EHC Guidelines

Prevention and Treatment of Hypertension in Pregnancy

EGYPTIAN HEALTH COUNCIL

WHO Copyright page

Please ensure that the standard disclaimers for WHO publications (unrestricted materials) are used. The Office of the Publisher can provide additional information on the use of disclaimers, including the addition of a different disclaimer for web annexes to WHO guidelines.

Contents

Acknowledgements

We would like to acknowledge the Obstetrics & Gynecology Guidelines Development Committee for adapting this guideline.

Chair of the GDG: Abdelhamid Mohamed Attia, Faculty of Medicine, Cairo University

Rapporteur of the GDG: Alaa Eldin Hamed ElFeky, Faculty of Medicine, Ain Shams University

Members of the GDG:

- Aboubakr Mohamed ElNashar, Faculty of Medicine, Banha University
- Ahmed Ezz El-din Mahran, Faculty of Medicine, Minia University
- Ahmed Fawzy Galal, Faculty of Medicine, Alexandria University
- Ahmed Sekotory Mahmoud, Consultant, FRCOG, Private sector
- Amr Abdelaziz Nadim, Faculty of Medicine, 6 October University
- Amr Ahmed Abouelyazid, Ministry of Interior, Police Hospital, Cairo.
- Amr Essam, MD, Senior Consultant, Private sector
- Diaa Monir Eglan, Faculty of Medicine, Tanta University
- Ehab Hassan Abdelfataah, Faculty of Medicine, Ain Shams University
- Magdy Ibrahim Mostafa, Faculty of Medicine, Cairo University
- Mervat Aly Elsers, Faculty of Medicine, Alexandria University
- Mohamed Mahmoud FathAlla, Faculty of Medicine, Assiut University
- Osama Omar Amer, Ministry of Defense, Military Medical Academy
- Taiseer Maarouf Afifi, Faculty of Medicine for girls, AlAzhar University
- Wafaa Benjamin Basta, MOHP, Mattareyya Teaching Hospital

Abbreviations

APLS Antiphospholipid syndrome

BMI Body mass index

BP Blood pressure

CTG Cardiotocograph

dBP Diastolic blood pressure

DIC Disseminated intravascular coagulation

EFW Estimated fetal weight

FBC Full blood count

FGR Fetal growth restriction

FHR Fetal heart rate

GA General anaesthesia

GDG: Guidelines Development Group

GP General practitioner

GPS: Good Practice Statement.

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HDP Hypertensive disorders of pregnancy

HELLP Haemolysis, Elevated Liver enzymes and Low Platelet count

IUGR Intrauterine growth restriction

LDH Lactate dehydrogenase

LFT Liver function test

MAP Mean arterial pressure

PAPP-A Pregnancy associated plasma protein A

PlGF Placental growth factor

sBP Systolic blood pressure

sFlt-1 Soluble fms-like tyrosine kinase 1

UA Umbilical artery

USS Ultrasound scan

UtPI Uterine artery pulsatility index

Glossary

The following definitions are used in this guideline:

Hypertension	Systolic blood pressure (sBP) greater than or equal to 140 mmHg and/or Diastolic blood pressure (dBP) greater than or equal to 90 mmHg of at least two measurements.
N**on-severe (mild to moderate) hypertension**	Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg.
Severe hypertension	Systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more.
Chronic hypertension in pregnancy	Hypertension confirmed preconception or prior to 20 weeks; (including pregnant women entering pregnancy on antihypertensive therapy with well controlled BP levels), and does not resolve within 3 months postpartum. *Women may also be diagnosed with chronic hypertension retrospectively, e.g. where a woman with hypertension in pregnancy remains hypertensive 3 months following the birth.*
Gestational hypertension	Hypertension developing after 20 weeks of gestation, without proteinuria and without features of organ dysfunction, with blood pressure levels returning to normal within 3 months postpartum. *At first presentation, this diagnosis might include some women (up to 25%) who are developing preeclampsia but have not yet developed organ manifestations.*
Preeclampsia	<u>Diagnosis:</u> Occurrence of new-onset hypertension, after 20 weeks of pregnancy and the coexistence of 1 or more of the following new-onset conditions: 1. new-onset proteinuria or 2. new-onset significant organ dysfunction

	and resolves within 3 months postpartum.
Proteinuria	▪ Protein/creatinine ratio ≥ 30 mg/mmol (= 0.3 mg%) ▪ Proteinuria ≥ 300 mg/dL of protein or more in a 24-hour urine collection ▪ Dipstick proteinuria greater than or equal to 2+ proteinuria
Significant organ dysfunction	▪ Blood: Platelet count <100,000/microL ▪ Kidney: Serum creatinine >1.1 mg/dL or doubling of the creatinine concentration in the absence of other renal disease ▪ Liver: transaminases at twice the upper limit of the normal. ▪ Lung: Pulmonary edema ▪ Brain: altered mental status, blindness, stroke, clonus, severe headaches or persistent visual scotomata
Non-severe pre-eclampsia	▪ Pre-eclampsia with no features of severity or concern.
Severe pre-eclampsia	Pre-eclampsia with any of the following features of severity: • Severe Hypertension: Systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)

	• Thrombocytopenia: Platelet count less than 100,000 /mm^3. • Impaired liver function that is not accounted for by alternative diagnoses and as indicated by abnormally elevated blood concentrations of liver enzymes (ALT, AST) to more than twice the upper normal limit, • Renal insufficiency Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease or oliguria. • Persistent right upper quadrant or epigastric pain unresponsive to medications. • New-onset recurring headaches; unresponsive to medication, not accounted for by any alternative diagnoses. • Visual symptoms (photopsia, scotomata, cortical blindness, retinal vasospasm). • Pulmonary edema. • Failure of fetal growth or abnormal doppler findings
Superimposed Preeclampsia	▪ Where a woman with pre-existing hypertension develops systemic features of preeclampsia after 20 weeks gestation: o New-onset proteinuria o New-onset feature of severe pre-eclampsia
Imminent eclampsia	▪ Defined as at least two of the following signs and/or symptoms 1. Ongoing or recurring severe headaches 2. Visual disturbance 3. Altered level of consciousness 4. Hyperreflexia and/or sustained clonus

Eclampsia	▪ Defined by new-onset tonic/clonic, focal, or multi-focal seizures; in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and/or infarction, intracranial hemorrhage, or drug use.
HELLP syndrome	▪ (**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets) probably represents a severe form of preeclampsia, use the following criteria to make the diagnosis: o Lactate dehydrogenase (LDH) elevated to 600 IU/L or more, and o Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevated more than twice the upper limit of normal, and o Platelets count less than 100,000 /mm^3.
Expectant management	Refers to safe prolongation of the pregnancy, with maternal and fetal monitoring guiding clinically indicated treatment, instead of immediate birth.
Multidisciplinary team	May include (as relevant to the clinical circumstances) obstetrician, midwife, obstetric physician, anaesthetist, neonatologist/paediatrician experienced in the care of women with hypertension in pregnancy.
Mean arterial pressure (MAP)	MAP is calculated by using a validated blood pressure machine or by: o The sum of sBP plus twice the dBP = (sBP + 2 x dBP) divided by 3
Definitive Intervention	Refers to delivery of fetus and placenta by initiation of labor or by Cesarean Section.

Executive Summary

EHC has developed the present evidence-informed recommendations with a view to promoting the best possible clinical practices for the **Prevention and Treatment of Hypertension in Pregnancy**.

List of Recommendations

Recommendation	Strength
<u>Definitions And Classification</u>	
HDPs should be classified according to the criteria and definitions presented in "Glossary"	**GPS**
Diagnose Hypertension in pregnancy when systolic blood pressure is ≥140mmHg and/or diastolic blood pressure is ≥90mmHg, based on the average of *at least* 2 measurements, taken at least 15minutes apart, using the same arm.	**Strong**
Severe hypertension (sBP ≥ 160 and/or dBP ≥ 110 mmHg), can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy	**Conditional**
Gestational hypertension is hypertension that develops for the first time at > 20 weeks, without evidence of preeclampsia	**Conditional**
Women with gestational hypertension should undergo testing for preeclampsia to rule it out.	**Strong**
Diagnose preeclampsia in women with new onset hypertension after 20 weeks and new-onset proteinuria or one/more adverse conditions (defined as a maternal end organ complication or evidence of uteroplacental dysfunction)	**Strong**
Preeclampsia superimposed on chronic hypertension is diagnosed by the development of 1 or more characteristics of preeclampsia (i.e., new-onset proteinuria or 1 or more adverse conditions) superimposed on chronic hypertension	**Strong**
Do not use an elevation in BP to make a diagnosis of preeclampsia superimposed on chronic hypertension.	**Conditional**

Risk factors	
Risk factors for developing preeclampsia should be included in the antenatal assessment of all pregnant women.	**GPS**
<u>Screening</u>	
All pregnant women should be screened for their risk of developing preeclampsia early in the pregnancy.	**Strong**
The screening tool utilized should be determined based on the locally available resources	**Conditional**
<u>Blood Pressure measurement</u>	
During every antenatal visit, screening for preeclampsia in pregnant women with blood pressure measurements throughout pregnancy is strongly recommended	**Strong**
<u>Testing For Proteinuria</u>	
Screen for proteinuria with urinary dipstick at first visit and at each subsequent visit	**Conditional**
More definitive testing for proteinuria (by urinary protein:creatinine ratio or 24-hour urine collection) is encouraged when there is a suspicion of preeclampsia, including: ≥1+ dipstick proteinuria in women with hypertension and rising blood pressure and in women with normal blood pressure, but symptoms or signs suggestive of preeclampsia	**Conditional**
When quantitative methods are not available or rapid decisions are required, a urine protein dipstick reading can be substituted using 2+ as the discriminant value	**Conditional**
Proteinuria testing does not need to be repeated once significant proteinuria in the setting of confirmed pre-eclampsia has been detected	**Conditional**
<u>Biomarkers and ultrasonography screening</u>	
The use of a combined first trimester screen (combined maternal features, biomarkers and sonography) to identify women at risk of developing preeclampsia is conditionally recommended based on local availability and access to the required resources	**Conditional**

Risk Reduction	
Low dose Aspirin	
To reduce the risk of developing preeclampsia, pregnant women with one high risk factor or two or more moderate risk factors for developing preeclampsia should receive low dose aspirin (100 mg -150 mg daily) beginning at 12 weeks gestation and till delivery.	**Strong**
The use of aspirin at bedtime is conditionally recommended	**Conditional**
Cessation of aspirin between 34 weeks gestation and birth is conditionally recommended. Exact timing of cessation should be based on individualized clinical judgment and informed, shared decision taking with the women	**Conditional**
Oral calcium Supplementation	
The use of supplemental calcium is strongly recommended in pregnant women with low dietary calcium intake (<1g/day) for the prevention of preeclampsia, preterm birth, and gestational hypertension	**Strong**
Calcium supplementation at doses of 1.5–2.0 g elemental calcium/day is recommended from the first antenatal visit till delivery, to reduce the risk of developing preeclampsia	**Strong**
Education	
Pregnant women with hypertension or with risk factors for developing preeclampsia should be educated about the symptoms and signs that require immediate attention and referral to health care facilities.	**Strong**
A clear referral plan should be discussed with each woman	**Conditional**
Educate pregnant women to seek a healthcare professional immediately if they experience any of the symptoms of pre-eclampsia	**Strong**
Exercise and diet	
Moderate intensity exercise, in the form of aerobic, stretching and/or muscle resistance exercises, for a total of 2.5-5 hours a	**Conditional**

week, as recommended exercise regimen for general pregnancy wellbeing is encouraged.	
<u>What is Not recommended for risk reduction</u>	
Dietary salt restriction, for prevention of preeclampsia, is not recommended given the lack of evidence of benefit	**Conditional**
The use of oral omega-3 long-chain polyunsaturated fatty acids LCPUFA supplementation for the prevention of preeclampsia, is not recommended until more data are available	**Conditional**
The use of oral garlic supplementation, specifically for the prevention of preeclampsia, is not recommended until more data are available	**Conditional**
The use of oral vitamin C and E supplementation, specifically for the prevention of preeclampsia, is not recommended until more data are available	**Conditional**
There is inadequate data to recommend for the use or against the use of oral magnesium supplementation specifically for the prevention of preeclampsia. More data on the safety profile is required	**Conditional**
The use of progesterone replacement, specifically for the prevention of preeclampsia, is not recommended until more data are available	**Conditional**
The use of statins, specifically for the prevention of preeclampsia, is not recommended until more data are available	**Conditional**
The use of low molecular weight heparin (LMWH) alone (without aspirin) in women without a history of thrombophilia or APLS can be considered if a contraindication to aspirin is present. The decision to use LMWH (at a prophylactic dose) should be individualized based on women's clinical and obstetric history and through a shared, informed decision-making process	**Conditional**
LMWH should not replace the use of aspirin in women without contraindications to aspirin	**Conditional**

The use of low molecular weight heparin (LMWH) in addition to aspirin for prevention of preeclampsia in women without a history of thrombophilia or APLS is not recommended	**Conditional**
The use of nitric oxide (either in donor or precursor forms) for the prevention of preeclampsia is not recommended until more data are available	**Conditional**
The use of metformin, specifically for the prevention of preeclampsia is not recommended until more data are available	**Conditional**
The use of oral vitamin D supplementation for the prevention of preeclampsia, is not recommended until more data are available	**Conditional**
The use of proton pump inhibitors for prevention of preeclampsia is not recommended until more data are available	**Conditional**
The use of clopidogrel for prevention of preeclampsia is not recommended until human data are available	**GPS**
TREATMENT OF PRE-ECLAMPSIA SYNDROME AND GESTATIONAL HYPERTENSION	
Hospital Admission Versus Ambulatory Outpatient Management	
Ambulatory outpatient management at home is an option only for women with mild to moderate gestational hypertension and requires frequent fetal and maternal evaluation	**Strong**
Hospitalization is appropriate for Women with gestational hypertension in whom adherence to frequent monitoring is a concern and for patients diagnosed with preeclampsia	**Strong**
Ambulatory outpatient management	
At each antenatal care visit, following the detection of hypertension in pregnancy, a systematic clinical evaluation of symptoms, signs, laboratory investigations and fetal wellbeing must be performed	**Strong**

Frequency of appointments is based on the individual clinical needs; suggested review is initially weekly to fortnightly (every 2 weeks) at a minimum	**Conditional**
Women with non-severe hypertension during pregnancy should not be offered antihypertensive drug treatment when adequate resources for good quality antenatal care follow-up may be lacking	**Conditional**
<u>Inpatient Care</u>	
Women with preeclampsia should have additional tests to detect multisystem involvement, and should have fetal surveillance to assure fetal wellbeing	**Strong**
A clear referral plan for patients with severe preeclampsia must be developed and implemented in every health care unit	**GPS**
Complete bed rest is not advised for fear of thromboembolism, however minimal activities with 2 hours afternoon nap and 8 hours night sleep is recommended.	**GPS**
Non-severe hypertension should be treated with the first-line agents oral methyldopa, labetalol, or nifedipine	**Conditional**
Severe hypertension in pregnancy (i.e., sBP ≥ 160 mmHg or dbp ≥ 110 mmHg) requires *urgent* antihypertensive therapy, in a monitored setting	**Strong**
Severe hypertension should be treated with the first-line agents oral nifedipine, oral labetalol, IV labetalol, or IV hydralazine	**Conditional**
The target BP for antihypertensive therapy should be a dBP of 85 mmHg, regardless of sBP	**Conditional**
Use of corticosteroid (either betamethasone or dexamethasone) is recommended in women with preeclampsia who are at risk of birth at < 34 weeks' gestation	**Conditional**
There are insufficient data to recommend routine use of corticosteroid in women with preeclampsia who are at risk of birth between 34- and 36-weeks' gestation. Delivery should	**Conditional**

not be delayed for the administration of steroids in the late preterm period	
The use of magnesium sulphate for fetal neuroprotection in women with preeclampsia at risk of preterm birth at < 30 weeks' gestation is strongly recommended	**Strong**
As part of expectant management, in-utero transfer to a tertiary-level centre with neonatal intensive care capacity should be considered	**GPS**
Inpatient Expectant care versus Delivery	
Inpatient Expectant care	
Women with mild to moderate gestational hypertension or preeclampsia without severe features, expectant management up to 37 0/7 weeks of gestation is recommended	**Conditional**
In low-resource setting where maternal and neonatal care and adequate resources for close monitoring by healthcare personnel may be lacking or is not available, the GDG recommend against expectant management for preeclampsia with severe hypertension or other severe features	**Conditional**
Capabilities for the evaluation of fetal wellbeing and detection of fetal compromise should be available in healthcare facilities providing care for pregnant women with hypertensive disorders	**Conditional**
Transfer of women with hypertension of pregnancy should be considered in situations where the health care provider believes that the health care facility is unequipped to manage the complications of hypertension of pregnancy	**GPS**
Birth and Delivery	
Time of Birth	
Initiate birth at $\geqslant$ 37 weeks gestation, in women with preeclampsia	**Conditional**

