification and monitoring of patients with hypertensive disorders of pregnancy.
sBP, systolic blood pressure; dBP, diastolic blood pressure; HT, hypertension; BP, blood pressure.

not associated with other conditions; renal insufficiency (serum creatinine concentration greater than 1.1 mg/dl or doubling of the serum creatinine concentration in the absence of renal disease); pulmonary edema; new-onset headache unresponsive to acetaminophen or the presence of visual disturbances.[2]

The presence of findings suggestive of newly developed proteinuria, maternal organ dysfunction, or uteroplacental dysfunction in pregnant women with chronic HT is considered superimposed PE. Approximately 25% of pregnant women with chronic HT develop superimposed PE.[1,10]

ACCORDING TO THE LATEST DEFINITION BY THE AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION THE CATEGORIZATION OF HYPERTENSION IN PREGNANCY IS STILL NOT CHANGED. SHOULD IT CHANGE?

The American College of Cardiology/American Heart Association classify BP between 130/80 and 140/90 mmHg as stage 1 HT. This definition is incompatible with the diagnostic and treatment strategies for hypertensive diseases in pregnancy.[11] Strong evidence suggests that the risk of cardiovascular disease is reduced in the general population when treatment is administered at lower blood pressure levels. Most cardiovascular disorders occur in individuals with sBP and dBP between 140-159 mmHg and 90-109 mmHg, respectively. Even in young individuals with HT, endothelial dysfunction and vascular remodeling are evident in the early phases, particularly in small arteries and arterioles. If left untreated, this can result in organ damage. The international consensus on the definition of HT for all expectant women is a blood pressure of 140/90 mmHg, despite the fact that treatment thresholds and targets differ among various societies.[11] Employing threshold values for diagnosing HT during pregnancy does not alter pregnancy outcomes and is not cost-effective in terms of diagnosis and treatment. Therefore, ACOG, the Society for Maternal-Fetal Medicine (SMFM), and NICE accept sBP ≥ 140 mmHg and dBP ≥ 90 mmHg as thresholds for the diagnosis of HT in pregnancy. Severe HT is still recognized as a sBP ≥ 160 mmHg and/or dBP ≥ 110 mmHg.[1,3]

SHOULD THE SECONDARY UNDERLYING CAUSES OF HYPERTENSION BE INVESTIGATED IN WOMEN WITH PRE-ECLAMPSIA? WHAT TESTS SHOULD BE REQUESTED AFTER PRE-ECLAMPSIA IS DIAGNOSED?

Unless there is clinical suspicion, the ISSHP does not advocate investigating secondary causes of HT during pregnancy. Consequently, the routine performance of procedures such as renal ultrasonography (USG) is unnecessary. The tests that should be requested following the diagnosis of PE are as follows: complete urinalysis, serum platelet, creatinine, serum transaminases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], complete urinalysis, platelet count, serum creatinine, oxygen saturation. Furthermore, angiogenic markers can be assessed in the event of an angiogenic imbalance, such as a high sFlt/PIGF ratio or low PIGF levels for gestational age.[1,12]

ANTEPARTUM FETAL SURVEILLANCE IN HYPERTENSIVE DISEASES OF PREGNANCY. WHAT METHODS SHOULD WE USE?

Women with severe chronic HT and chronic HT with end-organ dysfunction experience an elevation in perinatal morbidity and mortality. Neonates born to women with chronic HT exhibit an increased risk of low-birth weight [relative risk (RR): 2.7, 95% confidence interval (CI): 1.9-3.8], preterm birth (RR: 2.7, 95% CI: 1.9-3.6), perinatal mortality (RR: 4.2, 95% CI: 2.7-6.5), and neonatal intensive care unit (NICU) admission (RR: 3.2, 95% CI: 2.2-4.4).[13] Furthermore, the incidence of fetal growth restriction (FGR) is reported to be twice as high in pregnant women with chronic HT compared to normotensive pregnant women.[14] The risk of FGR, preterm delivery, and fetal demise increases to 25-40%, 67%, and 11%, respectively, in women with severe HT and in those with secondary HT and end-organ disease.[15,16]

Fetal biometry and uterine artery Doppler velocimetry can be employed to distinguish two subgroups of pregnancies that are impacted by HT: The group in which FGR is associated with placental vascular insufficiency and the other group, which is characterized by normal fetal and placental growth. In a study, when two groups of hypertensive pregnant women with or without FGR were compared, the FGR group exhibited unfavorable results in terms of sBP, mean gestational age at birth, birth weight percentile, Apgar score at birth, and admission to the NICU.[17] These results emphasize the need for conducting more intensive monitoring of the fetal and maternal status of hypertensive pregnant women complicated with FGR.

Prenatal Doppler USG examination of the uterine and umbilical circulation can provide significant information regarding placental function and fetal well-being. An association between increased first trimester preterm PE risk scores and increased rates of term or preterm spontaneous birth in women without PE was observed,[18] which also suggests a link between placental dysfunction and spontaneous birth.

The ASPRE (*Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Pre-eclampsia Prevention*) study revealed that in pregnancies identified as high risk for PE following screening with biomarkers at 11-13 weeks' gestation and certain maternal factors, aspirin administration decreased the rate of early PE at < 32 weeks' gestation by approximately 90% and early PE at < 37 weeks' gestation by 60%.[19] Previous studies have identified four potentially useful markers at 11-13 weeks of gestation: mean arterial pressure, uterine artery pulsatility index, serum placental growth factor, and serum pregnancy-associated plasma protein-A.[20,21] Therefore, first trimester PE screening is beneficial for identifying women who are at increased risk of PE and initiating aspirin treatment at an early stage.

Screening for preterm PE is conducted in accordance with the Fetal Medicine Foundation Guidelines, which involve the integration of maternal risk factors, the uterine artery pulsatility index, the mean arterial blood pressure, and the serum PIGF level. This method enables the effective prediction of the risk of preterm PE because

of placental dysfunction.[18,22] Furthermore, placental dysfunction is regarded as a precursor to spontaneous preterm labor.[18]

In addition to the teratogenic effect of medications, fetuses of women with chronic HT who are exposed to angiotensin converting inhibitors (ACEi) or angiotensin receptor blockers (ARBs) are reported to have an increased risk of birth defects, particularly renal defects, as well as a higher risk of congenital malformations such as cardiac septal defects, hypospadias, and esophageal atresia, as a result of the uncontrolled HT.[23] Therefore, these women should undergo a comprehensive fetal anatomic evaluation during the second trimester.

The necessity of antenatal fetal monitoring in women with mild HT is not well documented. Pregnant females who are on anti-hypertensive medications, exhibit end-organ damage, or manifest comorbidities like superimposed PE or FGR should undergo antenatal fetal testing.[24] However, the optimal timing and testing interval for antenatal fetal testing remain unclear. As uteroplacental insufficiency is associated with hypertensive diseases of pregnancy, it is recommended to perform fetal USG for assessment of fetal growth, amniotic fluid, and umbilical artery Doppler at the 28th, 32nd, and 36th weeks of pregnancy.[3] The ISSHP suggests that the fetuses of hypertensive mothers suspected to be experiencing FGR be monitored in accordance with the ISUOG guideline for FGR.[1,25] Doppler ultrasound may decrease perinatal mortality in high-risk pregnancies; however, the evidence is not definitive, and a standard Doppler assessment does not exclude fetal compromise, especially when performed near term.[1] It has been demonstrated that the neurological outcomes of survivors are enhanced and perinatal mortality is reduced in FGR cases < 34 weeks when ductus venosus Doppler assessment is conducted in conjunction with computerized-cardiotocography.[26,27] The efficacy of fetal heart rate monitoring in minimizing the adverse outcomes in hypertensive pregnancies has not yet been established; therefore, it is only advised when clinically indicated.[28] In the event of limited resources, performing cardiotocography four times a day has been conventionally recommended to monitor for placental abruption.[29] Biophysical profile scoring is not recommended due to its subjectivity and because a low score is a late finding in the diagnosis of fetal compromise.[1,30]

In general, among pregnant women, the risk of PE is higher in nulliparous women than in multiparous women. However, the risk of PE is comparable in nulliparous and multiparous pregnant women with type 1 diabetes, which is characterized by microvascular damage, elevated capillary permeability, and microalbuminuria. Therefore, it is essential to maintain glycemic control in all nulliparous and multiparous women with type 1 diabetes to mitigate the risk of PE.[31]

PROTEINURIA AND HYPERTENSIVE DISEASES OF PREGNANCY - DOES THE AMOUNT OF PROTEINURIA IMPACT PREGNANCY OUTCOMES?