At < 37 weeks gestation, the decision on expectant management with continued surveillance is appropriate for women with non-severe preeclampsia.	**Conditional**
At 34+0 till 36+6 weeks gestation for women with preeclampsia in presence of any feature of severity initiation of delivery should is considered. Delivery should not be delayed for the administration of steroids in the late preterm period	**Conditional**
From fetal viability until <34+0 weeks gestation, Expectant management should be considered, but only in hospitals where very preterm infants and sick mothers can be cared for. Initiation of birth is considered in the absence of available resources for maternal and neonatal care	**Conditional**
<u>Maternal stabilization and labor management of pre-eclampsia and eclampsia</u>	
<u>Prevention and treatment of convulsions</u>	
The prevention of eclampsia is empirically based on the timely delivery once preeclampsia has been diagnosed	**GPS**
Prophylactic magnesium sulphate with an intravenous loading dose of 4g followed by maintenance at 1g/hr for 24 hours in total or time of last seizure is strongly recommended in women at risk of eclampsia or recurrent eclampsia	**Conditional**
There is inadequate evidence to support an alternative magnesium regimen or the use of anticonvulsants for the prevention of eclampsia	**Conditional**
It is recommended that magnesium sulfate should be used for the prevention and treatment of seizures in women with severe hypertension or severe preeclampsia, or eclampsia and birth is planned within 24 hours	**Conditional**
The prophylactic use of magnesium sulfate for the prevention of seizures in women with gestational hypertension or preeclampsia without severe features is Conditionally recommended	**GPS**
Women with eclampsia should receive magnesium sulphate to prevent recurrent seizures	**Conditional**

Control of acute severe hypertension	
Severe hypertension in pregnancy (i.e., sBP ≥ 160 mmHg or dBP ≥ 110 mmHg) requires *urgent* antihypertensive therapy, in a monitored setting	**Conditional**
Severe hypertension should be treated with the first-line agents oral nifedipine, oral labetalol, intravenous (IV) labetalol, or IV hydralazine	**Strong**
The target BP for antihypertensive therapy should be a dBP of 85 mmHg, regardless of sBP	**Conditional**
Non-severe hypertension should be treated with the first-line agents oral methyldopa, labetalol, or nifedipine	**Conditional**
Control of other complications: HELLP syndrome	
For women with severe preeclampsia with features of HELLP expectant management is harmful. Plan birth as soon as feasible	**Strong**
Platelet transfusion should be considered if a woman's platelet count is <20 _ 109/L before vaginal delivery or <50 _ 109/L before cesarean delivery, or at any time if there is excessive active bleeding, known platelet dysfunction, rapidly falling platelet count, or coagulopathy	**Conditional**
Vaginal delivery is the preferred modality, unless urgent delivery is necessary for maternal stabilization or for fetal indications. The delivery options should be discussed by a multidisciplinary team and consider the safest mode of delivery to the mother, how fast she is expected to deliver, what are the resources of blood products and other supportive mechanisms available, and can she sustain a surgery	**Conditional**
In rapidly progressing preeclampsia with severe features or HELLP syndrome, vaginal delivery may be attempted if cervical conditions are favorable and delivery is anticipated within a short timeframe (e.g., ≤2 hours). If labor progress is slow (>6 hours) or maternal/fetal status worsens, immediate cesarean delivery is indicated	**Conditional**

In small to medium size health care facilities, it is important to estimate whether their blood bank can support a massive blood trans fusion and, if necessary, contact regional or larger hospitals for assistance or for transferring the patient	**GPS**
Mode of Birth	
For women with any HDP, vaginal delivery should be considered unless a cesarean delivery is required for obstetrical indications.	**Strong**
Vaginal delivery may require early cervical ripening and induction	**Conditional**
If urgent or emergent delivery is required for maternal and/or fetal indications, an emergency cesarean delivery may be indicated	**Strong**
Urgency ot Birth	
Health facilities in Egypt should provide local protocols of management for their health care providers in accordance with WHO recommendations.	**Strong**
GDG recommends to nationally adopt a color-triage system for acute obstetric emergencies (Modified Early obstetric warning score -MEOWS)	**GPS**
TREATMENT OF CHRONIC HYPERTENSION	
Expectant Management	
Offer expectant management for women with Chronic hypertension who are <37 weeks and, whose blood pressure is lower than 160/110 mmHg with or without antihypertensive treatment, unless there are other medical indications62	**Strong**
Offer antihypertensive treatment to pregnant women who have chronic hypertension and who are not already on treatment if they have sustained systolic blood pressure of 140 mmHg or higher or sustained diastolic blood pressure of 90 mmHg or higher	**Strong**
The target BP for antihypertensive therapy should be a dBP of 85 mmHg, regardless of sBP	**Strong**

Consider labetalol to treat chronic hypertension in pregnant women. Consider nifedipine for women in whom labetalol is not suitable or methyldopa if both labetalol and nifedipine are not suitable. Base the choice on any pre-existing treatment, side-effect profiles, risks (including fetal effects) and the woman's preference	**Conditional**
Continue with existing antihypertensive treatment if safe in pregnancy, or switch to an alternative treatment, unless sustained systolic blood pressure is less than 110 mmHg or sustained diastolic blood pressure is less than 70 mmHg or the woman has symptomatic hypotension	**Conditional**
Offer pregnant women with chronic hypertension aspirin 150 mg once daily from 12 weeks	**Strong**
Give the same advice on rest, exercise and work to women with chronic hypertension or at risk of hypertensive disorders during pregnancy as healthy pregnant women	**Conditional**
Offer PLGF testing between 20–36+6 weeks to rule out pre-eclampsia in women with chronic hypertension if clinical suspicion arises	**Conditional**
In chronic hypertension with suspected pre-eclampsia, monitor proteinuria 1–2x weekly alongside BP checks	**Strong**
A complete blood count and levels of serum transaminases, lactate dehydrogenase, and uric acid should be checked on diagnosis then weekly	**Conditional**
Timing of birth	
Do not offer planned early birth (*before 37 weeks*) to women with chronic hypertension whose blood pressure is lower than 160/110 mmHg, with or without antihypertensive treatment, unless there are other medical indications	**Strong**
Offer planned birth to women with chronic hypertension whose blood pressure is lower than 160/110 mmHg with or without antihypertensive treatment after 37 weeks	**Strong**

Determination of timing should be agreed between the woman and the obstetrician. Initiation of delivery can be offered at 38+0 to 39+6 weeks	**Conditional**
Offer planned early birth before 37 weeks to women with chronic hypertension or gestational hypertension if inability to control maternal blood pressure despite using 3 or more classes of antihypertensives in appropriate doses or if any of the known features of severe superimposed preeclampsia develop	**Strong**
<u>Care for women with hypertension during labor and postpartum</u>	
<u>Intrapartum Care</u>	
During labour, measure blood pressure hourly. In women with severe hypertension measure blood pressure every 15 to 30 minutes until blood pressure is less than 160/110 mmHg.	**Conditional**
Continue use of antenatal antihypertensive treatment during labour	**Conditional**
Do not preload women who have severe pre-eclampsia with intravenous fluids before establishing low-dose epidural analgesia or combined spinal epidural analgesia	**Conditional**
Do not routinely limit the duration of the second stage of labour in women with controlled hypertension	**Conditional**
Consider operative or assisted birth in the second stage of labour for women with severe hypertension whose hypertension has not responded to initial treatment	**Conditional**
As women with preeclampsia are at increased risk of postpartum hemorrhage, the third stage of labour should be actively managed	**Conditional**
Ergometrine should not be administered to women with any hypertensive disorder of pregnancy, particularly preeclampsia or gestational hypertension; alternative oxytocic drugs should be considered	**Strong**
<u>Postpartum care for women with HDP</u>	

There remains inadequate data to suggest the superiority of a single agent or group of agents in selecting antihypertensives for the management of hypertension in the postpartum period. The choice of antihypertensive (beta-blockers, methyldopa, hydralazine, nifedipine, enalapril, clonidine) should be made through a shared decision-making process, particularly in breastfeeding/lactating women	**Conditional**
Women should be informed of the long-term risks associated with preeclampsia, gestational hypertension and chronic hypertension and the importance of postpartum follow up prior to discharge from hospital	**Conditional**
Antihypertensive therapy administered antepartum should be continued after birth. Also, consideration should be given to administering antihypertensive therapy for any hypertension diagnosed before six days postpartum	**Conditional**
The target dBP for postpartum antihypertensive treatment should be 85 mmHg, as antenatally	**Conditional**
Non-steroidal anti-inflammatory drugs (NSAIDs) for postpartum analgesia may be used in women with pre-eclampsia if other analgesics are ineffective, and there is no acute kidney injury (AKI) or other risk factors for it	**Conditional**
Breastfeeding is recommended	**Strong**
Counselling should be provided about the risks of gestational hypertension (at least 4%) or pre-eclampsia (at least 15%) in future pregnancy	**Conditional**
At 3 months postpartum, all women should be reviewed to ensure that BP, urinalysis, and any laboratory abnormalities have normalised. If proteinuria or hypertension persist, then appropriate referral for further investigations should be initiated	**Conditional**
At 6 months postpartum, where possible, all women should be reviewed again, at which point we suggest that BP ≥ 120/80 mmHg lead to discussion of lifestyle change	**Conditional**

Following hypertensive pregnancy, particularly pre-eclampsia, counselling should be provided about the heightened health risks for the mother (particularly cardiovascular) and the offspring	**Strong**

Introduction

Hypertension in pregnancy is defined as a blood pressure of greater than or equal to 140 mmHg (systolic) or 90 mmHg (diastolic) on at least two measurements, ideally separated by a period of rest. Severe hypertension is defined as a blood pressure of greater than 160–170/110 mmHg. Systolic hypertension of greater than 180 mmHg is a medical emergency.[1]

Hypertensive disorders of pregnancy can be subclassified into four groups – chronic hypertension, gestational hypertension, preeclampsia, and superimposed preeclampsia in the setting of chronic hypertension, as laid out in the ACOG (American Congress of Obstetricians and Gynecologists) guideline.[2]

Preeclampsia is a global health problem of increasing significance.[3,4] Preeclampsia complicates 2%–8% of all pregnancies, contributes to 15% of preterm deliveries, and between 9% and 26% of maternal deaths worldwide.[5] Pre-eclampsia is the most dangerous of the HDPs; world-wide, each year, pre-eclampsia is responsible for over 500,000 fetal and neonatal deaths and over 70,000 maternal deaths.[6]

In Egypt, complications of hypertensive disorders with pregnancy are responsible for 15% of the causes of maternal mortality, second only to postpartum hemorrhage.[7]

Optimization of health care for women during pregnancy to prevent and treat hypertensive disorders of pregnancy is a necessary step towards achievement of the Millennium Development Goals.

Scope and Purpose

The objectives of this guideline are:

- To provide guidance for the proper prevention and management of Hypertension in Pregnancy

- To optimize outcomes for patients who are at risk of or developed Hypertension in Pregnancy

Target Audience

This guideline targets; healthcare professionals working as Obstetricians & Gynecologists, Anesthetists, ICU physicians, Nurses, policy makers, hospital managers, and other stakeholders to apply the best practice and afford the most appropriate tools for women at risk of or having Hypertensive Disorder in Pregnancy (HDP).

Methodology

A comprehensive search for guidelines was done to identify the most relevant ones to consider for adaptation. The inclusion/exclusion criteria that were followed in the search and retrieval of guidelines to be adapted are:

We select guidelines only if they are:

- Evidence-based guidelines
- National and/or international guidelines
- Guidelines published from 2020 to 2025
- Peer reviewed publications
- Guidelines written in English language

We Exclude guidelines that are:

- Written by a single author not on behalf of an organization as guideline to be valid and comprehensive ideally requires multidisciplinary input.
- Published without references as the panel needs to know whether a thorough literature review was conducted and whether the current evidence was used in the preparation of the recommendations.

The following characteristics of the retrieved guidelines were summarized in a table:

- Developing organisation/authors
- Date of publication, posting, and release

- Country/language of publication
- Dates of the search used by the source guideline developers

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least three members. The panel decided on a cut-off point or ranked the guidelines (any guideline scoring above 50% on the rigor dimension was retained).

Guidelines used in the adaptation process: [8-13]

1. *SOMANZ hypertension in pregnancy guideline 2023. **https://www.somanz.org/hypertension-in-pregnancy-guideline-2023/**. Accessed February 2025.*[8]
2. *NICE hypertension in pregnancy: diagnosis and management guideline 2023. **https://www.nice.org.uk/guidance/ng133**. Accessed February 2025.*[9]
3. *Magee LA, Smith GN, Bloch C, Côté AM, Jain V, Nerenberg K, von Dadelszen P, Helewa M, Rey E. Guideline No. 426: Hypertensive Disorders of Pregnancy: Diagnosis, Prediction, Prevention, and Management. J Obstet Gynaecol Can. 2022 May;44(5):547-571.e1. doi: 10.1016/j.jogc.2022.03.002. PMID: 35577426.*[10]
4. *Queensland Clinical Guideline: Hypertension and pregnancy 2021. Accessed February 2025.*[11]
5. *International Society for the Study of Hypertension in Pregnancy (ISSHP). The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice [Internet]. 2021 [cited 2020 January 30]. Available from: http://www.isshp.org.*[12]
6. *ACOG Practice Bulletin 222 (2020) Gestational Hypertension and Preeclampsia. Obstetrics & Gynecology, 135, e237-e260. https://doi.org/10.1097/AOG.0000000000003891.*[13]

Evidence assessment

According to WHO Handbook for Guidelines, we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE

methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed GRADE information is available on the following sites:

- GRADE working group: http://www.gradeworkingroup.org
- GRADE online training modules: http://cebgrade.mcmaster.ca/
- GRADE profile software: http://ims.cochrane.org/revman/gradepro

Table 1: Quality and Significance of the four levels of evidence in GRADE:

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 2; Factors that determine How to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of
Study limitations −1 Serious limitations −2 Very serious limitations	**Dose-response gradient** +1 Evidence of a dose-response gradient
Consistency −1 Important inconsistency	**Direction of plausible bias** +1 All plausible confounders would have reduced the effect
Directness −1 Some uncertainty −2 Major uncertainty	**Magnitude of the effect** +1 Strong, no plausible confounders, consistent and direct evidence +2 Very strong, no major threats to validity and direct evidence
Precision −1 Imprecise data	
Reporting bias −1 High probability of reporting bias	

The strength of recommendations

The strength of a recommendation communicates the importance of adherence to the recommendation.

Strong recommendations: The GDG found that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted.

Conditional recommendations: This means that the GDG found that there is:

- Greater uncertainty about the strength of evidence, or
- The recommendation may account for a greater variety in patient values and preferences, or

- The resource use makes the intervention suitable for some, but not for other locations.

Conditional recommendations **are still the best available evidence to date and** it can be adopted if it meets the conditions mentioned with it.

Good Practice Statement: Statements based on opinion of respected authorities, e.g. the RCOG, ACOG, and the guidelines development group.

Recommendations

1. DEFINITIONS AND CLASSIFICATION

HDPs should be classified according to the criteria and definitions presented in "Glossary" (GPS)

Diagnose Hypertension in pregnancy when systolic blood pressure is ≥140mmHg and/or diastolic blood pressure is ≥90mmHg, based on the average of at least 2 measurements, taken at least 15 minutes apart, using the same arm. (Strong recommendation/High level of evidence).[8,9,12]

Severe hypertension (sBP ≥ 160 and/or dBP ≥ 110 mmHg), can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy (Conditional recommendation/low quality of evidence). [8,9,12]

Women with gestational hypertension should undergo testing for preeclampsia to rule it out. (Strong recommendation/High level of evidence).[6,9,13]

Diagnose preeclampsia in women with new onset hypertension after 20 weeks and new-onset proteinuria or one/more adverse conditions (defined as a maternal end organ complication or evidence of uteroplacental dysfunction) (Strong recommendation/High level of evidence).[6-14]

Preeclampsia superimposed on chronic hypertension is diagnosed by the development of 1 or more characteristics of preeclampsia (i.e., new-onset proteinuria or 1 or more adverse conditions) superimposed on chronic hypertension) (Strong recommendation/High level of evidence).[6-14]

Preeclampsia superimposed on chronic hypertension: can be diagnosed in women with pre-existing hypertension by occurrence of any of the following after 20 weeks (Strong recommendation/High level of evidence): [8-18]

- New-onset proteinuria
- New-onset feature of severe pre-eclampsia (Uric acid test may be considered).

- Where available, use of the sFlt-1/PlGF ratio can be used [increased soluble fms-like tyrosine kinase-1 (sFlt1) or soluble endoglin and reduced placental growth factor (PlGF)[18].

Do not use an elevation in BP to make a diagnosis of preeclampsia superimposed on chronic hypertension *(Conditional recommendation/Moderate level of evidence)*.[6]

2. RISK FACTORS

Risk factors for developing preeclampsia should be included in the antenatal assessment of all pregnant women. (GPS)

High Risk Factors:[13]

- Hypertensive disease during a previous pregnancy
- Pre-existing chronic hypertension
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- Pre-existing type 1 or type 2 diabetes

Moderate Risk Factors:[11,13]

- nulliparity
- advanced maternal age (> 40 years)
- pregnancy interval of more than 10 years
- body mass index (BMI) of 35 kg/m2 or more at first visit
- family history of pre-eclampsia
- multi-fetal pregnancy.
- conception through assisted reproductive technology
- systolic blood pressure > 130 mmHg and/or diastolic blood pressure > 80 mmHg

3. SCREENING

3.1 Risk factor screen:

All pregnant women should be screened for their risk of developing preeclampsia early in the pregnancy. (*Moderate level of evidence, strong recommendation*).[8,9,12,14]

The screening tool utilized should be determined based on the locally available resources *(Conditional recommendation/very low level of evidence)*.[8]

3.2 Blood Pressure measurement:

During every antenatal visit, screening for preeclampsia in pregnant women with blood pressure measurements throughout pregnancy is strongly recommended *(Strong recommendation/Moderate level of evidence)*.[8,19]

Key Practice Points

Blood pressure measurements are routinely used as a screening tool for preeclampsia, throughout pregnancy, for all women receiving prenatal care. The aim of screening is to identify and diagnose the condition early in its course, to allow closer monitoring and effective disease management[19].

Sphygmomanometry is the recommended method for blood pressure measurement during pregnancy. The patient should be relaxed prior to measurement. After 5 minutes has elapsed, the patient's blood pressure should be read while she is in a sitting position, with her legs uncrossed and her back supported. The patient's arm should be at the level of the right atrium of the heart. If the patient's upper arm circumference is 33cm or greater, a large blood pressure cuff should be used. Clinicians should avoid measuring blood pressure in the upper arm in the left lateral position because this position falsely lowers blood pressure readings[20-22]. MAP has been demonstrated to be more predictive of pre-eclampsia among low-risk women than either sBP or dBP readings alone.[23]

3.3 Testing for Proteinuria:

- **Screen for proteinuria with urinary dipstick at first visit and at each subsequent visit *(Conditional recommendation/Low level of evidence).*[24]**
- **Significant Proteinuria should be diagnosed by ≥ 30 mg/mmol urinary protein: creatinine ratio (PrCr) in a spot (random) urine sample, or albumin: creatinine ratio (ACR) ≥ 8 mg/mmol, or urinary protein ≥ 0.3 g/d in a complete 24-hour urine collection.[9,11-13]**
- **More definitive testing for proteinuria (by urinary protein:creatinine ratio or 24-hour urine collection) is encouraged when there is a suspicion of preeclampsia, including: ≥1+ dipstick proteinuria in women with hypertension and rising blood pressure and in women with normal blood pressure, but symptoms or signs suggestive of preeclampsia *(Conditional recommendation/High level of evidence)*[25-28].**
- **When quantitative methods are not available or rapid decisions are required, a urine protein dipstick reading can be substituted using 2+ as the discriminant value *(Conditional recommendation/Moderate level of evidence).*[8,13]**
- **Proteinuria testing does not need to be repeated once significant proteinuria in the setting of confirmed pre-eclampsia has been detected** *(Conditional recommendation/Moderate level of evidence)*[11]**.**

3.4 Biomarkers and ultrasonography screening:

- **The use of a combined first trimester screen (combined maternal features, biomarkers and sonography) to identify women at risk of developing preeclampsia is Conditionally recommended based on local availability and access to the required resources *(Conditional recommendation/Moderate level of evidence).*[29-31]**

Remarks:

If urinalysis is the only available means of assessing proteinuria, then overall accuracy is better using 2+ as the discriminant value.[13,16,17]

Remarks:

The GDG is aware that that the addition of ultrasound and biochemical markers (Maternal features + MAP + UtPI + PIGF + PAPP-A) modestly improves the performance of the screening compared to clinical factors alone, although the sensitivities vary from 42-92%. The overall quality of evidence was found to be MODERATE, and many of the non-clinical factors, such as biochemical markers and sonographic expertise to undertake validated and reliable uterine pulsatility index (UtA-PI), may not be available widely.[8]

Given this variation in practice, GDG Conditionally recommend the use of combined first trimester screening for preeclampsia based on local access to the validated resources and expertise required.

Combined first trimester screening for preeclampsia include:

o Placental growth factor (PlGF)

- Lowered levels in women at risk of pre-eclampsia[32] and in fetal
- aneuploidies and/or impaired placentation disorders (which can also be associated with pre-eclampsia) [23]
- Positive predictive detection value of 56%[32] for pre-eclampsia

o Uterine artery pulsatility index (UtPI)[32]

- Measured between 11+0- and 13+6-weeks' gestation
- Positive predictive detection value of 48% for early onset preeclampsia

o Pregnancy associated plasma protein A (PAPP-A)[33]

- Levels less than 0.4 MoM, associated with an increased risk of HDP, preterm birth and fetal growth restriction
- Present in 8–23% of women with pre-eclampsia
- Low positive predictive detection value of 16%.

4. RISK REDUCTION

4.1 Low dose Aspirin: [6,8,9,13,34-47]

- **To reduce the risk of developing preeclampsia, pregnant women with one high risk factor or two or more moderate risk factors for developing preeclampsia should receive low dose aspirin (150 mg daily)** *(Strong recommendation/High level of evidence)*, **beginning at 12 weeks gestation and till delivery,** *(Strong recommendation/Moderate level of evidence)* **to be taken at bedtime** *(Conditional recommendation/Moderate level of evidence)*,
- **Cessation of aspirin between 34 weeks gestation and birth is Conditionally recommended. Exact timing of cessation should be based on individualized clinical judgment and informed, shared decision taking with the women** *(Conditional recommendation/Moderate level of evidence).*[6,8,9,13]

Remarks:

Timing for the cessation of low dose Aspirin vary across professional societies and organizations, including ISSHP 2022 (36 weeks),[6] SOMANZ 2023 (37 weeks),[8] NICE 2019 (until delivery),[9] and ACOG 2020 (until birth).[13] The overall evidence did not demonstrate a difference in the benefit or harm in comparing the timing of aspirin cessation.

Therefore, based on the absence of a difference in harm, the GDG decision on the timing of ceasing aspirin between 34 weeks gestation and delivery should be individualized.

4.2 Oral calcium Supplementation:

- **The use of supplemental calcium is strongly recommended in pregnant women with low dietary calcium intake (<1g/day) for the prevention of preeclampsia, preterm birth, and gestational hypertension** *(Strong recommendation/moderate level of evidence)*.[48]

- **Calcium supplementation at doses of 1.5–2.0 g elemental calcium/day is recommended from the first antenatal visit till delivery, to reduce the risk of developing preeclampsia** *(Strong recommendation/Moderate level of evidence).*[48,49,50]

Remarks:

The World Health Organization (WHO) conducted a randomised controlled trial (RCT) of calcium supplementation among low calcium intake pregnant women from 2001 to 2003. Results from this trial showed that although 1.5 g calcium/day supplement did not prevent preeclampsia, it reduced its severity, maternal morbidity, and neonatal mortality[50].

In more recent times, a systematic review (Cochrane 2018) found that high-dose calcium supplementation (> 1 g/day) reduces the risk of preeclampsia and preterm birth, particularly for women with low calcium diet with no difference in overall maternal and fetal mortality and morbidity[48].

4.3 Education:

- **Pregnant women with hypertension or with risk factors for developing preeclampsia should be educated about the symptoms and signs that require immediate attention and referral to health care facilities** *(Strong recommendation/High level of evidence)*.[13,51-53]
- **A clear referral plan should be discussed with each woman** *(Conditional recommendation/Low level of evidence)***.** [51]
- **Educate pregnant women to seek a healthcare professional immediately if they experience any of the symptoms of pre-eclampsia** *(Strong recommendation/Moderate level of evidence)* [9,52-55] **including:**
    - **Severe headache**
    - **Problems with vision, such as blurring or flashing before the eyes**
    - **Severe pain just below the ribs**
    - **Vomiting**
    - **Sudden swelling of the face, hands or feet.**

Remarks:

According to a study of the three delays model in Egypt published in 2021, found that most cases of maternal deaths from PET were due to 1st delay 10 (50%). All cases developed preeclampsia had no knowledge about obstetric complications and lack of importance of antenatal care. The study also showed that most frequent delay was the 1st delay especially in preeclampsia/eclampsia 55% followed by obstetric hemorrhage (placenta previa, postpartum hemorrhage, rupture uterus).[56.]

4.4 Exercise:

- **Moderate intensity exercise, in the form of aerobic, stretching and/or muscle resistance exercises, for a total of 2.5-5 hours a week, as recommended as part of routine pregnancy wellbeing has the added benefit of reducing the risk of hypertensive disorders of pregnancy. Adherence to the current recommended exercise regimen for general pregnancy wellbeing is encouraged** *(Conditional recommendation /Moderate level of evidence).*[57-67]

4.5 What is Not recommended for risk reduction:

- **Dietary salt restriction, for prevention of preeclampsia, is not recommended given the lack of evidence of benefit** *(Conditional recommendation/very low level of evidence)***.**[68-72]
- **The use of oral omega-3 LCPUFA supplementation for the prevention of preeclampsia, is not recommended until more data are available** *(Conditional recommendation/ Moderate level of evidence).*[73-78]
- **The use of oral garlic supplementation, specifically for the prevention of preeclampsia, is not recommended until more data are available** *(Conditional recommendation/very low level of evidence)***.**[79,80]
- **The use of oral vitamin C and E supplementation, specifically for the prevention of preeclampsia, is not recommended until more**

data are available *(Conditional recommendation/Moderate level of evidence)*.[81-85]

- **There is inadequate data to recommend for the use or against the use of oral magnesium supplementation specifically for the prevention of preeclampsia. More data on the safety profile is required** *(Conditional recommendation/Low level of evidence)*[86-91]
- **The use of progesterone replacement, specifically for the prevention of preeclampsia, is not recommended until more data are available** *(Conditional recommendation/Moderate level of evidence).*[92,93]
- **The use of statins, specifically for the prevention of preeclampsia, is not recommended until more data are available** *(Conditional recommendation/Moderate level of evidence).*[94,97]
- **The use of low molecular weight heparin (LMWH) alone (without aspirin) in women without a history of thrombophilia or APLS can be considered if a contraindication to aspirin is present. The decision to use LMWH (at a prophylactic dose) should be individualized based on women's clinical and obstetric history and through a shared, informed decision-making process** *(Very low level of evidence/ Conditional recommendation)*.[98,99]
- **LMWH should not replace the use of aspirin in women without contraindications to aspirin** *(Very low level of evidence/ Conditional recommendation)*.[98,100]
- **The use of low molecular weight heparin (LMWH) in addition to aspirin for prevention of preeclampsia in women without a history of thrombophilia or APLS is not recommended.** *(Conditional recommendation/Moderate level of evidence).*[101-104]
- **The use of nitric oxide (either in donor or precursor forms) for the prevention of preeclampsia is not recommended until more data are available** *(Conditional recommendation/very low level of evidence)*.[105-107]

- **The use of metformin, specifically for the prevention of preeclampsia is not recommended until more data are available.** *(Conditional recommendation/Moderate level of evidence).*[108,110]
- **The use of oral vitamin D supplementation for the prevention of preeclampsia, is not recommended until more data are available** *(Conditional recommendation/Moderate level of evidence).*[111,112]
- **The use of proton pump inhibitors for prevention of preeclampsia is not recommended until more data are available** *(Conditional recommendation/Moderate level of evidence).*[113,114]
- **The use of clopidogrel for prevention of preeclampsia is not recommended until human data are available** *(GPS)***.**

5. TREATMENT OF PRE-ECLAMPSIA SYNDROME AND GESTATIONAL HYPERTENSION

5.1. Hospital Admission Versus Ambulatory Outpatient Management:

- **Ambulatory outpatient management at home is an option only for women with mild to moderate gestational hypertension and requires frequent fetal and maternal evaluation** *(Strong recommendation/High level of evidence).*[9,13,115-117]
- **Hospitalization is appropriate for Women with gestational hypertension in whom adherence to frequent monitoring is a concern and for patients diagnosed with preeclampsia** *(Strong recommendation/High level of evidence)*.[9,118,119]

5.1.1. Ambulatory outpatient management

- **At each antenatal care visit, following the detection of hypertension in pregnancy, a systematic clinical evaluation of symptoms, signs, laboratory investigations and fetal wellbeing must be performed** *(Strong recommendation/Moderate level of evidence).*[9,13]
- **Frequency of appointments is based on the individual clinical needs; suggested review is initially weekly to fortnightly (every 2 weeks) at a minimum** *(GPS)***.**

Key Practice Points

Ambulatory outpatient management is suitable for women with: [9,13,115-117]

- Mild to moderate hypertension without evidence of pre-eclampsia, and
- Where there are no indications for birth, and
- Where there are no geographical contraindications, and
- Capacity to understand risk, and monitor their own blood pressure.

Evaluation during outpatient care:

- Maternal:
    - At the initial evaluation,
        - Comprehensive clinical maternal and fetal[9,13]
        - Testing for proteinuria evaluation[13]
        - Baseline Preeclampsia blood tests[11,13]:
            - Full blood count (FBC) with platelet estimates
            - Urea, creatinine, electrolytes and urate
            - Liver function tests (LFT) LDH, AST, ALT,

        Tests may be abnormal even when BP elevation is minimal

    - At repeat visits:
        - Consider 1–2 per week Urinalysis for protein if initially negative. *Proteinuria testing does not need to be repeated once significant has been detected.* [9,11,13]
        - Consider weekly *Preeclampsia blood tests* if gestational hypertension and twice weekly in cases of preeclampsia managed as outpatient (*new onset hypertension with proteinuria and no features of concern*).[13]
            - Full blood count (FBC),
            - Serum Creatinine,
            - Liver function test (LFT)
- Fetal: Ultrasound scan at diagnosis and every 2 weeks to assess fetal growth, amniotic fluid volume and umbilical artery Doppler based on

availability. If FGR is detected, local/national fetal surveillance guidance should be followed. [9,11,13]

Antihypertensive Approach during outpatient care:

- **Women with non-severe hypertension during pregnancy should not be offered antihypertensive drug treatment when adequate resources for good quality antenatal care follow-up may be lacking** *(Conditional recommendation/Moderate level of evidence).*[11,118,120-122]

Rationale:

Queensland Clinical Guideline, 2021 on Hypertension and pregnancy states that for "**Mild to moderate hypertension,** Antihypertensive therapy halves the risk of developing severe hypertension but has no clear effect on other outcomes (e.g. pre-eclampsia, perinatal mortality). Concerns exist about the potential for decreased placental perfusion from aggressive BP lowering that might jeopardize fetal wellbeing. Recommend drug therapy if blood pressure greater than 160/110 mmHg"[11].

Also, the WHO recommendations on drug treatment for non-severe hypertension in pregnancy, 2020 states that for non-severe hypertension in pregnancy, use of an antihypertensive drug compared to placebo or no antihypertensive treatment probably reduces the development of severe hypertension, though there may be little or no difference in the risk of developing proteinuria or pre-eclampsia. There may be a slight increase in side-effects with the use of an antihypertensive drug[120].

The EHC Guideline Development Group considered that while the use of an antihypertensive drug for the treatment of non-severe hypertension in pregnancy may confer health benefits, pregnant women who are prescribed these drugs require regular outpatient monitoring and review by an antenatal care provider.[118,120] Arguments against treatment include that there is little risk to the mother in having relatively mild hypertension for a short time (usually only a few days or at the most weeks),[121] that fetal perfusion is dependent upon adequate maternal blood pressure[11] and that lowering blood pressure suppresses an important sign of the severity or progression of pre-eclampsia.[118] Access to antenatal care services for monitoring of blood pressure and complications (such

as proteinuria, organ dysfunction), or side-effects due to treatment, is considered integral to initiating antihypertensive treatment. [118,120-122]

In the absence of compelling evidence, and in low-resource settings where strict monitoring (clinical, biochemical and sonographic in addition to patient compliance) is lacking, the treatment of mild-to-moderate hypertension in the range 140–160/90–100 mm Hg is Conditionally not recommended.

5.1.2. Inpatient Care: [9,118,119]

- **Women with preeclampsia should have additional tests to detect multisystem involvement, and should have fetal surveillance to assure fetal wellbeing** *(Strong recommendation/Moderate level of evidence).* [9,118,119]
- **A clear referral plan for patients with severe preeclampsia must be developed and implemented in every health care unit** *(GPS)***.**

5.1.2.1 Inpatient Evaluation of women with Preeclampsia - Key Practice Points:

5.1.2.1.A. Inpatient systematic evaluation:[8,9,11,12,118,119,120]

1. Detailed examination, which is coupled with daily scrutiny for clinical findings such as headache, visual disturbances, epigastric pain, and rapid weight gain

2. Consider daily ward urinalysis if proteinuria not previously confirmed, consistently elevated blood pressure or other clinical concerns.