Proteinuria was not considered a mandatory criterion of PE by ACOG in 2013, and it was determined that proteinuria of 5 g or more per day should not be classified as “severe pre-eclampsia”.[32] Prior to that, there was a propensity to believe that the absence of proteinuria was reassuring in patients with gestational HT and chronic HT. The amount of proteinuria was considered to be related to disease severity. However, certain authors discovered that severe HT posed the greatest risk of adverse maternal and perinatal outcomes. Women with severe gestational or chronic HT exhibited lower gestational age at delivery and significantly higher rates of low birthweight neonates than those with mild PE.[33,34] Conflicting research exists regarding the severity of proteinuria that leads to adverse maternal and perinatal outcomes. A retrospective cohort study revealed that 90% of PE patients experience an increase in protein excretion during pregnancy, and 30% of them develop severe proteinuria (≥ 5 g/day). However, there were no statistically significant differences in major maternal and perinatal outcomes (gestational age at delivery, eclampsia, HELLP syndrome, placental abruption and stillbirth) among those who experienced a marked proteinuria (≥ 2 g/day), mild proteinuria (< 2 g/day), or no increase in proteinuria.[35] In another retrospective study, the rates of maternal complications (i.e., HELLP, eclampsia, placental abruption) were comparable between severe (≥ 5 g/day) and massive proteinuria (≥ 10 g/day) groups. However, the massive proteinuria group patients exhibited a shorter gestational duration at delivery and poorer neonatal outcomes.[36] A multicenter prospective study also revealed no increase in composite adverse maternal outcomes in pre-eclamptic women with massive proteinuria when compared with those with mild or no proteinuria.[36] The severity of HT and end-organ injury are the most significant factors affecting the maternal and perinatal outcomes, even though certain levels of proteinuria are associated with adverse perinatal outcomes in some studies. The management of pre-eclamptic women should not be altered by the progression of proteinuria, as most of them will experience an increase in proteinuria. Prematurity is almost entirely responsible for the adverse neonatal outcomes, and the amount of proteinuria does not affect maternal outcomes. Consequently, the decision to deliver should not be based solely on the amount of proteinuria. Therefore, it is not recommended to conduct repeated measurements of protein excretion in the setting of PE.[5]

MILD AND SEVERE PRE-ECLAMPSIA. IS THERE A NEED FOR AN IMPORTANT DISTINCTION TO MAKE?

PE may first manifest and be diagnosed during the intrapartum or early postpartum period. A superimposed PE may develop in approximately 25% of women with chronic HT and an even greater number of women with underlying renal disease, including a kidney transplantation.[10,37] ISSHP does not recommend categorizing PE into severe or non-severe forms due to the potential for the disease’s severity to deteriorate abruptly in the absence of any prior symptoms or the sudden deterioration of maternal and fetal health in pre-eclamptic women. The non-severe form of PE may rapidly transition to the severe form.[1] Therefore, it is essential to consider the abrupt shift in the circumstances of women with PE.

WHAT IS THE MANAGEMENT IN PREGNANCIES WITH GESTATIONAL HYPERTENSION AND PRE-ECLAMPSIA WITHOUT SEVERE FEATURES? HOW SHOULD THE EXPECTANT CARE APPROACH (INPATIENT/OUTPATIENT SETTING) BE PLANNED?

In pre-eclamptic women, outcomes are dependent on the gestational age at which HT develops after 20 weeks.[1] Although the management of gestational HT and PE without severe features is similar in several aspects, both necessitate close monitoring during the pregnancy. Although gestational HT generally results in satisfactory outcomes, the concept that gestational HT is less serious and concerning than PE is entirely inaccurate.[38] Gestational HT may be linked to adverse outcomes, and it is not a distinct entity from PE.[39] Approximately 50% of women who present with gestational HT before 34 weeks will experience proteinuria, progression to PE, and poorer outcomes.[40,41] Gestational HT and PE are comparable in terms of long-term complications such as chronic HT.[42] Unless the evidence indicates otherwise, a woman who presents for antenatal care at > 20 weeks and is diagnosed with HT should be managed as if she has gestational HT or PE.[1] The management of pregnant women with gestational HT with no evidence of severe HT can safely be conducted as outpatients. It is recommended that patients undergo weekly antenatal visits, weekly in-office BP monitoring and urine protein excretion evaluation, and daily home BP measurements. Regular BP monitoring is particularly essential to maintain a BP of 110-140/80-90 mmHg.[43] Other non-pharmacological interventions like activity restriction, weight reduction, or diet modifications have demonstrated no impact on pregnancy outcomes.[32,44] It is recommended that women with HT undergo testing for PE. If angiogenic marker testing is available, the absence of angiogenic imbalance (normal PIGF levels or normal sFlt/PIGF ratio) indicates that there is no uteroplacental dysfunction, and thus, the diagnosis of gestational HT would be validated.[1] Each prenatal appointment should include proteinuria testing, which equates to once a week with blood pressure monitoring. A complete blood count, and liver and renal function tests should be performed at the initial visit and then repeated weekly.[3] Fetal USG should be conducted to monitor fetal growth, amniotic fluid levels, and umbilical artery Doppler indices. Fetal ultrasound should be performed at least once a month during the follow-up period. Cardiotocography may be conducted if clinically indicated.[3] The risk of adverse maternal outcomes increases with shorter gestational age at delivery. Women with gestational HT should be warned about the onset/deterioration of the PE symptoms such as headache, visual disturbances, chest pain, dyspnea, vaginal bleeding with abdominal pain, and elevated BP. The patient should undergo a reevaluation whenever PE is suspected.[1] The management of PE without severe features is the same as gestational HT.[45] The patient should be re-evaluated at least twice weekly in terms of the onset/worsening of the PE features such as headache, visual disturbances, chest pain, dyspnea, vaginal bleeding with abdominal pain, and elevated BP. Laboratory testing, including platelet count, serum creatinine, AST, and ALT should also be repeated twice weekly.[1] Fetal USG should be conducted every two weeks to determine amniotic fluid volume and umbilical artery Doppler indices.[3] Before selected cases are considered for outpatient care, women with PE should be managed in the hospital. However, the disease can progress abruptly without any warning symptoms.[46] After the initial evaluation in the hospital, some PE patients can be followed up in an outpatient setting with regular (ideally daily or twice a week) visits to the obstetrical unit. Patients deemed suitable for outpatient management should reside (if feasible) within a reasonable distance from the hospital, be informed about relevant warning symptoms, and be cared for by an experienced team.[1] Gestational HT patients who present with severe BP (sBP ≥ 160 mmHg and/or dBP ≥ 110 mmHg) should be managed in the same manner as PE patients with severe features.[3]

SHOULD WE USE ANTI-HYPERTENSIVE MEDICATION IN PREGNANCIES WITH GESTATIONAL HYPERTENSION OR PRE-ECLAMPSIA WITHOUT SEVERE FEATURES? IF YES, WHICH AGENTS SHOULD BE PREFERRED?

The treatment of HT during pregnancy is essential.[47] Anti-hypertensive therapy is recommended for patients with persistently high blood pressure of ≥ 140/90 mmHg, as untreated HT poses a risk to both the mother and the fetus.[48] The target BP for anti-hypertensive therapy should be a dBP of 85 mmHg, regardless of sBP.[49] Anti-hypertensive drugs should be lowered or ceased if dBP declines to ≤ 80 mmHg. However, if dBP rises to ≥ 85 mmHg or sBP is ≥ 160 mmHg, the patients should be started on anti-hypertensives, and if already on these drugs, their dose should be increased.[1] This simplified target on dBP is found to be linked to the control of sBP. The approach to HT is the same for women with gestational HT and PE with or without comorbidity.[49] Anti-hypertensive medications are generally safe, and the benefits exceed the risks. Non-severe HT should be treated with first-line medications such as alpha-methyldopa, labetalol, or nifedipine (Table 1).[2,44] Alpha-methyldopa is frequently used in pregnant women due to its extensive safety record and availability. Labetalol, a mixed alpha-adrenergic and beta-adrenergic blocker and is the most common beta-blocker used during pregnancy. Extended release nifedipine is a calcium channel blocker that is safe, effective, easy to administer, and reduces BP rapidly.[2,44] Anti-hypertensives should be initially administered as monotherapy from among the first-line drugs. There is no clear evidence that one drug is preferable to another.[11] If target BP levels cannot be achieved with regular dose monotherapy, additional anti-hypertensive medications should be utilized. Second-line agents include thiazide diuretics and hydralazine.[44] The use of diuretics may cause significant volume depletion, and in PE, which is already characterized by low plasma volume, it may aggravate volume depletion and promote reactive vasoconstriction.[11] Therefore, it is vital to closely monitor the volume status. The use of ACEi, ARBs, direct renin inhibitors, and mineralocorticoid receptor antagonists is strictly contraindicated in pregnancy.[44] Inpatient management and urgent anti-hypertensive treatment should be administered for patients with BP of ≥ 160/110 mmHg. If the patient exhibits pre-eclamptic symptoms, $MgSO_4$ should be administered to prevent eclampsia.[1] The drugs most preferred for acute HT treatment include parenteral hydralazine, labetalol, and oral nifedipine (Table 1).

TABLE 1. Anti-hypertensive Drugs to Treat Gestational Hypertension or Pre-eclampsia without Severe Features.[1,35]

	Agent	Dose	Recommendation	Side effects
First line	Labetalol (oral)	Initial dose: 100-200 mg twice a day Increase every 2-3 days Maximum dose 2,400 mg/day	Consider adding another low-dose medication if BP is not controlled with 200 mg, 3-4 times/day	Hypotension, increased liver enzyme levels, fetal bradycardia, neonatal hypoglycemia
	Extended release nifedipine (oral)	Initial dose: 30-60 mg every day Increase every 7-14 days Maximum dose 120 mg/day	Consider adding another low-dose medication if BP is not controlled with 60 mg/day	Risk of bronchospasm (avoid in asthma), severe headache, peripheral edema, anxiety, nightmares, dry mouth, hypotension. Contraindicated in aortic stenosis
	Alpha-methyldopa (oral)	Initial dose: 250 mg twice or three times a day Increase every two days Maximum dose 3,000 mg/day	Consider adding another low-dose medication if BP is not controlled with 500 mg, four times/day	Contraindicated in depression
Second or third line	Hydralazine	Initial dose: 10 mg four times a day Increase every 2-5 days Maximum dose 200 mg/day	Care should be taken when using because half of women experience associated side effects	Tachycardia (should never be used in isolation because of reflex tachycardia), headache, flushing, fetal distress, hypotension
	Hydrochlorothiazide	Initial dose: 12.5 mg every day Increase every 7-14 days Max. dose 200 mg/day	The use of thiazide diuretics can be associated with significant volume depletion within the first two weeks and intensive monitoring of volume status is recommended	Volume depletion, FGR, oligohydramnios

BP, blood pressure; FGR, fetal growth restriction.

Beta-blockers used for treating hypertensive diseases in pregnancy can also be employed to effectively and safely manage tachyarrhythmias. Propranolol and metoprolol are particularly favored in the treatment of tachyarrhythmias during pregnancy since they do not have adverse effects on fetal health.[50] Several studies exist that compare the effectiveness of beta-blockers with calcium channel blockers and other drugs in the treatment of HT during pregnancy, with conflicting results.[51-53] Certain beta-blockers may improve maternal outcomes in females with an elevated risk for hypertensive complications. There is no established difference between beta-blockers and calcium channel blockers/nifedipine or methyldopa in reducing the risk of severe HT in pregnancy. Beta-blockers may regulate abnormal hemodynamic changes prior to the development of severe HT and PE in high-risk pregnant women. In the context of beta-blocker use in pregnancy, individualized hemodynamic monitoring is a highly effective approach for maintaining optimal blood pressure while limiting potential perinatal adverse effects.[54]

WHAT IS THE APPROACH FOR PREGNANCIES WITH GESTATIONAL HYPERTENSION AND PRE-ECLAMPSIA WITHOUT SEVERE FEATURES BEFORE 34 WEEKS' GESTATION?

The only definitive treatment for hypertensive disorders of pregnancy is the delivery of the placenta. This inhibits disease progression, thus preventing adverse pregnancy outcomes. However, early delivery is associated with significant disadvantages regarding neonatal or maternal morbidity[55] and may result in preterm or early-term birth, which elevates the risk of neonatal complications.[56] Furthermore, induction of labor may reduce the need for a cesarean section and associated risks.[57] Consequently, the decisions regarding the timing of delivery and the management of pregnancies with hypertensive disorders should be determined by the balance between the risks of imminent delivery and the risks of continuing the pregnancy. Previability expectant care of PE is related to extremely perinatal mortality and frequent maternal complications, including death. Pregnancy termination should be discussed with the family, and a transfer to a tertiary-level hospital should be planned.[1] From the period of fetal viability to 33^{+6} weeks, expectant care is preferred when there is no obvious indication for inducing delivery. Interventionist treatment has been linked to a shorter gestational period at birth and comparable maternal outcomes in comparison to normal pregnancies but higher neonatal morbidity.[58]

WHAT IS THE APPROACH FOR PREGNANCIES WITH GESTATIONAL HYPERTENSION AND PRE-ECLAMPSIA WITHOUT SEVERE FEATURES BETWEEN 34-37 WEEKS' GESTATION? SHOULD WE CONSIDER THE INTERVENTIONIST OR EXPECTANT CARE?

The HYPITAT II (*Hypertension and Pre-eclampsia Intervention Trial at Near Term*) trial revealed minor maternal benefits of early delivery in mitigating the existing mild risk of adverse maternal outcomes in non-severe HT between 34 and 36^{+6} weeks. Since early delivery is associated with increased neonatal respiratory distress,

particularly when antenatal corticosteroids are not administered at this gestational age, routinely inducing early delivery for pregnant females with hypertensive disorders between 34 and 37 weeks of gestation is not recommended. Instead, expectant management with close surveillance until the clinical situation deteriorates may be considered.[55] Expectant care was associated with an increase in neonatal unit admissions in the PHOENIX (Planned early delivery or expectant management for late preterm PE) trial, but not with an increase in neonatal respiratory distress syndrome. This is due to the fact that the majority of women in the trial (60%) had received antenatal steroids.[59] The neurodevelopment of a child at the age of five appears to be comparable regardless of whether they receive interventionist or expectant care during this gestational period.[60] Thresholds for considering planned delivery before 37 weeks in gestational HT or PE patients may include any of the following, which are also features of severe PE: Inability to control maternal BP despite using three or more classes of anti-hypertensive medications, maternal oxygen saturation < 90%, progressive deterioration of liver or renal functions, hemolysis or reduced platelet count, ongoing neurological features, such as severe headache, visual symptoms, eclampsia, reversed end-diastolic flow on umbilical artery Doppler velocimetry, and a non-reassuring cardiotocography or stillbirth.[3]

WHAT ARE THE BENEFITS OF CONSIDERING BIRTH FOR PREGNANCIES WITH GESTATIONAL HYPERTENSION AND PRE-ECLAMPSIA WITHOUT SEVERE FEATURES BEYOND 37 WEEKS' GESTATION?

At term (≥ 37^{+0} weeks), women with gestational HT or PE without severe features should be offered induction of labor.[61] The HYPITAT trial demonstrated that inducing delivery significantly reduced the risks of adverse maternal outcomes for women with gestational HT and PE after 37 weeks, without affecting neonatal outcomes and risk of cesarean section.[61]

WHAT SHOULD BE THE GENERAL APPROACH IN PREGNANT WOMEN DIAGNOSED WITH SEVERE PRE-ECLAMPSIA? FOLLOW-UP VS. BIRTH? IN WHICH CASES SHOULD AN EMERGENCY BIRTH DECISION BE MADE?

Women experiencing severe PE should be hospitalized for maternal and fetal assessment. Maternal monitoring should include evaluation of vital signs, oral and i.v. intake, and urinary output. Laboratory tests (complete blood count, liver and kidney function tests, electrolytes, bleeding profile, lactic acid dehydrogenase) should be performed on presentation and then repeated every 6-12 hours. For eclampsia prophylaxis, $MgSO_4$ loading and $MgSO_4$ maintenance therapy should be administered as long as urine output exceeds 30 ml/hour. Maternal fluid replacement should be adjusted based on the urinary output. Rapid and large amounts of fluid replacement should be avoided in this patient group due to the high risk of third-space fluid loss.

For fetal evaluation, biometry, biophysical profile, and Doppler studies should be performed in cases of FGR. For patients presenting between the 23rd and 34th gestational weeks, antenatal steroids (betamethasone or dexamethasone) should be administered for fetal pulmonary maturation.

In situations where fetal viability is not achieved before the conclusion of the 23rd week or after the completion of the 34th week, pregnancy termination should be considered. Additionally, prompt delivery should be considered in the presence of indicators of maternal and/or fetal general status deterioration, such as maternal hemodynamic instability, severe HT unresponsive to treatment, headache, visual disturbances, epigastric pain, pulmonary edema, renal failure, intracranial bleeding, progressive elevation of liver enzyme levels, progressive decrease in platelet count, coagulopathy [disseminated intravascular coagulation (DIC)], HELLP syndrome, eclampsia, fetal distress, severe FGR, oligohydramnios, placental abruption, intrauterine fetal loss, preterm labor, and in the presence of premature rupture of membranes.[2]

IN WHICH CASES CAN FOLLOW-UP AND EXPECTANT MANAGEMENT BE PREFERRED AND HOW SHOULD THE MOTHER AND FETUS BE MONITORED?

Patients with PE can be monitored if the laboratory parameters (such as ALT, AST elevation, and thrombocytopenia) recover within 48 hours or if a response to anti-hypertensive treatment can be obtained in the presence of severe HT. Furthermore, when the maternal condition is stable and the fetal condition is reassuring, follow-up with close monitoring of maternal clinical and laboratory findings and fetal well-being may be preferred.[2]

SHOULD WE ADMINISTER ANTI-HYPERTENSIVE TREATMENT? WHICH AGENT SHOULD WE CHOOSE? WHAT SHOULD BE THE TARGET BLOOD PRESSURE VALUE?

Anti-hypertensive therapy (nifedipine, labetalol, hydralazine) should be administered immediately if the pregnant woman's BP is ≥ 160/110 mmHg. The target sBP and dBP should be 140-150 mmHg and 90-100 mmHg, respectively. Nifedipine 10-20 mg per oral every 30 minutes (maximum dose 50 mg) or labetalol 20-80 mg i.v. bolus over 10-15 minutes (maximum dose 220 mg) or hydralazine 5-10 mg i.v. bolus over 15-20 minutes (maximum dose 30 mg) can be administered. If there is no response following the 3rd dose when starting with labetalol, a switch to hydralazine or nifedipine may be made. If there is no response following the 2nd dose when starting with hydralazine, labetalol or nifedipine should be administered. If there is no response following the 3rd dose when starting with nifedipine, labetalol or hydralazine should be preferred. When target BP level is achieved, BP measurements should be obtained every 10 minutes in the first hour, every 15 minutes in the second hour, every 30 minutes in the third hour, and hourly from the 4th hour onward.[2] Table 1 illustrates the adverse effects of nifedipine, hydralazine, and labetalol.

WHAT ARE THE PROS AND CONS OF IMMEDIATE DELIVERY AND FOLLOW-UP MANAGEMENT IN TERMS OF MATERNO-FETAL OUTCOMES IN SEVERE PRE-ECLAMPSIA?

Maternal complications and perinatal morbidity and mortality cannot always be predicted at the time of admission in patients who present with severe PE. While the risks of maternal complications, placental abruption, and intrauterine fetal loss increase with the expectant strategy, an increase in prematurity-related complications as well as neonatal morbidity and mortality is observed with immediate delivery. Previous studies define the latent period as the period between the implementation of the expectant approach and birth. Since extending the latent period gives time to the fetus, it may complicate the maternal status.[62-64] Studies report an average latent period of 7-15 days in patients who received expectant management,[62,63] with fewer neonatal complications and a low rate of serious maternal complications (< 5%).[64] Conversely, the incidence of SGA babies and placental abruption was higher in the expectant management group; the advantage of waiting for the neonate has not been established.[65] Thus, in severe PE, the study results comparing the expectant approach with the immediate delivery following steroid administration for pulmonary maturity were contradictory in terms of neonatal benefits and maternal complication rates. We believe that in appropriate centers, where 24-hour emergency facilities are available and intensive care conditions are provided for the mother and neonate, it would be appropriate to adopt the expectant management approach by an experienced staff.