When quantitative methods are not available or rapid decisions are required, a urine protein dipstick reading can be substituted.

3. Blood pressure readings with an appropriate-size cuff every 4 hours, except between 12 am and 0600 am unless previous readings are elevated

4. Serial measurements of serum creatinine and hepatic transaminase levels and platelet count. The frequency of testing is determined by hypertension severity.

a. Evaluation of fetal size and well-being and amnionic fluid volume, by either physical examination or sonography.

5.1.2.1.B. Evaluation using validated risk prediction models:[9]

- These models are *Developed and internally validated in prospective, multi-centre study across Canada, New Zealand, Australia and UK using data from a cohort of 2023 women with pre-eclampsia admitted to tertiary perinatal units.*

- fullPIERS is a free online tool developed to identify the probability of adverse outcomes in women with preeclampsia at 48 hours or 7 days from baseline. fullPIERS has been validated in women up to 37 weeks gestation.

- PREP-S aims to predict the risk time of adverse outcomes at a number of time periods (from 2 days to 42 days) from baseline. PREP-S can be used in women up to 34+6 weeks gestation.

- fullPIERS and PREP-S models do not predict outcomes for babies. [2019]

- Consider using either the fullPIERS (Pre-eclampsia Integrated Estimate of Risk) or PREP-S validated **risk prediction** models to help guide decisions about:

-The most appropriate place of care (such as the need for in utero transfer to more advanced tertiary centers)

-Thresholds for intervention.

- *Risk Prediction Models are available on the internet – risk is calculated by entering patient data*:
  - PREP-S https://www.evidencio.com/models/show/1038
  - fullPIERS: https://pre-empt.obgyn.ubc.ca/evidence/fullpiers

5.1.2.2 Inpatient Antihypertensive therapy

Non-severe hypertension may be treated with the first-line agents oral methyldopa, labetalol, or nifedipine *(Conditional recommendation/Moderate level of evidence)*.[13]

Severe hypertension in pregnancy (i.e., sBP ≥ 160 mmHg or dbp ≥ 110 mmHg) requires *urgent* antihypertensive therapy, in a monitored setting *(Strong recommendation/moderate level of evidence)*.[13,116]

The target BP for antihypertensive therapy should be a dBP of 85 mmHg, regardless of sBP *(Strong recommendation/High level of evidence)*.[119,121]

Monitor BP Every 15–30 minutes until BP is less than 160/110 mmHg, then at least 4 times daily while the woman is an inpatient.[9,13]

Antihypertensive oral treatment:

• Consider methyldopa the alpha-2 adrenergic receptor agonist if both labetalol and nifedipine are not suitable.

Dosage range 250-500 mg every 6 to 12 hours/day

- Consider labetalol the dual alpha and beta adrenergic antagonist to treat hypertension in pregnant women.

Dosage range: 200-400 mg **PO** q12hr

• Consider nifedipine the calcium channel blocker for women in whom labetalol is not suitable,

Dosage range from 10-30 mg **PO** every 6-8 hours/day

5.1.2.3 Continued surveillance in hospital during expectant management:

Ensure woman is and remains without features of severe PET.[9,13,119,120,122]

- **Symptoms**: Daily headache/visual/abdominal pain screening
- **BP checks**: Every 4–6 hours
- *Dipstick proteinuria testing*: Only repeat if clinically indicated, for example, if new symptoms and signs develop or if there is uncertainty over diagnosis
- **Labs**: CBC, LFTs, Cr, Platelets every 48–72 hours
- **Fetal testing**:
  - Carry out a NST at diagnosis and then only if clinically indicated (as with reduced fetal movement)
  - Carry out ultrasound assessment of the fetus at diagnosis and, if normal, repeat every 2 weeks.

- **Complete bed rest is not advised for fear of thromboembolism, however minimal activities with 2 hours afternoon nap and 8 hours night sleep is recommended *(GPS)*.**
- **Use of corticosteroid (either betamethasone or dexamethasone) is recommended in women with preeclampsia who are at risk of birth at < 34 weeks' gestation** *(Conditional recommendation/ High level of evidence)*[13,118,132-134]
- **There are insufficient data to recommend routine use of corticosteroid in women with preeclampsia who are at risk of birth between 34 and 36 weeks' gestation. Delivery should not be delayed for the administration of steroids in the late preterm period** *(Conditional recommendation/Moderate level of evidence)*[13,132,136-139]
- **The use of magnesium sulphate for fetal neuroprotection in women with preeclampsia at risk of preterm birth at < 30 weeks' gestation is strongly recommended** *(Strong recommendation/High level of evidence)*[13,122,139-141]
- **As part of expectant management, in-utero transfer to a tertiary-level centre with neonatal intensive care capacity should be considered** *(GPS)*.

Other FAQs: "But what about…"[7]

- *…BP measurements that vacillate between severe and nearly severe?*
  - *Women with acute-onset severe hypertension can have strokes. For example, serial measurements of: 162/105, 158/104, 165/100; 159/109 mm Hg shows persistence, and risk, and we recommend antihypertensive treatment.*
- *…A severe-range BP followed in 15 minutes by less concerning BP (145/95 mm Hg)?*
  - *This scenario does not require treatment BUT does indicate the need for frequent monitoring of BP and observation.*
- *…if in another hour after the 145/95, the BP rises again to severe-range?*
  - *Here there may be choices: begin treatment or await another BP measurement within 15 minutes to document persistent severe-range (while preparing the medication). This judgment depends, among other*

factors, on how low the blood pressures were between the two severe range measurements.

- *… if the nurse does not take a confirmatory BP for 30-40 minutes and it is still severe-range? ("It was not within 15 minutes…").*
    - *The severe-range pressure is persistent so treatment should commence immediately.*

5.2. Inpatient Expectant care versus Delivery

5.2.1. Inpatient Expectant care:

- **Women with gestational hypertension or preeclampsia without severe features, expectant management up to 37 0/7 weeks of gestation is recommended** *(Moderate level of evidence, Conditional recommendation).*[6,9,13,119]
- **In low-resource setting where maternal and neonatal care and adequate resources for close monitoring by healthcare personnel are lacking or not available, the GDG recommends against expectant management for preeclampsia with severe hypertension or other severe features** *(Moderate level of evidence, Conditional recommendation).*[8,9,11,12,120]
- **Capabilities for the evaluation of fetal wellbeing and detection of fetal compromise should be available in healthcare facilities providing care for pregnant women with hypertensive disorders** *(Moderate level of evidence, Conditional recommendation).*[8,9,11,12,120]

Remarks:

The recommendation to continue expectant management till 37 0/7 weeks requires the ability of close surveillance for continued exclusion of features of severe preeclampsia and/or any concerns regarding maternal or fetal well-being. [8,9,11,12,120]

- **Transfer of women with hypertension of pregnancy should be considered in situations where the health care provider believes that the health care facility is unequipped to manage the complications of hypertension of pregnancy** *(GPS)***.**

Rationale:

Expectant management is intended to provide neonatal benefit at the expense of maternal risk.

The GDG is aware that expectant management of preeclampsia with severe features has become a standard treatment and is well accepted in developed countries, yet, it has never been proven safe or reproducible in the third world or in a low-resource setting[123].

Most studies with favorable outcomes of the expectant approach were conducted in tertiary centers with available facilities and care providers in Western countries. However, studies on expectant management in low-to-middle resource countries are very limited[123-125].

According to the American College of Obstetricians and Gynecologists (ACOG) guidelines, expectant management of preeclampsia with severe features prior to 34 weeks of pregnancy must be based on strict selection criteria and should be performed in a setting with available resources for maternal and neonatal care. It must be emphasized that in the standard guidelines, mothers undergoing expectant treatment must be taken care of by MFM specialists.[13,126] Nevertheless, expectant management is practiced in many countries with various availabilities of medical resources, and its outcomes have never been thoroughly evaluated[127].

Expectant management, which mainly focuses on delaying labor induction as much as possible, may cause maternal complications and require close monitoring from healthcare personnel. In many developing countries or geographical areas with low resources, expectant management of preeclampsia with severe features is very challenging[127].

Therefore, the GDG Conditionally recommends against expectant management for preeclampsia with severe hypertension or other severe features in low-resource setting where maternal and neonatal care and adequate resources for close monitoring by healthcare personnel may be lacking or not available.

Key Practice Points

Expectant Management with continued surveillance for women who fulfill all the following criteria:

1. No features of severe PET AND
2. GA < 37 weeks, AND
3. Controlled hypertension, (*if > 160/110 mmHg then all other features of severe PET must be absent and can be monitored to allow expectant management with continued surveillance)*, AND
4. Absent fetal compromise, AND
5. Patient is not in spontaneous active labor, AND
6. Maternal and fetal condition can be monitored.

Continued observation is appropriate for a woman with a preterm fetus if she has gestational hypertension or preeclampsia without severe features[128]. There are no randomized controlled trials in this population, but retrospective data suggest that without severe features, the balance should be in favor of continued monitoring until delivery at 37 0/7 weeks of gestation in the absence of abnormal antepartum testing, preterm labor, preterm prelabor rupture of membranes (also referred to as premature rupture of membranes) or vaginal bleeding, for neonatal benefit[129].

5.2.2 Birth and Delivery:

5.2.2.1 Timing of birth for women with preeclampsia

- **Initiate birth at ≥ 37 weeks gestation, in women with preeclampsia** *(Conditional recommendation/High level of evidence)***.**[9,13,118,119,122,139,142-144]
- **At < 37 weeks gestation, the decision on expectant management with continued surveillance is appropriate for women with non-severe preeclampsia** *(Conditional recommendation/High level of evidence)***.**[9,13,118,119,122,143,144.145.146]
- **Initiation of delivery at 34+0 till 36+6 weeks gestation for women with preeclampsia in presence of any feature of severity as maternal benefit outweighs fetal risks** *(Conditional recommendation/Moderate level of evidence)***.**[9,13,115,137,139,143.147]

- **Delivery should not be delayed for the administration of steroids in the late preterm period**. *(Conditional recommendation/Moderate level of evidence)*.[9,13,137,147]
- **From fetal viability until <34+0 weeks gestation, Expectant management should be considered, but only in hospitals where very preterm infants and sick mothers can be cared for. Initiation of birth is considered in the absence of available resources for maternal and neonatal care.** *(Conditional recommendation/Moderate level of evidence)*[9,13,118,119,122,139,147]

Key Practice Points Summary Timing of birth:

1. Mature fetus (37 weeks)

2. Planned early birth < 37 weeks if features of severe pre-eclampsia are present.

3. Patient in spontaneous active labor

4. Fetal compromise, fatal anomaly or death

5. Maternal and fetal condition cannot be monitored. This is an indication for birth. Preeclampsia must be efficiently monitored.

5.2.2.2. Maternal stabilization and labor management in women with pre-eclampsia and eclampsia:

2.2.2.1. Prevention and treatment of convulsions
2.2.2.2. Control of Severe Hypertension
2.2.2.3. Control of other complications: HELLP syndrome
2.2.2.4. Mode of Birth
2.2.2.5 Urgency ot Birth

5.2.2.2.1. Prevention and treatment of convulsions

5.2.2.2.1.A. Prevention of convulsions in severe PET:

- **The prevention of eclampsia is empirically based on the timely delivery once preeclampsia has been diagnosed (GPS).**
  - **Prophylactic magnesium sulphate with an intravenous loading dose of 4g followed by maintenance at 1g/hr for 24 hours in total or time of last**

seizure is strongly recommended in women at risk of eclampsia or recurrent eclampsia *(Conditional recommendation/High level of evidence)*.[8-14,118,119,139]

- **There is inadequate evidence to support an alternative magnesium regimen or the use of anticonvulsants for the prevention of eclampsia** *(Conditional recommendation/Low level of evidence)*.[13,119,148]
- **It is recommended that magnesium sulfate should be used for the prevention and treatment of seizures in women with severe hypertension or severe preeclampsia, or eclampsia and birth is planned within 24 hours** *(Conditional recommendation/High level of evidence)* **[8,9,11,12,120,148]**
- **The prophylactic use of magnesium sulfate for the prevention of seizures in women with gestational hypertension or preeclampsia without severe features is Conditionally recommended** *(GPS).*

Key Practice Points

Please Check the concentration of the available preparation. In Egypt two preparations are available:

- A 10% solution of 25ml Ampoules (Otsuka, 10th of Ramadan-Egypt). *Each ampoule (25 ml of a 10% solution) contains 2.5 grams Magnesium sulfate.*
- A 10% solution in 5 ml Ampoules (Memphis, Cairo-Egypt). Each *ampoule (5 ml of 10% solution) contains 0.5-gram Magnesium sulfate*

Resources required

- A dedicated, trained, healthcare provider, for the duration of therapy.
- Birth-suite or high dependency unit with resuscitation and ventilator support.
- Dedicated I.V. line for Magnesium Sulfate.
- Calcium Gluconate 1 gram Ampoule available in case of respiratory depression/overdose.

Contraindications and Precautions

- Maternal cardiac conduction disorders as heart block.

- Hypermagnesemia.
- Myasthenia gravis.
- Reduced renal function monitor plasma magnesium level/urine output.

Side effects

Related to hypermagnesemia

- Common (greater than 1%): nausea and vomiting, flushing
- Infrequent (0.1–1%): headache, dizziness

Administration

Intra-Venous administration of Magnesium sulfate:

- Loading dose

  4-6 grams, I.V. infusion, over 20-30 minutes, preferably via controlled syringe pump.

  - 2 ampoules of the 25 ml 10% preparation (5 grams), or
  - 10 ampoules of the 5 ml 10% preparation (5 grams).
  - Added to 50 ml of normal saline.
  - By syringe pump over 20-30 minutes, or
  - 50 -75 drops per minute in case using an infusion set (converting each 1 ml into 15 drops), or
  - 5 ml each minute by slow IV injection.

- Maintenance dose
  - 1-2g /hour, for 24 hours after last seizure or birth (whichever is latest), then review for continuation/cessation.
- Practical considerations:
  - Remember that the maximum fluid intake is restricted to 1500 ml over 24 hours.
  - The following calculations are based upon a dose of approximately 1 gram of $MgSO_4$ per hour.
  - *If you don't have an infusion pump, please use a dropper who converts each ml into 15 drops.*

- Prepare 3 bottles of 500 ml saline + 10 grams of $MgSO_4$:
- In case you are using the 10%, 25ml ampoule preparation: withdraw 100 ml from each of the bottles and add 4 ampoules to each of the bottles
- In case you are using the 10%, 5 ml ampoule preparation: withdraw 100 ml from each of the bottles and add 20 ampoules to each of the bottles
- Each of the 3 bottles will be given over 8 hours with the rate of 15 drops/minute.
- Continue the infusion for 24 hours after delivery or the last fit whatever is later.

Intra Muscular administration of Magnesium sulfate:

In case of difficulties with establishing venous access, magnesium sulfate can be administered by intramuscular (IM) injection,

- 10 g initially as a loading dose (5 g IM in each buttock), followed by 5 g into one buttock every 4 hours.
- Continue for 24 hours after delivery or the last fit whatever is later.
- The medication can be mixed with 1 mL of xylocaine 2% solution because the intramuscular administration is painful.
- The rate of adverse effects is also higher with the IM administration.

Baseline observations

- BP, pulse, respiratory rate, level of consciousness.
- Oxygen saturation (SpO2).
- Patellar reflex (or Biceps reflex if epidural analgesia is being administered).
- If antepartum, abdominal palpation, FHR/CTG.

Monitoring during loading dose

- BP, pulse, respiratory rate, SpO2 every 5 minutes, for a minimum 20 minutes,
- If in labor; monitor contractions for 10 minutes every 30 minutes.

- Continuous CTG if greater than 24 weeks gestation.
- Auscultation of FHR every 30 minutes if less than 24 weeks gestation.
- Observe for side effects.
- Check deep tendon reflexes after completion of loading dose. Notify if absent and do not commence maintenance dose.

Monitoring during maintenance infusion

- Serum Magnesium level monitoring is not required if renal functions are normal.
- Consider serum Magnesium monitoring in patients with mild renal failure (serum creatinine 1.0–1.5 mg/dL) or oliguria (less than 30 mL urine output per hour for more than 4 hours), restrict maintenance dose to only 1 gm/hour.
- If Creatinine levels are more than 1.5 mg/dl, reduce maintenance dose to 0.5 g/hour

Serum Magnesium Concentration

- Therapeutic range: 5-9 mg/dL, (2-3.5 mmol/L or 4-7 mEq/L)
- Loss of patellar reflexes: above 9 mg/dL (>3.5mmol/L or >7 mEq/L)
- Respiratory paralysis: above 12 mg/dL (>5 mmol/L or >10 mEq/L)
- Cardiac arrest: above 30 mg/dL. (>12.5 mmol/L or > 25 mEq/L)

Discontinuation and urgent clinical evaluation

- If Respiratory rate is less than 12 breaths/minute.
- dBP decreases more than 15 mmHg below baseline.
- Absent deep tendon reflexes.
- Urine output less than 80 mL/4 hours.
- Magnesium serum levels greater than therapeutic level. The following measures should be considered:
    - Discontinuation of maintenance dose.
    - Endotracheal intubation.
    - Correction with calcium gluconate 10% solution, 10 mL I.V. over 3 minutes, along with furosemide intravenously to accelerate the rate of urinary excretion.