SHOULD WE ADMINISTER $MGSO_4$ TO PATIENTS DIAGNOSED WITH SEVERE PRE-ECLAMPSIA? IN WHICH WEEK, HOW AND THE DURATION FOR WHICH $MGSO_4$ SHOULD BE USED?

In severe PE patients, $MgSO_4$ should be delivered as a loading dose and as maintenance treatment (as stated in detail below) for eclampsia prophylaxis and be continued if urinary output is ≥ 30 ml/hour. It is administered when the diagnosis of severe PE is confirmed, and can be discontinued after 48 hours if the patient has to wait for delivery. It is not recommended to administer $MgSO_4$ for more than 5-7 days during the antenatal period. $MgSO_4$ therapy is re-initiated before induction, cesarean section, or during labor. Treatment should be continued for at least 24 hours following the delivery or the last episode of convulsion. The MAGPIE study (*Magnesium sulfate for Prevention of Eclampsia*) reported that $MgSO_4$ needed to be administered to 60 patients to prevent the occurence of eclampsia in one patient among severe PE patients.[66]

In patients administered $MgSO_4$, vital signs, hourly deep tendon reflexes, and urine output need to be monitored. Maternal fluid replacement should be planned based on the urine output, and the hourly fluid replacement should not exceed 80 ml. Maintenance treatment should be continued in cases where the respiratory rate is at least 16/minute, patellar reflex responses are normal, and urine output is at least 30 ml/hour in the previous 4-hour period.

$MgSO_4$ loading dose:

- The loading dose is determined as 4-6 grams. Each 10 ml vial of 15% contains 1.5 g of $MgSO_4$; thus, a total of three vials (4.5 g $MgSO_4$) are required. It is administered as a slow i.v. infusion (over 20 minutes) in a 5% dextrose solution.

- If there is a standard, ready-made $MgSO_4$ solution (4 g in 100 ml), it is administered over 20 minutes.

- In cases where the i.v. route is unavailable, the same dose can be administered intramuscularly, although it is painful (due to the volume of 30 ml, this dose may be divided between both hips. Since intramuscular administration may be painful, it can be combined with 1 ml of 2% xylocaine).

$MgSO_4$ maintenance dose:

- A maintenance dose of 20 g $MgSO_4$ (13 vials) should be prepared in a 500 ml Ringer's lactate solution.

- $MgSO_4$ is administered as a continuous infusion at the rate of 1-2 g/hour (the rate of 25 ml/hour is used for administering 1 g/hour, 38 ml/hour for 1.5 g/hour, and 50 ml/hour for 2 g/hour).

- If a standard ready-made $MgSO_4$ solution is available (40 g in 1,000 ml), a rate of 25 ml/hour is applied for administering 1 g/h, 38 mL/hour for 1.5 g/hour, and 50 ml/hour for 2 g/hour).

- Alternatively (in conditions where i.v. treatment cannot be administered), 1.5 g $MgSO_4$ (1 vial/10 ml) is divided into two doses per hour and administered via intramuscular route as 5 ml to each hip.

The therapeutic blood level of $MgSO_4$ is 4-8 mg/dl (4-7 mEq/l, 2-3.5 mmol/l). When the blood level reaches 9-12 mg/dl (> 7 mEq/l, > 3.5 mmol/l), nausea, fever, double vision, drowsiness, flushing, weakness, and loss of deep tendon reflexes may be observed. If the dose attains a level of 15-17 mg/dl (> 10 mEq/l, > 5 mmol/l), muscular paralysis and respiratory depression may ensue. However, cardiac arrest may occur at levels ≥ 30 mg/dl (>25 mEq/l, 12.5 mmol/l).[2,67,68]

MANAGEMENT OF PREGNANCIES WITH CHRONIC HYPERTENSION. WHO NEEDS ECHOCARDIOGRAPHY/ NEPHROLOGICAL EVALUATION IN HYPERTENSIVE DISEASES OF PREGNANCY?

Chronic HT is one of the primary causes of adverse pregnancy outcomes such as PE, cerebrovascular accidents, FGR, preterm birth, maternal and perinatal mortality. Chronic HT patients should consider planned pregnancies, and the management should be initiated from the preconceptional period. Optimal BP control, the transition to the appropriate anti-hypertensive drugs, maternal weight control, a regular exercise program, and nutritional intervention (avoidance from excessive sodium and any caffeine or tobacco consumption) should be implemented in the preconceptional period.[24] Medical and family history should be elicited to determine the need for investigations for secondary causes of HT. The underlying etiology of a probable secondary HT should be examined if there is 1) Early-

onset HT (under the age of 30), 2) No familial history, 3) No associated co-morbidities like obesity or diabetes, 4) Presence of symptoms indicating any specific diseases (i.e., pheochromocytoma, Cushing syndrome, hyperthyroidism, obstructive sleep apnea), 5) Severe HT refractory to pharmacotherapy. Pregnant women with chronic HT should also be evaluated for end-organ damage. Urine microscopy, tests for proteinuria (PrCr, 24-hour urine protein level), ideally in prepregnancy counseling or at the first antenatal visit can detect those with chronic kidney disease and allows for timely referral to nephrology. This assessment will also serve as a baseline to identify superimposed PE in later gestational weeks. Conducting a complete blood count (hemoglobin and platelet count), serum creatinine level, liver function tests (ALT, AST) is also necessary to document the baseline parameters and diagnose a future superimposed PE. When the serum creatinine or urine analysis is abnormal, renal USG and serum electrolytes estimation should be performed. Lactate dehydrogenase levels (LDH) and peripheral blood smears (for schistocytes) can be examined to exclude hemolysis. Serum albumin level should be investigated if nephrotic syndrome is suspected. Patients with proteinuria, those who have red or white blood cells and casts in urine analysis (which suggests proliferative glomerular disorder), a family history of chronic kidney disease, increased serum creatinine levels, and abnormal serum electrolytes (particularly potassium levels) require nephrology evaluation.[1]

Patients with poorly controlled HT for more than four years and with advanced maternal age should undergo cardiac evaluation with electrocardiography (ECG) as an initial assessment. Findings suggestive of left ventricular hypertrophy on ECG, or comorbidities like obesity, diabetes or family history of cardiovascular diseases warrant further evaluation using echocardiography. Since women with chronic HT have also increased risk for development of gestational diabetes due to shared etiology like obesity, insulin resistance, endothelial dysfunction and systemic inflammation, they must undergo evaluation for gestational diabetes.[24] Given that superimposed PE may occur in women with chronic HT, and those with chronic renal disease, initiating low-dose (150 mg per night) aspirin prophylaxis beginning from the 16th until 36th weeks is recommended.[69]

Anti-hypertensive therapy is recommended by ACOG and SMFM for BP ≥ 140/90 mmHg, with a target BP < 140/90 mmHg based on the Chronic Hypertension and Pregnancy trial outcomes.[70,71] The first-line medications include labetalol, nifedipine, and alpha-methyldopa. Anti-hypertensive medication should be selected based on the probable side effects and patient characteristics (Table 1).[72] When standard-dosage monotherapy fails to reach the target blood pressure, a second agent from a different class should be introduced instead of persisting in increasing the dose of the initial drug.[1,73] Second-line anti-hypertensive agents include other beta-blockers (i.e., metoprolol), and hydrochlorothiazide. Atenolol is not recommended due to concerns about FGR. Amlodipine and diltiazem are not contraindicated, but data related to their safety are limited. There are some concerns regarding maternal tachycardia with the use of oral hydralazine, stillbirth with prazosin, reduction in maternal intravascular volume with diuretics.[1] Personalized anti-hypertensive management that considers maternal hemodynamics (heart rate, cardiac stroke volume, peripheral vascular resistance) and fetal condition (FGR) may lead to better BP control and obstetrical outcomes.

WHAT ARE THE INDICATIONS FOR DELIVERY IN PREGNANT WOMEN WITH CHRONIC HYPERTENSION AND WHEN SHOULD DELIVERY BE INDUCED IN PREGNANT WOMEN WITH OR WITHOUT SUPERIMPOSED PRE-ECLAMPSIA?

The ISSHP recommends delivery between 38^{+0} and 39^{+6} weeks in pregnant women with chronic HT unless any complications develop.[1] According to NICE, the delivery should not be scheduled before the 37th week for women with chronic HT and BP below 160/110 mmHg, regardless of whether they are receiving anti-hypertensive treatment or unless there is any additional medical indication. In such patients, it is recommended to schedule delivery after the 37th week.[3]

In the presence of the following findings in pregnant women with hypertensive disease, the decision to terminate pregnancy is made regardless of the gestational age: 1) pulmonary edema; 2) recurrent episodes of severe HT despite administering three different types of anti-hypertensive medications; 3) abnormal neurological findings, including severe headache, eclampsia, and recurrent visual scotomas; 4) the need for a blood product transfusion 5) a platelet count below ≤ 50,000/L; 6) abnormal and elevated liver enzyme levels; 7) abnormal and elevated serum creatinine levels; 8) hepatic dysfunction (INR > 2 without DIC or warfarin use), hepatic hematoma or rupture 9) compromised fetal status; and 10) placental abruption.