- If serum level decreases to less than 8.4 mg/dL. (7 mEq/L) the infusion can be restarted at a slower rate than previously used.

Ceasing Therapy

- Magnesium sulfate should not be discontinued until 24 hours after delivery or the occurrence of the last fit whichever comes last.
- Magnesium Sulfate may be continued up to 48 hours if clinical assessment indicted persistent symptoms of severity (persistent headache, epigastric pain).

5.2.2.2.1.B. Management of convulsions in Eclampsia

Defined as the occurrence of one or more seizures superimposed on preeclampsia.

- Immediate measures include[13]:
  - Calling for help,
  - Prevention of maternal injury,
  - Placement in lateral decubitus position,
  - Prevention of aspiration,
  - Administration of oxygen,
  - Monitoring vital signs, including oxygen saturation.

Treatment

- **Women with eclampsia should receive magnesium sulphate to prevent recurrent seizures** *(Conditional recommendation/High level of evidence)*.[8-14,118,119,139,148]
  - ***Magnesium sulfate regimens are considered in a separate section. Please refer to the section on Magnesium Sulfate.***
  - If convulsions recur, a further 2–4 grams of magnesium sulfate should be administered I.V. over 5 minutes[9].
  - If birth has not occurred, plan as soon as feasible and when the woman's condition is stable[11].
  - Close clinical surveillance is required in an appropriately staffed area[11].

- In the rare cases of an extremely agitated patient, IV clonazepam mg, diazepam 10 mg, or midazolam may be used for sedation to facilitate the placement of the IV lines and Foley catheter, and the collection of blood specimens. These drugs should be used cautiously and only if absolutely necessary because they inhibit laryngeal reflexes increasing the risk of aspiration and also may depress the central respiratory centers leading to apnea[13].
- In cases refractory to magnesium sulfate (still seizing at 20 minutes after the bolus or more than two recurrences)[13]:
    - Health care provider can use sodium amobarbital (250 mg IV in 3 minutes), Thiopental, or phenytoin (1,250 mg IV at a rate of 50 mg/minute)[1].
    - Endotracheal intubation and assisted ventilation are appropriate in these circumstances[13].
    - Head imaging should also be considered because most of cases refractory to magnesium sulfate therapy may prove to have abnormal findings on brain imaging[13].
- Women with eclampsia should be delivered in a timely fashion. However, eclampsia by itself is not an indication for cesarean delivery. Once the patient is stabilized, the method of delivery should depend, in part, on factors such as gestational age, fetal presentation, and the findings of the cervical examination[13].

5.2.2.2.2. Control of acute severe hypertension:

- **Severe hypertension in pregnancy (i.e., sBP ≥ 160 mmHg or dBP ≥ 110 mmHg) requires *urgent* antihypertensive therapy, in a monitored setting** *(Conditional recommendation/moderate level of evidence).*[13,118]
- **Severe hypertension should be treated with the first-line agents oral nifedipine, oral labetalol, intravenous (IV) labetalol, or IV hydralazine** *(Strong recommendation/Moderate level of evidence).*[9-13,121]
- **The target BP for antihypertensive therapy should be a dBP of 85 mmHg, regardless of sBP** *(Conditional recommendation/Low level of evidence).*[116,119]

- **Non-severe hypertension should be treated with the first-line agents oral methyldopa, labetalol, or nifedipine** *(Conditional recommendation/Moderate level of evidence).*[9,147]

Key Practice Points

Choice of Antihypertensive

- The antihypertensive agent of choice for acute control has not been established.
- Initial therapy can be with one of a variety of antihypertensive agents.
- Persistent or refractory severe hypertension may respond to repeated doses.
- Concurrent administration of long-acting oral agents achieves more sustained BP lowering effect

Treat women with severe hypertension who are in critical care during pregnancy or after birth immediately with one of the following:

- **Labetalol:**
  - 10-20 mg IV, then 20-80 mg every 10-30 minutes to a maximum cumulative dosage of 300 mg\day, Or
  - Constant infusion 1-2 mg/min. I.V. *(fewer adverse effects).*
    - Onset of action: 1–2 minutes.

    Caution: Avoid labetalol in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.

- **Nifedipine (immediate release):**
  - Nifedipine: 10-20 mg orally, repeat in 20 minutes if needed; then 10-20 mg every 2-6 hours; maximum daily dose is 180 mg.
    - Onset of action: 5-10 minutes.

    Caution: May lead to reflex tachycardia and headaches.

- **Intravenous Hydralazine**.

- 5 mg I.V. or I.M., then 5-10 mg I.V. every20-40 minutes to a maximum cumulative dosage of 20 mg/day; or
- Constant infusion of 0.5–10 mg/hour.
  - Onset of action: 10–20 minutes.

Caution: Higher or frequent doses are associated with maternal hypotension, headaches, and abnormal fetal heart rate tracings.

- **Diazoxide**
  - 15-45 mg as I.V. rapid bolus and repeat after 5 minutes
  - Maximum 150 mg/dose.
  - Onset: 3–5 minutes.
  - Caution: Monitor Blood Glucose Levels.
- **Sodium Nitroprusside and Glyceryl Trinitrate (Tridil)**
  - Only recommended when other methods have failed and delivery is imminent.

The following drugs are NOT recommended for treatment of hypertension in pregnancy:

- Magnesium Sulfate (although may be indicated for prevention of eclampsia)[11].
- High dose Diazoxide[11].
- Nimodipine[11].
- Chlorpromazine[11].
- ACE inhibitors[9,11].
- Sodium Nitroprusside or Glyceryl Trinitrate are only recommended when other treatments have failed, and birth is imminent[11].

5.2.2.2.3. Control of other complications: HELLP syndrome:

- **For women with severe preeclampsia with features of HELLP expectant management is harmful. Plan birth as soon as feasible** *(Moderate level of evidence, strong recommendation).*[12,13,117]
- **Platelet transfusion should be considered if a woman's platelet count is <20 _ 109/L before vaginal delivery or <50 _ 109/L before cesarean delivery, or at any time if there is excessive active bleeding, known**

platelet dysfunction, rapidly falling platelet count, or coagulopathy *(Conditional recommendation/moderate level of evidence).*[13,119,149-151]

- **Vaginal delivery is the preferred modality, unless urgent delivery is necessary for maternal stabilization or for fetal indications. The delivery options should be discussed by a multidisciplinary team and consider the safest mode of delivery to the mother, how fast she is expected to deliver, what are the resources of blood products and other supportive mechanisms available, and can she sustain a surgery** *(Conditional recommendation/moderate level of evidence).*[6,13,152,153,154]
- **In rapidly progressing preeclampsia with severe features or HELLP syndrome, vaginal delivery may be attempted if cervical conditions are favorable and delivery is anticipated within a short timeframe (e.g., ≤2 hours). If labor progress is slow (>6 hours) or maternal/fetal status worsens, immediate cesarean delivery is indicated** *(Conditional recommendation/moderate level of evidence).*[6,13,152,155]
- **In small to medium size health care facilities, it is important to estimate whether their blood bank can support a massive blood trans fusion and, if necessary, contact regional or larger hospitals for assistance or for transferring the patient** *(GPS).*

<u>Key Practice Points:</u>

- HELLP syndrome often is characterized by progressive and sometimes sudden deterioration in maternal and fetal condition with increased rates of maternal morbidity and mortality[8,13], women with HELLP syndrome should be delivered regardless of their gestational age[13].
- The presence of HELLP syndrome is associated with significant maternal mortality and morbidity including acute renal and liver failure, disseminated intravascular coagulopathy and pulmonary oedema. Approximately 70% of pregnancies complicated by HELLP syndrome require preterm birth with 15% occurring at extremely preterm gestational age (before 27 completed weeks' gestation)[8].
- Evidence is insufficient to support the use of corticosteroids for attenuation of the disease process in HELLP syndrome[8,9,11].

- Very close monitoring is required in HELLP syndrome until delivery and in the postpartum period, with laboratory testing at least at 12-hour intervals[13].
- During the aggravation slope in the disease evolution, platelet count usually decreases at an average rate of approximately 40% per day, whereas the liver enzymes values tend to increase[1]. The lowest observed platelet count occurs at a mean of 23 hours after delivery. The disease may achieve peak intensity during the first 2 days after delivery, including a downward trend in hematocrit[13].
- If the platelet count continues to drop and liver enzymes to increase after 4 days postpartum, the validity of the initial diagnosis of HELLP syndrome should be reassessed[13].
- With supportive care alone, 90% of patients with HELLP syndrome will have platelet count more than 100,000 3 109/L and reversed trend (decrease) in liver enzymes values within 7 days after delivery[13].
- Women with HELLP syndrome are also at increased risk of pulmonary edema, acute respiratory distress syndrome and renal failure[13].
- <u>Management of the Hypercoagulation type of coagulopathy</u> resulting from endothelial cell dysfunction:[156-161]
    - Successful management of DIC is grounded on identification and treatment of the underlying cause concurrent with product replacement and circulatory support. Importantly, delivery and pregnancy termination often save the pregnant patient's life.
    - Adequate perfusion restores hepatic and endothelial synthesis of procoagulants and permits prompt removal of activated coagulation factors, fibrin, and fibrin degradation products.
    - Targeted blood component replacement with FFP, fibrinogen and platelets should be initiated as the cause of DIC is removed, otherwise the replacement given will be used to worsen DIC and generate more FDPs.
    - Targeted blood component replacement FFP, Platelets, Fibrinogen:

- Restore Platelet count greater than 75000/ul by Platelet Concentrate, where 1 unit/10kg raise platelets count ~20-50x1000 /ul
- Restore Prothrombin time (PT) and Activated partial thromboplastin time (APTT) to less than 1.5 times normal by Fresh Frozen Plasma FFP, where 10ml/kg raise clotting factors by ~25%
- Restore Fibrinogen greater than 200 mg% by Cryoprecipitate, where 1 unit/10kg raise fibrinogen ~100mg%

5.2.2.2.4. Mode of Birth

- **For women with any HDP, vaginal delivery should be considered unless a cesarean delivery is required for obstetrical indications** *(Strong recommendation/moderate level of evidence)*.[12,13]
- **Vaginal delivery may require early cervical ripening and induction** *(Conditional recommendation/moderate level of evidence)*[9,152]
- **If urgent or emergent delivery is required for maternal and/or fetal indications, an emergency cesarean delivery may be indicated** *(Strong recommendation/High level of evidence).*[13,115]

Remarks:

- The only possible cure for pre-eclampsia is the birth of the baby. Theoretically, the benefits of faster interruption of pregnancy through a cesarean section would be greater. Longer inductions may be expected when severe pre-eclampsia occurs before 34 weeks and cervical conditions are not favourable. In the meantime, maternal complications may arise or worsen. There is also a concern for fetal well-being, because of the potential risk of fetal distress and fetal death due to placental dysfunction[162].
- The mode of delivery in women with gestational hypertension or preeclampsia (with or without severe features) should be determined by routine obstetric considerations. Vaginal delivery often can be accomplished, but with labor induction in preeclampsia with severe

features this is less likely with decreasing gestational age at diagnosis. For gestational hypertension or preeclampsia without severe features, vaginal delivery is preferred[163-65]. The decision to perform cesarean delivery should be individualized, based on anticipated probability of vaginal delivery and on the nature and progression of preeclampsia disease state[13].

5.2.2.2.5. Urgency of birth:

Health facilities in Egypt should provide local protocols of management for their health care providers in accordance with WHO recommendations, that address the following *(Strong recommendation/Moderate level of evidence)*:[166]

1. Consider what adaptations are necessary for the local context, and any modifications should be made in an explicit and transparent manner and based on clear justification.
2. Develop clear and practical clinical protocols that reflect the recommendations applicable to the local facility resources.
3. Ensure that policies include clear job descriptions, and physician privileges
4. All health care providers, in the most peripheral settings, who care for pregnant women or women in labor must be competent to
    a. Detect and manage pre-eclampsia and eclampsia,
    b. Initiate emergency supportive care as early as possible when complications are detected.
    c. Be able to refer women who need a higher level of care or skill without delay and essential local protocols should be put forward to allow such referral.

GDG recommends to <u>nationally adopt a color-triage system for acute obstetric emergencies (Modified Early obstetric warning score -MEOWS)</u>. *(GPS)*

Rationale:

Early Warning score is validated as a useful tool to:

1. Facilitate early recognition of critically ill women (early recognition and initiation of care is key to improve patient outcome)

2. Standardize escalation of care,
3. Provide standard evidence-based decision-making tool across health facilities in Egypt.

6. TREATMENT OF CHRONIC HYPERTENSION

6.1. Expectant Management in women with chronic hypertension

- **Offer expectant management for women with Chronic hypertension who are <37 weeks and, whose blood pressure is lower than 160/110 mmHg with or without antihypertensive treatment, unless there are other medical indications** *(Moderate level of evidence/Strong recommendation)*.[6,9,13,116,167]
- **Offer antihypertensive treatment to pregnant women who have chronic hypertension and who are not already on treatment if they have sustained systolic blood pressure of 140 mmHg or higher or sustained diastolic blood pressure of 90 mmHg or higher** *(Strong recommendation/Moderate level of evidence).* [6,9,13,116,167]
- **The target BP for antihypertensive therapy should be a dBP of 85 mmHg, regardless of sBP** *(Strong recommendation/High level of evidence).* [6,9,13,116,167]
- **Consider labetalol to treat chronic hypertension in pregnant women. Consider nifedipine for women in whom labetalol is not suitable or methyldopa if both labetalol and nifedipine are not suitable. Base the choice on any pre-existing treatment, side-effect profiles, risks (including fetal effects) and the woman's preference** *(Conditional recommendation/Moderate level of evidence)*. [6,9,13,116,167]
- **Continue with existing antihypertensive treatment if safe in pregnancy, or switch to an alternative treatment, unless sustained systolic blood pressure is less than 110 mmHg or sustained diastolic blood pressure is less than 70 mmHg or the woman has symptomatic hypotension** *(Conditional recommendation/Moderate level of evidence)*.[9,168]

- **Offer pregnant women with chronic hypertension aspirin 150 mg once daily from 12 weeks** *(High quality of evidence/Strong recommendation).*[43,169]
- **Give the same advice on rest, exercise and work to women with chronic hypertension or at risk of hypertensive disorders during pregnancy as healthy pregnant women** *(Conditional recommendation/Moderate level of evidence)***.**[8,170,171]
- **If women with chronic hypertension are suspected of developing pre-eclampsia:**
    - **Offer PLGF testing between 20–36+6 weeks to rule out pre-eclampsia in women with chronic hypertension if clinical suspicion arises** *(Conditional recommendation/Moderate level of evidence)*.[9,172]
    - **In chronic hypertension with suspected pre-eclampsia, monitor proteinuria 1–2x weekly alongside BP checks** *(Strong recommendation/Moderate level of evidence)*. [6,9,13,51,154,]
    - **A complete blood count and levels of serum transaminases, lactate dehydrogenase, and uric acid should be checked on diagnosis then weekly** *(Conditional recommendation/Moderate level of evidence)*[8,9,13]

6.2. Termination of pregnancy in women with chronic hypertension:

Timing of birth

- **Do not offer planned early birth (before 37 weeks) to women with chronic hypertension whose blood pressure is lower than 160/110 mmHg, with or without antihypertensive treatment, unless there are other medical indications** *(Strong recommendation/Moderate level of evidence)*[9,12,145,168,173]
- **Offer planned birth to women with chronic hypertension whose blood pressure is lower than 160/110 mmHg with or without antihypertensive treatment after 37 weeks** *(Strong recommendation/Moderate level of evidence)***,**[9,12,145,168,173]

Determination of timing should be agreed between the woman and the obstetrician. Initiation of delivery can be offered at 38+0 to 39+6 weeks *(Conditional recommendation/Low quality of evidence).* [9,12,168,173]

Remarks: Women with chronic hypertension, may benefit from birth at 38+0 to 39+6 weeks for neonatal benefits, but in terms of reduced incidence of severe hypertension, stillbirth, and cesarean delivery the evidence is observational in nature.[9,12,145,168,173]

Offer planned early birth before 37 weeks to women with chronic hypertension or gestational hypertension if inability to control maternal blood pressure despite using 3 or more classes of antihypertensives in appropriate doses or if any of the known features of severe superimposed preeclampsia develop *(Strong recommendation/High level of evidence)*[12,116,142,168,174-176]

Remarks: If planned early birth (*before 37 weeks*) is indicated, offer a course of antenatal corticosteroids and magnesium sulfate if indicated.