A comprehensive maternal and fetal evaluation, as well as platelet count, serum creatinine, AST, ALT, LDH, and proteinuria tests, should be conducted prior to determining whether to deliver or implement expectant management. Uric acid testing may be recommended in chronic HT patients with suspected superimposed PE. In fetal USG examination, estimated fetal weight, amniotic fluid volume, and the other parameters representing antepartum well-being should be evaluated.[2]

WHAT IS THE ROUTE OF DELIVERY IN PATIENTS WITH GESTATIONAL HYPERTENSIVE DISEASES? WHEN SHOULD A CESAREAN SECTION BE PERFORMED?

To date, no randomized trials have been undertaken to determine the optimal delivery method in patients with hypertensive disorders of pregnancy.[74] A cesarean section should not be indicated only in the presence of gestational HT without other obstetric causes; rather, the decision should be made on a case-to-case basis. The mode of delivery varies depending on the gestational duration, fetal well-being, fetal presentation, severity of FGR, oligohydramnios, umbilical artery flow pattern, biophysical profile scoring, fetal heartbeat pattern, onset

of labor, and Bishop score. The presence of PE and severe findings is not an indication for cesarean section. Cesarean section rates rise as the gestational week decreases.[2] If fetal or maternal condition is compromised, cesarean delivery should be performed.

Cesarean delivery should be the preferred option in cases of severe FGR, oligohydramnios, or a biophysical profile score of ≤ 4 in women under 28 weeks of gestation, or in cases of reverse flow in the umbilical artery at or below 32 weeks of gestation, according to the most recent scientific evidence.[75]

HOW SHOULD INTRAPARTUM FETAL AND MATERNAL MONITORING BE PERFORMED?

Under situations of stress such as maternal disease or placental insufficiency, the transfer capacity of oxygen and nutrients from the mother to the fetus, as well as the transfer capacity of metabolic products from the fetus to the mother, is reduced. Consequently, the fetus's capacity to compensate through the cardiovascular, respiratory, and other systems is diminished. In PE patients, especially those with severe PE, all these alterations can occur, and the risk of placental abruption is elevated. Therefore, continuous fetal heart monitoring and uterine activity during delivery is essential. The initial indications of placental abruption may include tachysystole or recurrent fetal heart rate decelerations. In women with PE, severe features may develop due to cardiac output and stress hormone level alterations during delivery.[76] Consequently, it is imperative to closely monitor the symptoms of severe disease and conduct hourly blood pressure monitoring. Oxygen saturation can be monitored using pulse oximetry, and if it is low (oxygen saturation < 95%), oxygen should be administered while closely monitoring for pulmonary edema and cardiomyopathy. Systemic opiate or epidural anesthesia may be administered for pain management. Anesthesia may be administered through epidural, spinal, or combined methods. General anesthesia should not be performed due to the risk of aspiration, difficulty in intubation due to airway edema, and increased intracranial pressure during intubation and extubation.[77] Nevertheless, regional anesthesia cannot be administered in the presence of coagulopathy or thrombocytopenia.[78]

HOW SHOULD THE MANAGEMENT BE STRUCTURED TO MINIMIZE MORBIDITY DURING DELIVERY (NEONATOLOGY ORGANIZATION, DELAYED UMBILICAL CORD CLAMPING, RESUSCITATION PLANNING)?

A neonatologist and NICU should be provided for the neonate, as severe FGR is prevalent in the offspring of women with PE and the risk of preterm delivery is elevated.[2] The necessity of intensive care for pre-eclamptic expectant women is typically dependent upon the severity of the condition and the presence of complications. In the intensive care unit, intravenous anti-hypertensive drugs can be administered to manage elevated blood pressure that is not controlled by oral agents. Since PE can lead to deterioration of renal and liver functions, intensive care follow-up may be required to support and monitor these functions. Intensive care may be needed in patients with a high risk for developing eclampsia, eclamptic convulsions, cardiac failure, coagulopathy, or pulmonary edema. In severe PE patients symptoms such as headaches, visual disturbances, and other neurological symptoms may necessitate intensive care.[3]

In patients with no risk of bleeding or hemodynamic instability (i.e., placental abruption, abnormal placentation or placenta previa), and where there is no need for urgent neonatal resuscitation (e.g., ablation, cord avulsion, blood flow abnormality on Doppler, severe FGR), it is permissible to delay cord clamping for 30-60 seconds. Delayed cord clamping is recommended, especially in preterm deliveries. Nevertheless, in fetuses < 28 weeks, cord milking is not recommended due to the potential for intracranial fetal hemorrhage. Delayed cord clamping is not advisable in monochorionic twin pregnancies and severe FGR.[79]

WHAT IS THE APPROPRIATE METHOD FOR MANAGING HYPERTENSION AND REPLACING FLUIDS DURING THE INTRAPARTUM PERIOD?

Gestational hypertensive diseases, particularly PE, are characterized by imbalances in intravascular and extravascular fluid distribution. Therefore, fluid replacement must be executed with caution. Due to increased vascular permeability, there is a risk of developing pulmonary and cerebral edema with excessive fluid administration. An average of 80 ml/hour (between 60 and 125 ml) i.v. Ringer's lactate solution should be administered.[80] In the event of severe heart failure, severe renal disease, HT resistant to treatment, and oligo-anuria, it is critical to conduct meticulous monitoring for pulmonary edema caused by fluid excess. Severe HT also elevates the risk of maternal intracranial bleeding, hypertensive encephalopathy, eclampsia, placental abruption, and cardiac failure.

All hypertensive pregnant patients do not require anti-hypertensive therapy during the intrapartum period. Anti-hypertensive treatment is administered to prevent congestive heart failure, myocardial ischemia, renal injury or failure, intracranial bleeding, and stroke. Since the risk of complications such as stroke, and intracranial hemorrhage increases in patients with sBP ≥ 160 and dBP ≥ 110, anti-hypertensive treatment should be initiated above these cutoff values. The goal is to maintain the sBP between 135 and 145 and the dBP between 95 and 100 mmHg without compromising uterine perfusion. Increased maternal BP causes a decrease in intravascular volume, and with aggressive anti-hypertensive treatment, cardiac output and uterine perfusion may decline, resulting in fetal compromise.[2,49] Many drugs can be safely administered for treating hypertensive emergency. The choice of drug varies according to maternal characteristics, contraindications of the drug, and the preference of the patient or physician. The most utilized anti-hypertensive drugs include nifedipine, labetolol, and hydralazine.[2] In PE patients, there is no clinically significant interaction between nifedipine and $MgSO_4$, particularly in the context of neurological block and severe hypotension. Nifedipine represents a viable option for treating severe HT in pregnant women receiving $MgSO_4$.[81]

SHOULD EVERY WOMAN WITH PRE-ECLAMPSIA RECEIVE MAGNESIUM ROUTINELY? HOW SHOULD DOSING AND MONITORING BE PERFORMED FOR $MgSO_4$ AND HOW LONG SHOULD THE DRUG BE CONTINUED IN THE POSTPARTUM PERIOD?

The routine use of $MgSO_4$ in PE patients is controversial due to the elevated risk of cesarean delivery, adverse maternal outcomes, and increased costs. The decision to administer $MgSO_4$ to women with PE should be based on individual factors and the severity of the condition. In patients with eclampsia, HELLP syndrome, severe HT, and severe clinical features, $MgSO_4$ therapy should be maintained both during the antenatal period and after delivery. In the absence of severe features, there is no requirement for $MgSO_4$ prophylaxis in PE and gestational HT.[1] The dosage, route of administration, and duration of $MgSO_4$ treatment may differ based on the patient's clinical condition and specific treatment protocol.[2]

ANESTHESIA AND ANALGESIA IN HYPERTENSIVE DISEASES OF PREGNANCY

As severe PE can lead to life-threatening complications like cerebral hemorrhage, eclampsia, acute kidney injury, pulmonary edema, hepatic rupture, placental abruption, and DIC, preanesthetic assessment should focus on disease severity, end-organ involvement, coagulation parameters, and hemodynamic status. Pre-eclamptic patients may experience an exaggerated hypertensive response to intubation. Pre-eclamptic patients may experience an exaggerated hypertensive response to intubation. Furthermore, endotracheal intubation can be challenging because of edema and predisposition to bleeding with airway instrumentation. Thus, the health team should be prepared for difficult and emergent airway management on the labor floor, as well as the possibility of eclamptic seizures or magnesium toxicity. $MgSO_4$ prophylaxis against eclamptic seizures may prolong the action of non-depolarizing neuromuscular blocking agents like vecuronium, rocuronium, and cisatracurium. Due to these concerns regarding general anesthesia, neuraxial anesthesia should be prioritized in pregnant women with HT. However, regional anesthesia is contraindicated in patients with coagulopathy or with a platelet count $< 75{,}000/mm^3$. Neuraxial anesthesia may lead to abrupt maternal hypotension. Caution should be exercised to prevent hypotension during neuraxial anesthesia to avoid fetal compromise in pre-eclamptic women on account of reduced uteroplacental perfusion. Targeting a BP level < 160/110 mmHg during anesthesia is safe to maintain uteroplacental perfusion while preventing the risk of stroke.[82,83] Intravenous fluid administration during initiation of neuraxial labor analgesia or neuraxial anesthesia, as well as during anesthesia for cesarean delivery, should be restricted to 80-100 ml/hour. This includes oxytocin and $MgSO_4$ infusion in severe PE patients, as they are prone to pulmonary edema due to elevated systemic vascular resistance, diminished colloid oncotic pressure with capillary leak, and myocardial dysfunction. In pre-eclamptic patients who are likely to require frequent blood sampling and active hemodynamic management, radial artery catheterization should be considered prior to the induction of general anesthesia. This is particularly true for those who have severe BP elevations, pulmonary edema, and DIC.