7. CARE FOR WOMEN WITH HYPERTENSION DURING LABOR AND POSTPARTUM

7.1 Intrapartum Care for Women with HDP: [8,9,11,12,13,177]

During labour, measure blood pressure hourly. In women with severe hypertension measure blood pressure every 15 to 30 minutes until blood pressure is less than 160/110 mmHg *(Conditional recommendation/Moderate level of evidence)*[8,9,11,12,178]

Continue use of antenatal antihypertensive treatment during labour *(Conditional recommendation/Moderate level of evidence)*[9,11,13]

Do not preload women who have severe pre-eclampsia with intravenous fluids before establishing low-dose epidural analgesia or combined spinal epidural analgesia *(Conditional recommendation/Moderate level of evidence)*[179]

Do not routinely limit the duration of the second stage of labour in women with controlled hypertension *(Conditional recommendation/Moderate level of evidence)*[13,180]

Consider operative or assisted birth in the second stage of labour for women with severe hypertension whose hypertension has not responded to initial treatment *(Conditional recommendation/Low level of evidence).*[9]

As women with preeclampsia are at increased risk of postpartum hemorrhage, the third stage of labour should be actively managed *(Conditional recommendation/moderate level of evidence).*[177,180]

Ergometrine should not be administered to women with any hypertensive disorder of pregnancy, particularly preeclampsia or gestational hypertension; alternative oxytocic drugs should be considered *(Strong recommendation/moderate level of evidence).*[9,12,180]

Key Practice Points Summary

1. **BP Monitoring: Hourly (or 15-30 min if severe)**
2. **Antihypertensives: Continue during labour**
3. **Fluids: No preloading before epidural**
4. **Second Stage: No routine time limit unless severe refractory HTN**
5. **Third Stage: Active management with oxytocin**
6. **Ergometrine: Avoid in all hypertensive disorders**

Key Practice Points

- Monitoring
  - Monitor BP ½ hourly as a minimum.
  - Continuous CTG is recommended.
  - I.V. access is required.
  - An epidural (in the absence of contraindications) is a useful adjunct therapy for BP control (Different options to be discussed with anesthetist).
  - Fluid Management:

- Administration of large volumes of intravenous fluids before or after birth may contribute to a risk of pulmonary oedema or worsen peripheral oedema [18,123]
- Consider additional fluid administration only prior to intravenous hydralazine, regional anaesthesia, immediate delivery, or in oliguric patients where a volume deficit is suspected[18]
- Maintain strict hourly fluid balance monitoring[12]
- An indwelling urinary catheter for hourly measurements may be required[2]
- Diuretics are usually not recommended[123] unless there is fluid overload or pulmonary oedema[141]

    - Drug Therapy
        - Continue antihypertensive drug therapy throughout labor and birth.
- Second Stage
    - Assisted operative delivery is required if:
        - BP is poorly controlled
        - Progress is inadequate
        - There are premonitory signs of eclampsia
- Third Stage
    - Active management of third stage is recommended to decrease risk of postpartum hemorrhage.
    - DO NOT GIVE Ergometrine or Syntometrine as it may produce an acute rise in BP.

7.2 Postpartum Care for Women with HDP:[8,9,11,12,13]

There remains inadequate data to suggest the superiority of a single agent or group of agents in selecting antihypertensives for the management of hypertension in the postpartum period. The choice of antihypertensive (beta-blockers, methyldopa, hydralazine, nifedipine, enalapril, clonidine) should be made through a shared decision-making process, particularly in breastfeeding/lactating women *(Conditional recommendation/ Very low quality of evidence).*[12,13]

- **Women should be informed of the long-term risks associated with preeclampsia, gestational hypertension and chronic hypertension and the importance of postpartum follow up prior to discharge from hospital** *(Conditional recommendation/ Very low quality of evidence).*[115,182]
- **Antihypertensive therapy administered antepartum should be continued after birth. Also, consideration should be given to administering antihypertensive therapy for any hypertension diagnosed before six days postpartum** *(Low quality of evidence/Conditional recommendation).*[183]
- **The target dBP for postpartum antihypertensive treatment should be 85 mmHg, as antenatally** *(Low quality of evidence/Conditional recommendation).*[116]
- **Non-steroidal anti-inflammatory drugs (NSAIDs) for postpartum analgesia may be used in women with pre-eclampsia if other analgesics are ineffective, and there is no acute kidney injury (AKI) or other risk factors for it** *(Low quality of evidence/Conditional recommendation).*[147]
- **Breastfeeding is recommended** *(Moderate of evidence/Strong recommendation).*[184]
- **Counselling should be provided about the risks of gestational hypertension (at least 4%) or pre-eclampsia (at least 15%) in future pregnancy** *(Conditional recommendation/ Very low quality of evidence)*[185]
- **At 3 months postpartum, all women should be reviewed to ensure that BP, urinalysis, and any laboratory abnormalities have normalised. If proteinuria or hypertension persist, then appropriate referral for further investigations should be initiated** *(Conditional recommendation/ Very low quality of evidence)*[186]
- **At 6 months postpartum, where possible, all women should be reviewed again, at which point we suggest that BP ≥ 120/80 mmHg lead to discussion of lifestyle change** *(Moderate of evidence/Conditional recommendation).*[187]
- **Following hypertensive pregnancy, particularly pre-eclampsia, counselling should be provided about the heightened health risks for the mother**

(particularly cardiovascular) and the offspring *(Moderate of evidence/Strong recommendation).*[188]

Key Practice Points

- Hypertension, proteinuria, eclampsia and other adverse conditions of preeclampsia may develop for the first time during the postpartum period.
    - De novo postpartum hypertension is most common on days 3–6
    - Peak postpartum BP occurs on days 3–6
    - 44% of eclampsia occurs in the postpartum period, usually in the first 48 hours after birth
- After birth, clinical and laboratory derangements of preeclampsia recover, often taking several days
    - Liver enzyme elevations and thrombocytopenia will often worsen in the first few days after birth before they improve
- Target Blood Pressure is 130/85
- Continue close monitoring (4 hourly or more frequently) including BP, pulse rate, respiratory rate and oxygen saturation until:
    - BP is stable
    - Urine output has normalized
    - Blood investigations are stable or improving
- Frequency of monitoring is reduced after approval of the multidisciplinary team.
- Ask women about severe headache and epigastric pain each time BP is measured

Drug Therapy

- Antihypertensive therapy
    - Continue use of antenatal antihypertensive drug therapy.
    - Cease or reduce when hypertensive changes are resolving.
    - Avoid abrupt withdrawal to avoid rebound hypertension.

        - If persistently hypertensive (sBP greater than or equal to 140 mmHg or dBP greater than or equal to 90 mmHg), start antihypertensive drug therapy (if not commenced prior to birth).
        - If severe hypertension persists; refer to the section on severe hypertension.
        - If Methyldopa was initiated during pregnancy, cease postpartum and commence alternative therapy as it is associated with psychologic depression.
        - For women on beta blockers, consult with the neonatologist for possible neonatal hypoglycemia and arrange for neonatal blood glucose monitoring.
- Venous Thromboprophylaxis
    - Actively consider VTE prophylaxis
- NSAIDs
    - Non-steroidal anti-inflammatory drugs (NSAIDS) are not generally recommended because of the risk of worsening hypertension and renal impairment, especially in volume depleted women.

<u>Breast Feeding</u>

- Antihypertensive drugs without reported adverse reactions in breastfed infants include:
    - Nifedipine
    - Enalapril
    - Captopril
    - Metoprolol
    - Atenolol (other agents may be preferred if nursing a preterm infant)
    - Labetalol (other agents may be preferred if nursing a preterm infant)

<u>Psychological Support</u>

- Offer postnatal counselling regarding the pregnancy and birth experience including formal postnatal review to discuss the events of the pregnancy if required.
- Discharge and follow up
- Following a pregnancy complicated by hypertensive disorders of pregnancy, the woman has an increased risk in future pregnancies for development of gestational hypertension and preeclampsia, as well as an increased risk of longer term cardiovascular and medical conditions.
    - Consider the risk of late seizures and the peak postpartum BP when timing discharge.
    - Recommend follow-up after 6 weeks to ensure resolution of pregnancy-related changes and ascertain the need for ongoing care.
    - Provide a detailed report or form about the events of the pregnancy and birth.
    - Provide advice regarding future pregnancy risk reduction (e.g., calcium supplementation, low dose aspirin).
    - Counsel for contraception.
    - Arrange for screening for pre-existing hypertension and underlying renal disease to women with a history of early onset preeclampsia, or antiphospholipid antibodies.
    - Arrange for assessment of cardiovascular risk markers for women who became normotensive following a hypertensive disorder of pregnancy (e.g., Frequent BP check, serum lipids and blood glucose)

<u>Lifestyle Advices and Modifications</u>

- Advise women that they will benefit from avoiding smoking, maintaining a healthy weight, exercising regularly and eating a healthy diet.
- Overweight and obese women should be helped to attain a healthy BMI for long term health and to decrease the risks of hypertensive disorders in future pregnancies.

Implementation considerations

Several barriers may hinder the effective implementation and scale-up of the recommendations in this guideline. These factors may be related to the behaviours of patients (or families), the behavior of healthcare professionals, the organization of care, health service delivery or financial arrangements.

Obstacles to effective implementation include:

- Patient engagement
- Collaboration; person centered, team based collaboration between clinician, dietitian, pharmacist and others involved in care delivery
- Behavior changes: information, guidance and support delivered easily and consistently can help assess sustained behavioral changes.

Research needs

Areas for research needed in Hypertensive Disorders in Pregnancy:

- Further studies on more refined triage systems.
- Further studies on the optimum reasonable Decision-to-placental Birth interval in cases of severe Preeclampsia/eclampsia.

Clinical Quality Standards for Monitoring

➢ **Hospital admission**	
QS.1	All women with non-severe preeclampsia are offered hospital admission.
QM.1	**Numerator:** number of women admitted with non-severe preeclampsia **Denominator:** total number of women admitted with HDP
➢ **Diagnosis**	
QS.1	All women with non-severe preeclampsia are offered investigations to rule out severe features.
QM.1	**Numerator:** number of women admitted with non-severe preeclampsia and offered Baseline Preeclampsia blood tests: Full blood count (FBC) with platelet estimates, Urea, creatinine, electrolytes and urate, Liver function tests (LFT) [LDH, AST, ALT] and Fetal Ultrasound scan. **Denominator:** total number of women admitted with diagnosis of non-severe preeclampsia
➢ **Treatment**	
QS.1	All women with severe preeclampsia are offered termination of pregnancy.
QM.1	**Numerator:** number of women diagnosed with one or more severe preeclampsia feature(s) and offered birth. **Denominator:** total number of women diagnosed with one or more severe preeclampsia feature(s) admitted.

Updating of the guidelines

This guideline will be updated whenever there is new evidence.

References

1 *Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy Hypertens. 2014;4(2):97–104. doi: 10.1016/j.preghy.2014.02.001.).*

2 *American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy Hypertension in pregnancy: report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122–1131. doi: 10.1097/01.AOG.0000437382.03963.88.).*

3 *Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33(3):130–137. doi: 10.1053/j.semperi.2009.02.010.*

4 *World Health Organisation . The World Health Report 2005: Make Every Mother and Child Count. Geneva, Switzerland: World Health Organization; 2005.)*

5 *Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376(9741):631–644. doi: 10.1016/S0140-6736(10)60279-6.).*

6 *Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, Kenny LC, McCarthy F, Myers J, Poon LC, Rana S, Saito S, Staff AC, Tsigas E, von Dadelszen P. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2022 Mar;27:148-169. doi: 10.1016/j.preghy.2021.09.008. Epub 2021 Oct 9. PMID: 35066406.).*

7 *Frequency of Hypertension Associated with Pregnancy among The Pregnant Women Attending Maternal and Child Care Centers in Belbeis City. The Egyptian Journal of Community Medicine, 2017; 35(3): 83-91.*

8 *SOMANZ hypertension in pregnancy guideline 2023. https://www.somanz.org/hypertension-in-pregnancy-guideline-2023/. Accessed February 2025*

9 *1. National Institute for Health and Care Excellence (NICE). Hypertension in pregnancy: diagnosis and management. NICE guideline [NG133]. London: NICE; 2023 Jun [updated 2023 Jun; cited 2024 Month Day]. Available from: https://www.nice.org.uk/guidance/ng133*

10 *Magee LA, Smith GN, Bloch C, Côté AM, Jain V, Nerenberg K, von Dadelszen P, Helewa M, Rey E. Guideline No. 426: Hypertensive Disorders of Pregnancy: Diagnosis, Prediction, Prevention, and Management. J Obstet Gynaecol Can. 2022 May;44(5):547-571.e1. doi: 10.1016/j.jogc.2022.03.002. PMID: 35577426*

11 *Queensland Clinical Guideline: Hypertension and pregnancy 2021. Accessed February 2025*

12 *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. 2021;27:148-169. doi:10.1016/j.preghy.2021.09.008.

13 *ACOG Practice Bulletin 222 (2020) Gestational Hypertension and Preeclampsia. Obstetrics & Gynecology, 135, e237-e260*

14 *Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P; Canadian Hypertensive Disorders of Pregnancy (HDP) Working Group. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens. 2014 Apr;4(2):105-45. doi: 10.1016/j.preghy.2014.01.003. Epub 2014 Feb 25. PMID: 26104418*

15 *R. Akaishi, T. Yamada, M. Morikawa, R. Nishida, H. Minakami, Clinical features of isolated gestational proteinuria progressing to pre-eclampsia: retrospective observational study, BMJ Open 4 (2014), e004870.*

16 *Phelan LK, Brown MA, Davis GK, Mangos G. A prospective study of the impact of automated dipstick urinalysis on the diagnosis of preeclampsia. Hypertens Pregnancy 2004;23:135–42. (Level II-3)*

17 *North RA, Taylor RS, Schellenberg JC. Evaluation of a definition of pre-eclampsia. Br J Obstet Gynaecol 1999;106:767–73 (Level II-2)*

18 *M.Y. Tan, D. Wright, L. Koutoulas, R. Akolekar, K.H. Nicolaides, Comparison of screening for pre-eclampsia at 31–34 weeks' gestation by sFlt-1/PlGF ratio and a method combining maternal factors with sFlt-1 and PlGF, Ultrasound Obstet. Gynecol. 49 (2017) 201–208*

19 *US Preventive Services Task Force. Screening for Preeclampsia. In: DiGiuseppi C, Atkins D, Woolf S, et al. (eds). Guide to Clinical Preventive Services. 2nd ed. Baltimore, MD: Williams and Wilkins; 1996. p. 419-24*

20 *Siu AL; U.S. Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163(10):778-786*

21 *Higgins JR, de SwietM. Blood-pressure measurement and classification in pregnancy. Lancet. 2001;357(9250):131-135.*

22 *Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation. 2005;111(5):697-716*

23 *Park HJ, Shim SS, Cha DH. Combined screening for early detection of pre-eclampsia. International Journal of Molecular Sciences 2015;16(8):17952-74.*

24 *Ramos JGR, Ranzani OT, Perondi B, Dias RD, Jones D, Carvalho CRR, et al. A decision-aid tool for ICU admission triage is associated with a reduction in potentially inappropriate intensive care unit admissions. J Crit Care. 2019;51:77–83*

25 *T.J. Cade, P.C. de Crespigny, T. Nguyen, J.R. Cade, M.P. Umstad, Should the spot albumin-to-creatinine ratio replace the spot protein-to-creatinine ratio as the primary screening tool for proteinuria in pregnancy? Pregnancy Hypertens. 5 (2015) 298–302*

26 *A.M. Cote, M.A. Brown, E. Lam, et al., Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in Hypertensive pregnant women: systematic review, BMJ 336 (2008) 1003–1006*

27 *P.J. Saudan, M.A. Brown, T. Farrell, L. Shaw, Improved methods of assessing proteinuria in hypertensive pregnancy, Br. J. Obstet. Gynaecol. 104 (1997) 1159–1164*

28 *J. Waugh, R. Hooper, E. Lamb, et al., Spot protein-creatinine ratio and spot albumin-creatinine ratio in the assessment of pre-eclampsia: a diagnostic accuracy study with decision-analytic model-based economic evaluation and acceptability analysis, Health Technol. Assess. 21 (2017) 1–90*

29 *Sonek J, Krantz D, Carmichael J, Downing C, Jessup K, Haidar Z, et al. First-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume. Am J Obstet Gynecol. 2018;218(1):126.e1-.e13*

30 *Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. Fetal Diagn Ther. 2013;33(1):8-15*

31 *Tan MY, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers:results of SPREE. Ultrasound Obstet Gynecol. 2018;51(6):743-50*

32 *Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. 2019; 145(S1):1-33*

33 *Patil M, Panchanadikar TM, Wagh G. Variation of PAPP-A level in the first trimester of pregnancy and its clinical outcome. Journal of Obstetrics and Gynaecology of India. [Internet]. 2014 [cited 2020 July 9]; 64(2):116-9 DOI:10.1007/s13224-013-0481-4*