Neuraxial analgesia should be preferred for analgesia during labor if no contraindications exist. There was no discernible difference in neonatal APGAR scores, hypotension, or route of delivery between neuraxial labor analgesia and patient-controlled systemic analgesia with opioids. Systemic meperidine administration has been linked to higher rates of naloxone administration in the neonates.[84] Neuraxial analgesia provides superior pain relief than systemic analgesics and reduces hypertensive response to labor pain. It can potentially enhance uteroplacental circulation and prevent the need for generalized anesthesia in patients requiring an emergent cesarean section.[85]

Non-steroid anti-inflammatory drugs (NSAIDs) are not contraindicated in the postpartum period unless the patient has acute or chronic kidney disease, and risk factors for acute kidney disease such as sepsis, thrombocytopenia, coagulopathy, postpartum bleeding, or uncontrolled BP. Postpartum NSAIDs do not elevate BP or necessitate an increase in the dose of anti-hypertensives.[86] ACOG recommends that NSAIDs be preferred over opioids for postpartum or postoperative analgesia for patients with hypertensive diseases of pregnancy.[2]

WHAT MEASURES SHOULD BE UNDERTAKEN DURING POSTPARTUM FOLLOW-UP AND WHAT ARE THE MOST COMMON COMPLICATIONS? WHAT ARE THE PROBLEMS THAT AWAIT THE WOMAN IN THE LONG-TERM?

In women with antepartum HT, the maximum BP after delivery is typically observed between the 3rd and 7th days postpartum. Therefore, the patient should be followed closely during the postpartum period. Anti-hypertensive treatment should be maintained following delivery if it was initiated prior to pregnancy.[1] Postpartum use of ACEi (such as captopril, enalapril, and quinapril) and many anti-hypertensive agents is not a contraindication for breastfeeding.[87] Additionally, anti-hypertensive treatment may be considered in HT diagnosed before six days postpartum. With anti-hypertensive therapy, the dBP target in the postpartum period is ≤ 85 mmHg. It is recommended to verify that the BP as well as the laboratory and urinary parameters have stabilized in the third postpartum month. It is recommended that additional pathologies be identified through additional examinations if proteinuria or HT persists after this period. Patients should be re-evaluated at the sixth postpartum month, and lifestyle changes may be recommended if BP is ≥ 120/80 mmHg. The patient should be apprised about the risks of cardiovascular and hypertensive diseases in subsequent pregnancies. Effective BP management in the subsequent months is associated with lowered aortic stiffness, reduced BP, and a lower risk of cardiovascular disease.[1,88,89] Additionally, it is recommended that triglycerides, low-density lipoprotein, total cholesterol, fasting blood glucose, hemoglobin A1C, high-sensitive C-reactive protein, and urinary ACR be assessed during the initial postpartum year. For women with a history of hypertensive disease during pregnancy, it is recommended that they undergo annual examinations for a period of 5-10 years postpartum. These women should be advised to adopt healthy eating habits, engage in exercise, attain ideal

weight, maintain a smoke-free lifestyle, and have a BP below 120/80 mmHg.[1]

It has been reported that the risk of mortality from cardiovascular disease, especially in women with a history of early-onset PE, is five times higher than in women without a history of PE, and is 1.65 times higher in women with late-onset PE.[90] In general, HT is one of the most significant risk factors for heart disease, including myocardial infarction.[91] Women with a history of PE are at a five- to twelvefold increased risk of developing end-stage renal disease.[92,93] The risk of renal disease is higher in women with early-onset PE than those with late-onset disease.[94] PE may lead to neurological complications such as cognitive disorders, stroke, cerebral white matter lesions, and posterior reversible encephalopathy syndrome in the long-term. Again, these neurological complications are more common in women with early-onset PE.[95] Several investigations have demonstrated that PE impacts certain types of malignancies. In a meta-analysis of over 5 million women, it was concluded that the history of PE was associated with a lower risk of breast cancer but a higher risk of ovarian cancer.[96] Long-term complications of PE also include persistent HT, diabetes mellitus, venous thromboembolism, and vascular dementia. Due to the elevated risk of chronic renal and cardiovascular diseases in the future for children of hypertensive pregnant women, it is imperative that these families promote a healthy lifestyle in order to mitigate the elevated risk of cardiovascular disease.[1]

RECOMMENDATIONS

- During pregnancy, the cutoff values for sBP and dBP for HT are 140 mmHg and 90 mmHg, respectively. It is considered as severe HT, if sBP is ≥ 160 mmHg and/or dBP is ≥ 110 mmHg.

- Using the PrCr in spot urine (≥ 30 mg/mmol) to diagnose proteinuria is a simple and practical method. Diagnosis can be based on proteinuria in a 24-hour urine sample (≥ 300 mg), ACR (≥ 8 mg/mmol), or ≥ +2 protein by dipstick technique in spot urine sample.

- If thrombocytopenia (<100 x 10^9/l), ≥ 2-fold increase in liver transaminases, persistence of pain in the right upper quadrant of the abdomen or epigastrium, occurrence of renal failure, pulmonary edema, new-onset headache, or visual symptoms occur after the 20th week of gestation in a hypertensive woman with no proteinuria, the patient can be considered to have PE. Therefore, pregnant women with HT should be assessed carefully in terms of these clinical conditions.

- The use of ACEi and ARBs is not recommended in pregnant women with chronic HT due to their potential teratogenic effects (renal failure, cardiac septal defects, hypospadias and esophageal atresia).

- Although there are contradictory opinions, fetal USG for evaluating fetal growth, amniotic fluid volume and umbilical artery Doppler examination may be recommended at 28th, 32nd and 36th weeks in hypertensive pregnant women who are receiving anti-hypertensive treatment or with end-organ damage, superimposed PE, or FGR.

- In hypertensive pregnancies complicated by FGR before 34th weeks, ductus venosus Doppler assessment and computerized-cardiotocography are suitable methods because they reduce perinatal mortality and enhance neurological outcomes.

- Since the benefit of fetal heart rate monitoring in mitigating adverse outcomes in hypertensive pregnancies have not yet been proven, it is only recommended when clinically indicated.

- Biophysical profile scoring is not advised because it is subjective, and a low score is a late finding for identifying at-risk fetuses.

- Adverse maternal and perinatal outcomes in pre-eclamptic women are determined by the severity of HT and the existence of end-organ damage rather than the amount of proteinuria. Therefore, the amount of proteinuria alone should not modify the management of PE.

- PE should not be classified as severe or non-severe due to the possibility of unanticipated worsening or deterioration in maternal and/or fetal health.

- For women with gestational HT without severe features, weekly antenatal visits and daily BP measurements at home are recommended. In such women, the tests employed for diagnosing PE, including complete blood count, liver and renal functions and proteinuria, can be repeated weekly if necessary.

- Some PE patients without severe symptoms should be assessed biweekly to identify possible clinical signs of severe PE.

- Anti-hypertensive treatment should be initiated in pregnant women with persistently high blood pressure ≥ 140/90 mmHg. The target BP for anti-hypertensive therapy should be a dBP of 85 mmHg, irrespective of sBP. Patients with gestational HT and PE are typically managed similarly.

- In the treatment of non-severe HT in pregnancies, alpha-methyldopa, labetalol or nifedipine can be used as the first-line medications. There is no clear evidence that one drug is superior to another.

- The first-choice drugs in the treatment of acute HT include parenteral hydralazine, labetalol and oral nifedipine.

- PE patients with previable gestations may be offered the choice of terminating the pregnancy due to the significant risk of maternal/perinatal mortality and morbidity. Expectant management is preferred from viability to 33^{+6} weeks, if there is no obvious indication for delivery.

- Some women with PE or gestational HT without severe features or exhibit decline in fetal well-being can be managed expectantly with close monitoring between 34 and 37 weeks. The option of delivery should be offered to women at term (≥ 37^{+0} weeks) with gestational HT or PE without severe features.

- For pre-eclamptic pregnancies with severe characteristics, pregnancy termination should be planned in cases before fetal viability (before the completion of the 23rd weeks) or after the completion of the 34th weeks.

- Pre-eclamptic women with severe features should be hospitalized for close maternal and fetal monitoring. In such patients, $MgSO_4$ infusion for eclampsia prophylaxis and between the 23rd and 34th gestational weeks, antenatal corticosteroid therapy should be administered. When the general condition of the mother and/or the fetus deteriorates, pregnancy termination should be considered regardless of the gestational age.

- In acute severe HT, the treatment targets for sBP and dBP are 140-150 mmHg and 90-100 mmHg, respectively.

- $MgSO_4$ therapy is initiated in severe PE patients. Treatment should be continued for at least 24 hours after birth or following the last episode of convulsions.

- Pregnant women with chronic HT should be evaluated for end-organ damage. Urine analysis and serum creatinine levels for possible renal damage; cardiac evaluation with ECG; basal values of serum transaminases and platelet levels for the diagnosis of possible superimposed PE in the subsequent weeks, should be investigated.

- The first-line drugs in the treatment of pregnant women with chronic HT are alpha-methyldopa, labetalol and nifedipine, while the second-line medications are beta-blockers (i.e., metoprolol), and hydrochlorothiazide. If target BP levels are not attained with the first-line monotherapy, second-line therapy can be initiated rather than increasing the dose of the first-line drug.

- Delivery is recommended between 38 and 39^{+6} weeks for women with chronic HT exhibiting normal maternal and fetal status.

- Because neuraxial analgesia provides superior pain relief than systemic analgesics and reduces hypertensive response to labor pain, it should be preferred for labor analgesia.