34 *Hoffman MK, Goudar SS, Kodkany BS, Metgud M, Somannavar M, Okitawutshu J, et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, doubleblind, placebo-controlled trial. 2020; 395(10220):285-93*

35 *Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews. [Internet]. 2019; DOI:10.1002/14651858.CD004659.pub3*

36 *Miciak-Ławicka E, Begier-Krasińska B, Tykarski A, Krasiński Z. Does the timing of aspirin administration influence its antiplatelet effect - review of literature on chronotherapy. Polish journal of cardio-thoracic surgery 2018;15(2):125-9.*

37 *Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. American Journal of Obstetrics and Gynecology 2018;218(3):287-93*

38 *Beaufils M, Uzan S, Donsimoni R, Colau JC. Prevention of pre-eclampsia by early antiplatelet therapy. Lancet. 1985;1(8433):840-2*

39 *CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. Lancet (London, England). 1994;343(8898):619-29*

40 *Rotchell YE, Cruickshank JK, Gay MP, Griffiths J, Stewart A, Farrell B, et al. Barbados Low Dose Aspirin Study in Pregnancy (BLASP): a randomized trial for the prevention of pre-eclampsia and its complications. Br J Obstet Gynaecol. 1998;105(3):286-92*

41 *Caritis S, Sibai B, Hauth J, Lindheimer MD, Klebanoff M, Thom E, 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(11):701-5*

42 *Park F, Russo K, Williams P, Pelosi M, Puddephatt R, Walter M, et al. Prediction and prevention of early-onset pre-eclampsia: impact of aspirin after first-trimester screening. Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2015;46(4):419-23*

43 *Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med. 2017;377(7):613-22.*

44 *Meher S, Duley L, Hunter K, Askie L. Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis. Am J Obstet Gynecol. 2017;216(2):121-8 e2*

45 *Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstetrics and gynecology. 2010;116(2 Pt 1):402-14*

46 *Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. Am J Obstet Gynecol. 2017;216(2):110-20 e6*

47 *Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. Chronobiol Int. 2013;30(1-2):260-79*

48 *Hofmeyr GJ, Lawrie TA, Atallah Á, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2018;10:CD001059.*

49 *G.J. Hofmeyr, A.P. Betran, M. Singata-Madliki, et al., Prepregnancy and early pregnancy calcium supplementation among women at high risk of pre-eclampsia: a multicentre, double-blind, randomised, placebo-controlled trial, Lancet 393 (2019) 330–339.*

50 *Villar J, Abdel-Aleem H, Merialdi M, Mathai M, Ali MM, Zavaleta N, et al. World Health Organization Randomised trial of calcium supplementation among low calcium intake pregnant women. Am J Obstet Gynecol. 2006;194(3):639-49.*

51 *Society for Maternal-Fetal Medicine. SMFM Consult Series #59: Patient counseling for preeclampsia. Am J Obstet Gynecol. 2023;228(4):B15-B24. doi:10.1016/j.ajog.2023.02.002.*

52 *ACOG Committee Opinion No. 736 (2023 Update). Obstet Gynecol. 2023;141(2):e1-e12.*

53 *WHO Standards for Maternal Education (2021). WHO Recommendations on Antenatal Care (2021), p.87.*

54 *MOTHER RCT (AJOG 2022). Am J Obstet Gynecol. 2022;226(4):S1-S10.*

55 *Global Preeclampsia Registry (2023). Hypertension. 2023;81(3):e25-e33.*

56 *Magdy Mohamed Amin, Mohamed Sabry Ibrahim, et al. Three Delays Model to Maternal Mortality Scenarios at Sohag Univeristy Hospital Bidirectional Cohort Study 2021. The Egyptian Journal of Hospital Medicine (April 2021) Vol. 83, Page 812-816.*

57 *Weissgerber TL, Wolfe LA, Davies GA. The role of regular physical activity in preeclampsia prevention. Med Sci Sports Exerc. 2004;36(12):2024-31.*

58 *Clapp JF. The effects of maternal exercise on fetal oxygenation and fetoplacental growth. Eur J Obstet Gynecol Reprod Biol. 2003;110 Suppl 1:S80-5.*

59 *Barakat R, Refoyo I, Coteron J, Franco E. Exercise during pregnancy has a preventative effect on excessive maternal weight gain and gestational diabetes. A Randomised controlled trial. Braz J Phys Ther. 2019;23(2):148-55.*

60 *da Silva SG, Hallal PC, Domingues MR, Bertoldi AD, Silveira MFD, Bassani D, et al. A Randomised controlled trial of exercise during pregnancy on maternal and neonatal outcomes: results from the PAMELA study. Int J Behav Nutr Phys Act. 2017;14(1):175.*

61 *de Oliveria Melo AS, Silva JL, Tavares JS, Barros VO, Leite DF, Amorim MM. Effect of a physical exercise program during pregnancy on uteroplacental and fetal blood flow and fetal growth: a Randomised controlled trial. Obstet Gynecol. 2012;120(2 Pt 1):302-10.*

62 *Ruiz JR, Perales M, Pelaez M, Lopez C, Lucia A, Barakat R. Supervised exercise-based intervention to prevent excessive gestational weight gain: a Randomised controlled trial. Mayo Clin Proc. 2013;88(12):1388-97.*

63 *Tomić V, Sporiš G, Tomić J, Milanović Z, Zigmundovac-Klaić D, Pantelić S. The effect of maternal exercise during pregnancy on abnormal fetal growth. Croat Med J. 2013;54(4):362-8.*

64 *Wang C, Wei Y, Zhang X, Zhang Y, Xu Q, Sun Y, et al. A Randomised clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve*

pregnancy outcome in overweight and obese pregnant women. Am J Obstet Gynecol. 2017;216(4):340-51.

65 *Jayashree R, Malini A, Rakhshani A, Nagendra H, Gunasheela S, Nagarathna R. Effect of the integrated approach of yoga therapy on platelet count and uric acid in pregnancy: A multicenter stratified Randomised single-blind study. Int J Yoga. 2013;6(1):39-46.*

66 *Rakhshani A, Nagarathna R, Mhaskar R, Mhaskar A, Thomas A, Gunasheela S. The effects of yoga in prevention of pregnancy complications in high-risk pregnancies: a Randomised controlled trial. Prev Med. 2012;55(4):333-40.*

67 *Kasawara KT, Burgos CS, do Nascimento SL, Ferreira NO, Surita FG, Pinto E Silva JL. Maternal and Perinatal Outcomes of Exercise in Pregnant Women with Chronic Hypertension and/or Previous Preeclampsia: A Randomised Controlled Trial. ISRN Obstet Gynecol. 2013;2013:857047.*

68 *Gennari-Moser C, Escher G, Kramer S, Dick B, Eisele N, Baumann M, et al. Normotensive blood pressure in pregnancy: the role of salt and aldosterone. Hypertension. 2014;63(2):362-8.*

69 *Farese S, Shojaati K, Kadereit B, Frey FJ, Mohaupt MG. Blood pressure reduction in pregnancy by sodium chloride. Nephrol Dial Transplant. 2006;21(7):1984-7.*

70 *Duley L, Henderson-Smart D, Meher S. Altered dietary salt for preventing pre-eclampsia, and its complications. Cochrane Database Syst Rev. 2005(4):CD005548.*

71 *Delemarre FM, van Leest LA, Jongsma HW, Steegers EA. Effect of low-sodium diet on uteroplacental circulation. J Matern Fetal Med. 2000;9(4):197-200.*

72 *van Buul BJ, Steegers EA, Jongsma HW, Rijpkema AL, Eskes TK, Thomas CM, et al. Dietary sodium restriction in the prophylaxis of hypertensive disorders of pregnancy: effects on the intake of other nutrients. Am J Clin Nutr. 1995;62(1):49-57.*

73 *Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. Cochrane Database Syst Rev. 2018;11:CD003402.*

74 *Rani A, Wadhwani N, Chavan-Gautam P, Joshi S. Altered development and function of the placental regions in preeclampsia and its association with long-chain polyunsaturated fatty acids. Wiley Interdiscip Rev Dev Biol. 2016;5(5):582-97.*

75 *Kulkarni AV, Mehendale SS, Yadav HR, Joshi SR. Reduced placental docosahexaenoic acid levels associated with increased levels of sFlt-1 in preeclampsia. Prostaglandins Leukot Essent Fatty Acids. 2011;84(1-2):51-5.*

76 *Olesen C, Søndergaard C, Thrane N, Nielsen GL, de Jong-van den Berg L, Olsen J, et al. Do pregnant women report use of dispensed medications? Epidemiology. 2001;12(5):497-501.*

77 *Onwude JL, Lilford RJ, Hjartardottir H, Staines A, Tuffnell D. A randomized double blind placebo controlled trial of fish oil in high risk pregnancy. Br J Obstet Gynaecol. 1995;102(2):95-100*

78 *Horvaticek M, Djelmis J, Ivanisevic M, Oreskovic S, Herman M. Effect of eicosapentaenoic acid and docosahexaenoic acid supplementation on C-peptide preservation in pregnant women with type-1 diabetes: Randomised placebo controlled clinical trial. Eur J Clin Nutr. 2017;71(8):968-72.*

79 *Amin G SAZ, Jafariazar Z , Vosoogh S, Shariat M, et al. The effect of garlic capsule on the prevention of preeclampsia in high-risk Turkmen pregnant women. J undishapur J Nat Pharm Prod2020.*

80 *Ziaei S, Hantoshzadeh S, Rezasoltani P, Lamyian M. The effect of garlic tablet on plasma lipids and platelet aggregation in nulliparous pregnants at high risk of preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2001;99(2):201-6.*

81 *Costantine MM, Cleary K, Hebert MF, Ahmed MS, Brown LM, Ren Z, et al. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot Randomised controlled trial. Am J Obstet Gynecol. 2016;214(6):720.e1-.e17..*

82 *Mikhail MS, Anyaegbunam A, Garfinkel D, Palan PR, Basu J, Romney SL. Preeclampsia and antioxidant nutrients: decreased plasma levels of reduced ascorbic acid, alpha-tocopherol, and beta-carotene in women with preeclampsia. Am J Obstet Gynecol. 1994;171(1):150-7.*

83 *Chappell LC, Seed PT, Kelly FJ, Briley A, Hunt BJ, Charnock-Jones DS, et al. Vitamin C and E supplementation in women at risk of preeclampsia is associated with changes in indices of oxidative stress and placental function. Am J Obstet Gynecol. 2002;187(3):777-84.*

84 *Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. Lancet. 1999;354(9181):810-6.*

85 *Chan AC. Partners in defense, vitamin E and vitamin C. Can J Physiol Pharmacol. 1993;71(9):725-31.*

86 *Araújo CAL, Lorena SB, Cavalcanti GCS, Leão GLS, Tenório GP, Alves JGB. Oral magnesium supplementation for leg cramps in pregnancy-An observational controlled trial. PLoS One. 2020;15(1):e0227497.*

87 *Bullarbo M, Mattson H, Broman AK, Ödman N, Nielsen TF. Magnesium Supplementation and Blood Pressure in Pregnancy: A Double-Blind Randomised Multicenter Study. J Pregnancy. 2018;2018:4843159.*

88 *D'Almeida A, Carter JP, Anatol A, Prost C. Effects of a combination of evening primrose oil (gamma linolenic acid) and fish oil (eicosapentaenoic + docahexaenoic acid) versus magnesium, and versus placebo in preventing pre-eclampsia. Women Health. 1992;19(2-3):117-31.*

89 *Martin RW, Perry KG, Hess LW, Martin JN, Morrison JC. Oral magnesium and the prevention of preterm labor in a high-risk group of patients. Am J Obstet Gynecol. 1992;166(1 Pt 1):144-7.*

90 *Sibai BM, Villar MA, Bray E. Magnesium supplementation during pregnancy: a double-blind Randomised controlled clinical trial. Am J Obstet Gynecol. 1989;161(1):115-9.*

91 *Spätling L, Spätling G. Magnesium supplementation in pregnancy. A double-blind study. Br J Obstet Gynaecol. 1988;95(2):120-5.*

92 *Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, Spong CY, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. N Engl J Med. 2007;357(5):454-61.*

93 *Norman JE, Mackenzie F, Owen P, Mactier H, Hanretty K, Cooper S, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and metaanalysis. Lancet. 2009;373(9680):2034-40.*

94 *de Alwis N, Beard S, Mangwiro YT, Binder NK, Kaitu'u-Lino TJ, Brownfoot FC, et al. Pravastatin as the statin of choice for reducing pre-eclampsia associated endothelial dysfunction. Pregnancy Hypertens. 2020;20:83-91.*

95 *Pánczél Z, Kukor Z, Supák D, Kovács B, Kecskeméti A, Czizel R, et al. Pravastatin induces NO synthesis by enhancing microsomal arginine uptake in healthy and preeclamptic placentas. BMC Pregnancy Childbirth. 2019;19(1):426.*

96 *Wang GJ, Yang Z, Huai J, Xiang QQ. Pravastatin alleviates oxidative stress and decreases placental trophoblastic cell apoptosis through IL-6/STAT3 signaling pathway in preeclampsia rats. Eur Rev Med Pharmacol Sci. 2020;24(24):12955-62.*

97 *Döbert M, Varouxaki AN, Mu AC, Syngelaki A, Ciobanu A, Akolekar R, et al. Pravastatin Versus Placebo in Pregnancies at High Risk of Term Preeclampsia. Circulation. 2021;144(9):670-9.*

98 *Singh S, Sinha R, Kaushik M. Prophylactic Low Molecular Weight Heparin Improving Perinatal Outcome in Non-thrombophilic Placental-Mediated Complications. J Obstet Gynaecol India. 2016;66(6):436-40.*

99 *Mello G, Parretti E, Fatini C, Riviello C, Gensini F, Marchionni M, et al. Low-molecular-weight heparin lowers the recurrence rate of preeclampsia and restores the physiological vascular changes in angiotensin-converting enzyme DD women. Hypertension. 2005;45(1):86-91.*

100 *Gris JC, Chauleur C, Molinari N, Marès P, Fabbro-Peray P, Quéré I, et al. Addition of enoxaparin to aspirin for the secondary prevention of placental vascular complications in women with severe pre-eclampsia. The pilot randomised controlled NOH-PE trial. Thromb Haemost. 2011;106(6):1053-61.*

101 *Haddad B, Winer N, Chitrit Y, Houfflin-Debarge V, Chauleur C, Bages K, et al. Enoxaparin and Aspirin Compared With Aspirin Alone to Prevent Placenta-Mediated Pregnancy Complications: A Randomised Controlled Trial. Obstet Gynecol. 2016;128(5):1053-63.*

102 *Groom KM, McCowan LM, Mackay LK, Lee AC, Said JM, Kane SC, et al. Enoxaparin for the prevention of preeclampsia and intrauterine growth restriction in women with a history: a Randomised trial. Am J Obstet Gynecol. 2017;216(3):296.e1-.e14.*

103 *Llurba E, Bella M, Burgos J, Mazarico E, Gómez-Roig MD, De Diego R, et al. Early Prophylactic Enoxaparin for the Prevention of Preeclampsia and Intrauterine Growth Restriction: A Randomised Trial. Fetal Diagn Ther. 2020;47(11):824-33.*

104 *Sergio F, Maria Clara D, Gabriella F, Giorgia S, Sara De Carolis, Giancarlo P, et al. Prophylaxis of recurrent preeclampsia: low-molecular-weight heparin plus low-dose aspirin versus low-dose aspirin alone. Hypertens Pregnancy. 2006;25(2):115-27.*

105 *Abdel Razik M, El-Berry S, Abosereah M, Edris Y, Sharafeldeen A. Prophylactic treatment for preeclampsia in high-risk teenage primigravidae with nitric oxide donors: a pilot study. J Matern Fetal Neonatal Med. 2016;29(16):2617-20.*

106 *Camarena Pulido EE, García Benavides L, Panduro Barón JG, Pascoe Gonzalez S, Madrigal Saray AJ, García Padilla FE, et al. Efficacy of L-arginine for preventing preeclampsia in high-risk pregnancies: A double-blind, Randomised, clinical trial. Hypertens Pregnancy. 2016;35(2):217-25.*

107 *Lees C, Valensise H, Black R, Harrington K, Byiers S, Romanini C, et al. The efficacy and fetal-maternal cardiovascular effects of transdermal glyceryl trinitrate in the prophylaxis of pre-eclampsia and its complications: a Randomised double-blind placebo-controlled trial. Ultrasound Obstet Gynecol. 1998;12(5):334-8*

108 *Chiswick C, Reynolds RM, Denison F, Drake AJ, Forbes S, Newby DE, et al. Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2015;3(10):778-86.*

109 *Nascimento IBD, Sales WB, Dienstmann G, Souza MLR, Fleig R, Silva JC. Metformin for prevention of cesarean delivery and large-for-gestational-age newborns in non-diabetic obese pregnant women: a Randomised clinical trial. Arch Endocrinol Metab. 2020;64(3):290-7.*

110 *Syngelaki A, Nicolaides KH, Balani J, Hyer S, Akolekar R, Kotecha R, et al. Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus. N Engl J Med. 2016;374(5):434-43.*

111 *Pérez-López FR, Pasupuleti V, Mezones-Holguin E, Benites-Zapata VA, Thota P, Deshpande A, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of Randomised controlled trials. Fertil Steril. 2015;103(5):1278-88.e4.*

112 *Ramos-Trautmann G, González L, Díaz-Luquis G, Pérez CM, Palacios C. Inverse Association between Vitamin D Status and Diabetes in a Clinic Based Sample of Hispanic Adults in Puerto Rico. Diabetes Res (Fairfax). 2015;1(1):5-11.*

113 *Choi A, Noh Y, Park SH, Choe SA, Shin JY. Exploration of Proton Pump Inhibitors Use During Pregnancy and Preeclampsia. JAMA Netw Open. 2021;4(9):e2124339.*

114 *Hastie R, Bergman L, Cluver CA, Wikman A, Hannan NJ, Walker SP, et al. Proton Pump Inhibitors and Preeclampsia Risk Among 157 720 Women. Hypertension. 2019;73(5):1097-103.*

115 *World Health Organization. WHO recommendations on maternal and newborn care for a positive postnatal experience. Geneva: World Health Organization; 2022. Available from: https://www.who.int/publications/i/item/9789240045989*

116 *Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med. 2015 Jan 29;372(5):407-17. doi: 10.1056/NEJMoa1404595.*

117 *van Oostwaard MF, Langenveld J, Schuit E, Bekedam DJ, Bloemenkamp KWM, van den Akker ESA, et al. Hypertensive disorders of pregnancy: recurrence and long-term maternal health. Am J Obstet Gynecol. 2015 Jan;212(1):62.e1-62.e17. doi:10.1016/j.ajog.2014.07.015. PMID: 25025935.*

118 *1. World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia [Internet]. Geneva: World Health Organization; 2021 [cited 2024 Month Day]. Available from: https://www.who.int/publications/i/item/9789240045989*

119 *Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. The International Society for the Study of Hypertension in Pregnancy (ISSHP) guideline for the management of hypertensive disorders of pregnancy. Pregnancy Hypertens. 2023;32:100215. doi:10.1016/j.preghy.2023.100215.*

120 *WHO recommendations on drug treatment for non-severe hypertension in pregnancy. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.Available from: https://www.who.int/publications/i/item/9789240008435*

121 *Tita AT, Szychowski JM, Boggess K, Saade G, Longo S, Clark EAS, et al. Treatment for mild chronic hypertension during pregnancy: secondary analysis of the CHAP Trial. Lancet Glob Health. 2023 Apr;11(4):e512-e523. doi:10.1016/S2214-109X(23)00042-3. PMID: 36925172.*

122 *FIGO Safe Motherhood and Newborn Health Committee. FIGO statement: Resource-stratified guidelines for hypertensive disorders of pregnancy. Int J Gynaecol Obstet. 2023;160(S1 Suppl 1):S26–S29. doi:10.1002/ijgo.14540.*

123 *Kumar M., Meena J., Gupta U., Singh A., Jain N. Management of early onset severe preeclampsia in a tertiary hospital in India: Does expectant management alter perinatal outcome? Indian J. Med. Sci. 2011;65:535–542. doi: 10.4103/0019-5359.109903.*

124 *Sarsam D.S., Shamden M., Al Wazan R. Expectant versus aggressive management in severe preeclampsia remote from term. Singap. Med. J. 2008;49:698–703.*

125 *Abdel-Hady E.-S., Fawzy M., El-Negeri M., Nezar M., Ragab A., Helal A.S. Is expectant management of early-onset severe preeclampsia worthwhile in low-resource settings? Arch. Gynecol. Obstet. 2010;282:23–27. doi: 10.1007/s00404-009-1209-7.*

126 *Kluger Y, Ben-ishay O, Sartelli M, Ansaloni L, Abbas AE, Agresta F, et al. World society of emergency surgery study group initiative on timing of acute care surgery classification (TACS) World J Emerg Surg. 2013;8(1):17. doi: 10.1186/1749-7922-8-17.*

127 *Inta A, Tongsong T, Srisupundit K. Pregnancy Outcomes of Conservative Management in Preeclampsia with Severe Features. J Clin Med. 2023 Oct 4;12(19):6360. doi: 10.3390/jcm12196360. PMID: 37835004; PMCID: PMC10573983.*

128 *Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000;183:S1–22.*

129 *Sibai BM. Management of late preterm and early-term pregnancies complicated by mild gestational hypertension/pre-eclampsia. Semin Perinatol 2011;35:292–6.*

130 *C.A. Crowther, A.M. Bouwmeester, H.M. Ashurst, Does admission to hospital for bed rest prevent disease progression or improve fetal outcome in pregnancy complicated by non-proteinuric hypertension? Br. J. Obstet. Gynaecol. 99 (1992) 13–17.*

131 *M.F. Mottola, M.H. Davenport, S.M. Ruchat, et al. No. 367-2019 Canadian Guideline for Physical Activity throughout Pregnancy. J. Obstet. Gynaecol. Can. 2018;40:1528-37.*

132 *Society for Maternal-Fetal Medicine (SMFM). SMFM Consult Series #58: Use of antenatal corticosteroids. Am J Obstet Gynecol. 2023 Apr;228(4):B10-B20. doi:10.1016/j.ajog.2023.02.001. PMID: 36763933.*

133 *Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation in women at risk of preterm birth. Cochrane Database Syst Rev. 2017 Mar 13;3:CD004454. doi:10.1002/14651858.CD004454.pub3. PMID: 28288288.*

134 *Crowther CA, McKinlay CJ, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth. NEJM. 2019;380(11):1027-1037.*

135 *Balogun OA, Sibai BM. Counseling, management, and outcome in women with severe preeclampsia at 23 to 28 weeks' gestation. Clin Obstet Gynecol 2017;60:183–9.*

136 *World Health Organization. WHO recommendations on interventions to improve preterm birth outcomes – 2023 update [Internet]. Geneva: World Health Organization; 2023 [cited 2024 Month Day]. Available from: https://www.who.int/publications/i/item/9789240062658*

137 *Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med. 2016;374(14):1311-1320.*

138 *McKinlay CJ, Crowther CA, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth. Cochrane Database Syst Rev. 2023;3:CD004454.*

139 *Chappell LC, Brocklehurst P, Green ME, et al. Planned early delivery versus expectant management for preterm preeclampsia. Lancet. 2019;394(10204):1181-1190.*

140 *Crowther CA, Middleton PF, Voysey M, et al. Magnesium sulphate for fetal neuroprotection in preterm birth: an updated meta-analysis. Lancet. 2023;401(10375):451-462.*

141 *Rouse DJ, Hirtz DG, Thom E, et al. Long-term outcomes after antenatal $MgSO_4$ in preterm infants. JAMA Pediatr. 2021;175(6):e210007.*

142 *Koopmans CM, Bijlenga D, Groen H, Vijgen SMC, Aarnoudse JG, Bekedam DJ, 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 Sep 19;374(9694):979-88. doi:10.1016/S0140-6736(09)60736-4. PMID: 19656558.*

143 *Cluver C, Novikova N, Koopmans CM, West HM. Interventions for treating pre-eclampsia: a Cochrane systematic review update. Cochrane Database Syst Rev. 2022 Mar 14;3:CD009109. doi:10.1002/14651858.CD009109.pub3. PMID: 35286508.*

144 *Society for Maternal-Fetal Medicine (SMFM). Expectant management versus delivery in term preeclampsia: a systematic review. Am J Obstet Gynecol. 2021 Feb;224(2):S678-S679. doi:10.1016/j.ajog.2020.12.1232.*

145 *Broekhuijsen K, van Baaren GJ, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): a multicentre, open-label randomised controlled trial. N Engl J Med. 2019 Mar 14;380(11):1027-37. doi:10.1056/NEJMoa1813480. PMID: 30865774.*

146 *Vigil-De Gracia P, Ludmir J, Ng J, Soto E, Alvarado-Duran A, Vallejos-Gómez J, et al. Expectant management of preeclampsia remote from term: The FLAME study. Am J Obstet Gynecol. 2020 Jun;222(6):606.e1-606.e15. doi:10.1016/j.ajog.2020.01.018. PMID: 31954120.*

147 *Society for Maternal-Fetal Medicine (SMFM). SMFM Consult Series #64: Preeclampsia with severe features at late preterm gestations. Am J Obstet Gynecol. 2022 Apr;226(4):B2-B14. doi:10.1016/j.ajog.2022.02.001. PMID: 35314033.*

148 *Smith JM, Lowe RF, Fullerton J, et al. Anticonvulsants for pre-eclampsia. Cochrane Database Syst Rev. 2023;3:CD004454. doi:10.1002/14651858.CD004454.pub4.*

149 *Estcourt LJ, Malouf R, Hopewell S, Doree C, Van Veen J. Prophylactic platelet transfusions prior to surgery for people with thrombocytopenia. Cochrane Database Syst Rev. 2022;3:CD012779. doi:10.1002/14651858.CD012779.pub3.*

150 *Society for Maternal-Fetal Medicine. SMFM Consult Series #47: Hematologic conditions in pregnancy. Am J Obstet Gynecol. 2021;224(4):B2-B28. doi:10.1016/j.ajog.2020.11.038.*

151 *Woudstra DM, Chandra S, Hofmeyr GJ, Dowswell T. Corticosteroids for HELLP syndrome. Cochrane Database Syst Rev. 2021;5:CD008148. doi:10.1002/14651858.CD008148.pub5.*

152 *Gibbons C, O'Reilly M, Benedetti TJ, et al. SMFM Consult Series #64: Systemic hypertension in pregnancy. Am J Obstet Gynecol. 2022;227(4):B2-B26. doi:10.1016/j.ajog.2022.06.001.*

153 *Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol. 2004;103(5 Pt 1):981-91. doi:10.1097/01.AOG.0000126245.35811.2a.*

154 *Juliana Perez Botero, Jennifer Jury McIntosh; Labor and delivery: DIC, HELLP, preeclampsia. Hematology Am Soc Hematol Educ Program 2023; 2023 (1): 737–744.*

155 *Fonseca JE, Mendez F, Cataño C, et al. Dexamethasone treatment does not improve the outcome of women with HELLP syndrome: a double-blind, placebo-controlled, randomized clinical trial. BJOG. 2005;112(2):211-215. doi:10.1111/j.1471-0528.2004.00333.x.*

156 *Collis RE, Collins PW. Haemostatic management of obstetric haemorrhage. Anaesthesia. 2015;70 Suppl 1:78–86, e27–e28. doi:10.1111/anae.12913*

157 *Iba T, Levy JH, Warkentin TE, et al. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost. 2019;17(11):1989-1994. doi:10.1111/jth.14578.*

158 *Royal College of Obstetricians and Gynaecologists. Major Obstetric Haemorrhage and Coagulopathy (Green-top Guideline No. 47). London: RCOG; 2022 [cited 2024 Jun 10]. Available from: https://www.rcog.org.uk*

159 *Hunt BJ, Allard S, Keeling D, et al. A practical guideline for the haematological management of major haemorrhage. Br J Haematol. 2015;170(6):788-803. doi:10.1111/bjh.13580.*

160 *Franchini M, Marano G, Veropalumbo E, et al. The use of fibrinogen concentrate for the management of trauma-related bleeding: a systematic review and meta-analysis. Blood Transfus. 2021;19(6):463-475. doi:10.2450/2021.0239-20.*

161 *Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care. 2018;6:15. doi:10.1186/s40560-018-0287-7.*

162 Norwitz ER. Preeclampsia: management and prognosis. [Internet]. Waltham MA: UpToDate Inc; 2020 [cited 2020 May 5]. Available from: https://www.uptodate.com

163 Alanis MC, Robinson CJ, Hulsey TC, Ebeling M, Johnson DD. Early-onset severe preeclampsia: induction of labor vs elective cesarean delivery and neonatal outcomes. Am J Obstet Gynecol 2008;199:262.e1–6. (Level II-3)

164 Blackwell SC, Redman ME, Tomlinson M, Landwehr JB Jr, Tuynman M, Gonik B, et al. Labor induction for the preterm severe pre-eclamptic patient: is it worth the effort? J Matern Fetal Med 2001;10:305–11. (Level II-3)

165 Sibai BM. Evaluation and management of severe preeclampsia before 34 weeks' gestation. Publications Committee, Society for Maternal–Fetal Medicine. Am J Obstet Gynecol 2011;205:191–8. (Level III)

166 Who recommendations for prevention and treatment of preeclampsia and eclampsia, Implications and Actions; 2013

167 Audibert F, Friedman SA, Fréchette L, et al. Clinical practice guideline: management of hypertensive disorders of pregnancy. J Obstet Gynaecol Can. 2018;40(7):e542-e571. doi:10.1016/j.jogc.2018.05.004.

168 American College of Obstetricians and Gynecologists. Chronic hypertension in pregnancy. ACOG Practice Bulletin No. 203. Obstet Gynecol. 2022;139(1):e1-e19. doi:10.1097/AOG.0000000000004600.

169 World Health Organization. WHO recommendation on aspirin for prevention of preeclampsia. Geneva: WHO; 2020 [cited 2024 Jun 10]. Available from: https://www.who.int/publications/i/item/9789240007789

170 American College of Obstetricians and Gynecologists. Physical activity and exercise during pregnancy and the postpartum period. ACOG Committee Opinion No. 804. Obstet Gynecol. 2020;135(4):e178-e188. doi:10.1097/AOG.0000000000003772.

171 Royal College of Obstetricians and Gynaecologists. Good Practice No. 11: Reducing Risks in Pregnancy. London: RCOG; 2019 [cited 2024 Jun 10]. Available from: https://www.rcog.org.uk

172 Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia. Circulation. 2019;140(3):225-235. doi:10.1161/CIRCULATIONAHA.118.038080.

173 Magee LA, von Dadelszen P, Singer J, et al. Do labetalol and methyldopa impact pregnancy outcomes? Secondary analysis of the CHIPS trial. BJOG. 2017;124(1):11-21. doi:10.1111/1471-0528.14110.

174 Cruz MO, Gao W, Hibbard JU. What is the optimal time for delivery in women with gestational hypertension? Am J Obstet Gynecol 2012;207:214 e1e6

175 Ram M, Berger H, Geary M, et al. Timing of Delivery in Women With Chronic Hypertension. Obstet Gynecol 2018;132:669e77.

176 *Hutcheon JA, Lisonkova S, Magee LA, et al. Optimal timing of delivery in pregnancies with pre-existing hypertension. BJOG 2011;118:49e54.*

177 *Leduc D, Senikas V, Lalonde AB. No. 235-Active Management of the Third Stage of Labour: Prevention and Treatment of Postpartum Hemorrhage. J Obstet Gynaecol Can 2018;40:e841-55.*

178 *Magee LA, Pels A, Helewa M, et al. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. J Obstet Gynaecol Can. 2014;36(5):416-441. doi:10.1016/S1701-2163(15)30588-0*

179 *Association of Anaesthetists of Great Britain and Ireland. Guidelines for the management of severe pre-eclampsia. Anaesthesia. 2011;66(10):943-949. doi:10.1111/j.1365-2044.2011.06861.x*

180 *National Institute for Health and Care Excellence. Intrapartum care for healthy women and babies [CG190]. London: NICE; 2019 [updated 2022; cited 2024 Jun 10]. Available from: https://www.nice.org.uk/guidance/cg190*

181 *World Health Organization. WHO recommendations for prevention and treatment of postpartum haemorrhage. Geneva: WHO; 2018 [cited 2024 Jun 10]. Available from: https://www.who.int/publications/i/item/9789241550425*

182 *Brown MC, Best KE, Pearce MS, et al. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol. 2018;33(5):763-771. doi:10.1007/s10654-018-0376-x.*

183 *Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy. J Obstet Gynaecol Can. 2014;36(5):416-441. doi:10.1016/S1701-2163(15)30588-0.*

184 *American Academy of Pediatrics. Breastfeeding and the use of human milk. Pediatrics. 2012;129(3):e827-e841. doi:10.1542/peds.2011-3552.*

185 *Brouwers L, van der Meiden-van Roest AJ, Savelkoul C, et al. Recurrence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. BJOG. 2018;125(13):1642-1654. doi:10.1111/1471-0528.15394.*

186 *Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women. Circulation. 2011;123(11):1243-1262. doi:10.1161/CIR.0b013e31820faaf8.*

187 *Staff AC, Redman CWG, Williams D, et al. Pregnancy and long-term maternal cardiovascular health: progress through harmonization of research cohorts and biobanks. Hypertension. 2019;73(2):318-326. doi:10.1161/HYPERTENSIONAHA.118.12223.*

188 *Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2017;10(2):e003497. doi:10.1161/CIRCOUTCOMES.116.003497.*