- Blood pressure may increase in hypertensive pregnant women, especially during the first postpartum week. Therefore, treatment should be continued in the postpartum period for women who were initiated on antepartum anti-hypertensive agents. The target dBP value during the postpartum period should be ≤ 85 mmHg.

- Women with a history of early-onset PE have an increased long-term risk of cardiovascular, renal and neurological diseases, venous thromboembolism, diabetes mellitus and persistent HT.

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REFERENCES

1. Magee LA, Brown MA, Hall DR, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens.* 2022;27:148-169. [CrossRef]
2. No authors listed. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. *Obstet Gynecol.* 2020;135:237-260. [CrossRef]
3. NICE Guidelines. Hypertension in pregnancy: diagnosis and management. Published: 25 June 2019 Last updated: 17 April 2023. [CrossRef]
4. Henderson JT, Thompson JH, Burda BU, Cantor A, Preeclampsia screening: evidence report and systematic review for the US preventive services task force. *JAMA.* 2017;317:1668-1683. [CrossRef]
5. Fishel Bartal M, Lindheimer MD, Sibai BM. Proteinuria during pregnancy: definition, pathophysiology, methodology, and clinical significance. *Am J Obstet Gynecol.* 2022;226(Suppl 2):819-834. [CrossRef]
6. Baffero GM, Somigliana E, Crovetto F, et al. Confined placental mosaicism at chorionic villous sampling: risk factors and pregnancy outcome. *Prenat Diagn.* 2012;32:1102-1108. [CrossRef]
7. Spinillo SL, Farina A, Sotiriadis A, et al. Pregnancy outcome of confined placental mosaicism: meta-analysis of cohort studies. *Am J Obstet Gynecol.* 2022;227:714-727. [CrossRef]
8. Tsakiridis I, Giouleka S, Arvanitaki A, et al. Chronic hypertension in pregnancy: synthesis of influential guidelines. *J Perinat Med.* 2021;49:859-872. [CrossRef]
9. Cífková R. Hypertension in pregnancy: a diagnostic and therapeutic overview. *High Blood Press Cardiovasc Prev.* 2023;30:289-303. [CrossRef]
10. Majak GB, Reisaeter AV, Zucknick M, et al, Preeclampsia in kidney transplanted women; Outcomes and a simple prognostic risk score system. *PLoS One.* 2017;12:e0173420. [CrossRef]
11. Garovic VD, Dechend R, Easterling T, et al. Hypertension in Pregnancy: Diagnosis, Blood Pressure Goals, and Pharmacotherapy: A Scientific Statement from the American Heart Association. *Hypertension.* 2022;79:21-41. [CrossRef]
12. Rana S, Burke SD, Karumanchi SA. Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders. *Am J Obstet Gynecol.* 2022;226(Suppl 2):1019-1034. [CrossRef]
13. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. *BMJ.* 2014;348:2301. [CrossRef]
14. Panaitescu AM, Baschat AA, Akolekar R, Syngelaki A, Nicolaides KH. Association of chronic hypertension with birth of small-for-gestational-age neonate. *Ultrasound Obstet Gynecol.* 2017;50:361-366. [CrossRef]
15. Vigil-De Gracia P, Lasso M, Montufar-Rueda C. Perinatal outcome in women with severe chronic hypertension during the second half of pregnancy. *Int J Gynaecol Obstet.* 2004;85:139-144. [CrossRef]
16. Sibai B. Chronic hypertension in pregnancy. *Obstet Gynecol.* 2002;100:369-377. [CrossRef]
17. Ferrazzi E, Zullino S, Stampalija T, et al. Bedside diagnosis of two major clinical phenotypes of hypertensive disorders of pregnancy. *Ultrasound Obstet Gynecol.* 2016;48:224-231. [CrossRef]
18. Cavoretto PI, Farina A, Salmeri N, Syngelaki A, Tan MY, Nicolaides KH. First trimester risk of preeclampsia and rate of spontaneous birth in patients without preeclampsia. *Am J Obstet Gynecol.* 2024:S0002-9378(24)00022-X. [CrossRef]
19. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med.* 2017;377:613-622. [CrossRef]
20. O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. *Am J Obstet Gynecol.* 2016;214:103. [CrossRef]
21. Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. *Prenat Diagn.* 2011;31:66-74. Erratum in: *Prenat Diagn.* 2011;31:832. [CrossRef]
22. Tan MY, Syngelaki A, Poon LC, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol.* 2018;52:186-195. [CrossRef]
23. van Gelder MM, Van Bennekom CM, Louik C, Werler MM, Roeleveld N, Mitchell AA. Maternal hypertensive disorders, antihypertensive medication use, and the risk of birth defects: a case-control study. *BJOG.* 2015;122:1002-1009. [CrossRef]

24. Battarbee AN, Sinkey RG, Harper LM, Oparil S, Tita ATN. Chronic hypertension in pregnancy. *Am J Obstet Gynecol*. 2020;222:532-541. [CrossRef]
25. Lees CC, Stampalija T, Baschat A, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol*. 2020;56:298-312. [CrossRef]
26. Visser GHA, Bilardo CM, Derks JB, et al. Fetal monitoring indications for delivery and 2-year outcome in 310 infants with fetal growth restriction delivered before 32 weeks' gestation in the TRUFFLE study. *Ultrasound Obstet Gynecol*. 2017;50:347-352. [CrossRef]
27. Frusca T, Todros T, Lees C, Bilardo CM; TRUFFLE Investigators. Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe. *Am J Obstet Gynecol*. 2018;218(Suppl 2):783-789. [CrossRef]
28. No authors listed. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol*. 2019;133:1 [CrossRef]
29. Odendaal HJ, Hall DR, Grové D. Risk factors for and perinatal mortality of abruptio placentae in patients hospitalised for early onset severe pre-eclampsia - a case controlled study. *J Obstet Gynaecol*. 2000;20:358-364. [CrossRef]
30. Turan OM, Turan S, Gungor S, et al. Progression of Doppler abnormalities in intrauterine growth restriction. *Ultrasound Obstet Gynecol*. 2008;32:160-167. [CrossRef]
31. Castiglioni MT, Valsecchi L, Cavoretto P, et al. The risk of preeclampsia beyond the first pregnancy among women with type 1 diabetes parity and preeclampsia in type 1 diabetes. *Pregnancy Hypertens*. 2014;4:34-40. [CrossRef]
32. No authors listed. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol*. 2013;122:1122-1131. [CrossRef]
33. Caritis S, Sibai B, Hauth J, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med*. 1998;338:701-705. [CrossRef]
34. Hauth JC, Ewell MG, Levine RJ, et al. Pregnancy outcomes in healthy nulliparas who developed hypertension. Calcium for Preeclampsia Prevention Study Group. *Obstet Gynecol*. 2000;95:24-28. [CrossRef]
35. Schiff E, Friedman SA, Kao L, Sibai BM. The importance of urinary protein excretion during conservative management of severe preeclampsia. *Am J Obstet Gynecol*. 1996;175:1313-1316. [CrossRef]
36. Newman MG, Robichaux AG, Stedman CM, et al. Perinatal outcomes in preeclampsia that is complicated by massive proteinuria. *Am J Obstet Gynecol*. 2003;188:264-268. [CrossRef]
37. Wiles K, Bramham K, Seed PT, et al. Diagnostic indicators of superimposed preeclampsia in women with CKD. *Kidney Int Rep*. 2019;4:842-853. [CrossRef]
38. Homer CS, Brown MA, Mangos G, Davis GK. Non-proteinuric pre-eclampsia: a novel risk indicator in women with gestational hypertension. *J Hypertens*. 2008;26:295-302. [CrossRef]
39. Pettit F, Brown MA. The management of pre-eclampsia: what we think we know. *Eur J Obstet Gynecol Reprod Biol*. 2012;160:6-12. [CrossRef]
40. Saudan P, Brown MA, Buddle ML, Jones M. Does gestational hypertension become pre-eclampsia? *Br J Obstet Gynaecol*. 1998;105:1177-1184. [CrossRef]
41. Magee LA, von Dadelszen P, Bohun CM, et al. Serious perinatal complications of non-proteinuric hypertension: an international, multicentre, retrospective cohort study. *J Obstet Gynaecol Can*. 2003;25:372-382. [CrossRef]
42. Williams D. Long-term complications of preeclampsia. *Semin Nephrol*. 2011;31:111-122. [CrossRef]
43. Beech A, Mangos G. Management of hypertension in pregnancy. *Aust Prescr*. 2021;44:148-152. [CrossRef]
44. Khedagi AM, Bello NA. Hypertensive Disorders of Pregnancy. *Cardiol Clin*. 2021;39:77-90. [CrossRef]
45. Folk DM. Hypertensive Disorders of Pregnancy: Overview and Current Recommendations. *J Midwifery Womens Health*. 2018;63:289-300. [CrossRef]
46. Malik R, Kumar V. Hypertension in Pregnancy. *Adv Exp Med Biol*. 2017;956:375-393. [CrossRef]
47. Sinkey RG, Battarbee AN, Bello NA, Ives CW, Oparil S, Tita ATN. Prevention, Diagnosis, and Management of Hypertensive Disorders of Pregnancy: a Comparison of International Guidelines. *Curr Hypertens Rep*. 2020;22:66. [CrossRef]
48. Metoki H, Iwama N, Hamada H, et al. Hypertensive disorders of pregnancy: definition, management and out-of-office blood pressure measurement. *Hypertens Res*. 2022;45:1298-1309. [CrossRef]
49. Magee LA, Singer J, von Dadelszen P; CHIPS Study Group. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med*. 2015;372:2367-2368. [CrossRef]
50. Martinez A, Lakkimsetti M, Maharjan S, et al. Beta-Blockers and Their Current Role in Maternal and Neonatal Health: A Narrative Review of the Literature. *Cureus*. 2023;15:e44043. [CrossRef]
51. Bone JN, Sandhu A, Abalos ED, et al. Oral Antihypertensives for nonsevere pregnancy hypertension: systematic review, network meta- and trial sequential analyses. *Hypertension*. 2022;79:614-628. [CrossRef]
52. Awaludin A, Rahayu C, Daud NAA, Zakiyah N. Antihypertensive medications for severe hypertension in pregnancy: a systematic review and meta-analysis. *Healthcare (Basel)*. 2022;10:325. [CrossRef]
53. Alavifard S, Chase R, Janoudi G, et al. First-line antihypertensive treatment for severe hypertension in pregnancy: a systematic review and network meta-analysis. *Pregnancy Hypertens*. 2019;8:179-187. [CrossRef]
54. Katsi V, Papakonstantinou IP, Papazachou O, Makris T, Tsioufis K. Beta-Blockers in Pregnancy: Clinical Update. *Curr Hypertens Rep*. 2023;25:13-24. [CrossRef]
55. Broekhuijsen K, van Baaren GJ, van Pampus MG, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial. *Lancet*. 2015;385:2492-2501. Erratum in: *Lancet*. 2016;387:848. [CrossRef]
56. Teune MJ, Bakhuizen S, Gyamfi Bannerman C, et al. A systematic review of severe morbidity in infants born late preterm. *Am J Obstet Gynecol*. 2011;205:374. [CrossRef]
57. Mishanina E, Rogozinska E, Thatthi T, Uddin-Khan R, Khan KS, Meads C. Use of labour induction and risk of cesarean delivery: a systematic review and meta-analysis. *CMAJ*. 2014;186:665-673. [CrossRef]
58. Caradeux J, Martinez-Portilla RJ, Basuki TR, Kiserud T, Figueras F. Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2018;218(Suppl 2):774-782. [CrossRef]
59. Chappell LC, Brocklehurst P, Green ME, et al. Planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial. *Lancet*. 2019;394:1181-1190. [CrossRef]
60. Zwertbroek EF, Zwertbroek J, Broekhuijsen K, et al. Neonatal developmental and behavioral outcomes of immediate delivery versus expectant monitoring in mild hypertensive disorders of pregnancy: 5-year outcomes of the HYPITAT II trial. *Eur J Obstet Gynecol Reprod Biol*. 2020;244:172-179. [CrossRef]
61. Koopmans CM, Bijlenga D, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet*. 2009;374:979-988. [CrossRef]
62. Odendaal HJ, Pattinson RC, Bam R, Grove D, Kotze TJ. Aggressive or expectant management for patients with severe preeclampsia between 28-34 weeks' gestation: a randomized controlled trial. *Obstet Gynecol*. 1990;76:1070-1075. [CrossRef]
63. Sibai BM, Mercer BM, Schiff E, Friedman SA. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks' gestation: a randomized controlled trial. *Am J Obstet Gynecol*. 1994;171:818-822. [CrossRef]
64. Magee LA, Yong PJ, Espinosa V, Côté AM, Chen I, von Dadelszen P. Expectant management of severe preeclampsia remote from term: a structured systematic review. *Hypertens Pregnancy*. 2009;28:312-347. [CrossRef]
65. Vigil-De Gracia P, Reyes Tejada O, Calle Miñaca A, et al. Expectant management of severe preeclampsia remote from term: the MEXPRE Latin Study, a randomized, multicenter clinical trial. *Am J Obstet Gynecol*. 2013;209:425. [CrossRef]
66. Altman D, Carroli G, Duley L, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet*. 2002;359:1877-1890. [CrossRef]
67. Sibai BM. Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. *Am J Obstet Gynecol*. 2004;190:1520-1526. [CrossRef]
68. Okusanya BO, Oladapo OT, Long Q, et al. Clinical pharmacokinetic properties of magnesium sulphate in women with pre-eclampsia and eclampsia. *BJOG*. 2016;123:356-366. [CrossRef]
69. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *N Engl J Med*. 2017;377:613-622. [CrossRef]
70. Tita AT, Szychowski JM, Boggess K, et al. Treatment for Mild Chronic Hypertension during Pregnancy. *N Engl J Med*. 2022;386:1781-1792. [CrossRef]

71. Society for Maternal-Fetal Medicine; Publications Committee. Electronic address: pubs@smfm.org. Society for Maternal-Fetal Medicine Statement: Antihypertensive therapy for mild chronic hypertension in pregnancy-The Chronic Hypertension and Pregnancy trial. *Am J Obstet Gynecol.* 2022;227:B24-B27. [CrossRef]
72. Levene I, Wilkinson D. Identification and management of neonatal hypoglycaemia in the full-term infant (British Association of Perinatal Medicine-Framework for Practice). *Arch Dis Child Educ Pract Ed.* 2019;104:29-32. [CrossRef]
73. Butalia S, Audibert F, Côté AM, et al. Hypertension Canada's 2018 Guidelines for the Management of Hypertension in Pregnancy. *Can J Cardiol*. 2018;34:526-531. [CrossRef]
74. Amorim MM, Souza ASR, Katz L. Planned caesarean section versus planned vaginal birth for severe pre-eclampsia. *Cochrane Database Syst Rev.* 2017;10:CD009430. [CrossRef]
75. Coviello EM, Iqbal SN, Grantz KL, Huang CC, Landy HJ, Reddy UM. Early preterm preeclampsia outcomes by intended mode of delivery. *Am J Obstet Gynecol*. 2019;220:100. [CrossRef]
76. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. *Obstet Gynecol*. 2019;133:26-50. [CrossRef]
77. Wallace DH, Leveno KJ, Cunningham FG, Giesecke AH, Shearer VE, Sidawi JE. Randomized comparison of general and regional anesthesia for cesarean delivery in pregnancies complicated by severe preeclampsia. *Obstet Gynecol.* 1995;86:193-199. [CrossRef]
78. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 197: Inherited Thrombophilias in Pregnancy. *Obstet Gynecol.* 2018;132:18-34. Erratum in: *Obstet Gynecol.* 2018;132:1069. [CrossRef]
79. No authors listed. Committee Opinion No. 684: Delayed Umbilical Cord Clamping After Birth. *Obstet Gynecol*. 2017;129:1. [CrossRef]
80. Anthony J, Schoeman LK. Fluid management in pre-eclampsia. *Obstet Med.* 2013;6:100-104. [CrossRef]
81. Magee LA, Miremadi S, Li J, et al. Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. *Am J Obstet Gynecol.* 2005;193:153-163. [CrossRef]
82. Martin JN Jr, Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstet Gynecol*. 2005;105:246-254. [CrossRef]
83. Ayhan A, Akovalı N, Camkıran Fırat A. Can Hypotension Episodes that were not Identified in the Non-Invasive Blood Pressure be Detected during Cesarean Section? A Randomized Controlled Trial. *Balkan Med J.* 2022;39:358-365. [CrossRef]
84. Head BB, Owen J, Vincent RD Jr, Shih G, Chestnut DH, Hauth JC. A randomized trial of intrapartum analgesia in women with severe preeclampsia. *Obstet Gynecol.* 2002;99:452-457. [CrossRef]
85. Patel P, Desai P, Gajjar F. Labor epidural analgesia in pre-eclampsia: A prospective study. *J Obstet Gynaecol Res.* 2005;31:291-295. [CrossRef]
86. Bellos I, Pergialiotis V, Antsaklis A, Loutradis D, Daskalakis G. Safety of non-steroidal anti-inflammatory drugs in postpartum period in women with hypertensive disorders of pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2020;56:329-339. [CrossRef]
87. Drugs and Lactation Database (LactMed) [Internet]. National Library of Medicine (US), 2006. [CrossRef]
88. Ying W, Catov JM, Ouyang P. Hypertensive Disorders of Pregnancy and Future Maternal Cardiovascular Risk. *J Am Heart Assoc.* 2018;7:e009382. [CrossRef]
89. Cairns AE, Tucker KL, Leeson P, et al. Self-Management of Postnatal Hypertension: The SNAP-HT Trial. *Hypertension.* 2018;72:425-432. [CrossRef]
90. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. *Hypertension*. 2010;56:166-171. [CrossRef]
91. Kayikcioglu M, Ozkan HS, Yagmur B. Premature myocardial infarction: A rising threat. *Balkan Med J.* 2022;39:83-95. [CrossRef]
92. Paauw ND, Luijken K, Franx A, Verhaar MC, Lely AT. Long-term renal and cardiovascular risk after preeclampsia: towards screening and prevention. *Clin Sci (Lond).* 2016;130:239-246. [CrossRef]
93. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. *N Engl J Med*. 2008;359:800-809. [CrossRef]
94. Dall'Asta A, D'Antonio F, Saccone G, et al. Cardiovascular events following pregnancy complicated by pre-eclampsia with emphasis on comparison between early-and late-onset forms: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2021;57:698-709. [CrossRef]
95. Dimitriadis E, Rolnik DL, Zhou W, et al. Author Correction: Pre-eclampsia. *Nat Rev Dis Primers.* 2023;9:35. Erratum in: *Nat Rev Dis Primers.* 2023;16:8. [CrossRef]
96. Wang F, Zhang W, Cheng W, Huo N, Zhang S. Preeclampsia and cancer risk in women in later life: a systematic review and meta-analysis of cohort studies. *Menopause.* 2021;28:1070-1078. [CrossRef]