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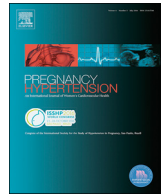
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## The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice

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These recommendations from the ISSHP are based upon available literature and expert opinion. It is intended that this be a 'living' document, to be updated when needed as more research becomes available to influence good clinical practice. Unfortunately there is a relative lack of high quality randomised trials in the field of Hypertension in Pregnancy compared with studies in essential hypertension outside of pregnancy and ISSHP encourages greater funding and uptake of collaborative research in this field. Accordingly, the quality of evidence for the recommendations in this document has not been graded, though relevant references and explanations are provided for each recommendation. The document will be a 'living' guideline and we hope to be able to grade recommendations in the future.

Guidelines and recommendations for management of hypertension in pregnancy are typically written for implementation in an ideal setting. It is acknowledged that in many parts of the world, it will not be possible to adopt all of these recommendations; for this reason, options for management in less-resourced settings are discussed separately in relation to diagnosis, evaluation, and treatment.

This document has been endorsed by the International Society of Obstetric Medicine (ISOM) and the Japanese Society for the Study of Hypertension in Pregnancy (JSSHP).

### 1. Key points

All units managing hypertensive pregnant women should maintain and review uniform departmental management protocols and conduct regular audits of maternal & fetal outcomes.

The cause(s) of pre-eclampsia and the optimal clinical management of the hypertensive disorders of pregnancy remain uncertain; therefore, we recommend that every hypertensive pregnant woman be offered an opportunity to participate in research, clinical trials and follow-up studies.

#### 1.1. Classification

1. Hypertension in pregnancy may be chronic (pre-dating pregnancy or diagnosed before 20 weeks of pregnancy) or de novo (either pre-eclampsia or gestational hypertension).
2. Chronic hypertension is associated with adverse maternal and fetal outcomes and is best managed by tightly controlling maternal blood pressure (BP 110–140/85 mmHg), monitoring fetal growth and repeatedly assessing for the development of pre-eclampsia and maternal complications. This can be done in an outpatient setting.
3. White-coat hypertension refers to elevated office/clinic ( $\geq 140/90$  mmHg) blood pressure but normal blood pressure measured at home or work ( $< 135/85$  mmHg); it is not an entirely benign condition and conveys an increased risk for pre-eclampsia.
4. Masked hypertension is another form of hypertension, more difficult to diagnose, characterised by blood pressure that is normal at a clinic or office visit but elevated at other times, most typically diagnosed by 24 h ambulatory BP monitoring (ABPM) or automated home blood pressure monitoring (HBPM).
5. Gestational hypertension is hypertension arising de novo after 20 weeks' gestation in the absence of proteinuria and without

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biochemical or haematological abnormalities. It is usually not accompanied by fetal growth restriction. Outcomes in pregnancies complicated by gestational hypertension are normally good, but about a quarter of women with gestational hypertension (particularly those who present at < 34 weeks) will progress to pre-eclampsia and have poorer outcomes.

6. Pre-eclampsia is a complex medical disorder; world-wide, each year, it is responsible for over 500,000 fetal and neonatal deaths and over 70,000 maternal deaths. Pre-eclampsia can deteriorate rapidly and without warning; we do not recommend classifying it as 'mild' or 'severe'.
7. Proteinuria is not mandatory for a diagnosis of pre-eclampsia. Rather, this is diagnosed by the presence of de novo hypertension after 20 weeks' gestation accompanied by proteinuria **and/or** evidence of maternal acute kidney injury, liver dysfunction, neurological features, hemolysis or thrombocytopenia, **and/or** fetal growth restriction. Pre-eclampsia may develop or be recognised for the first time intra-partum or early post-partum in some cases.
8. The HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low platelets) is one (serious) manifestation of pre-eclampsia and not a separate disorder.

#### 1.2. Diagnosis of hypertension and proteinuria

9. Home blood pressure monitoring is a useful adjunct in the management of chronic hypertension and is mandatory in the management of white-coat hypertension.
10. Proteinuria is optimally assessed by screening with automated dipstick urinalysis and then if positive quantifying with a urine protein/creatinine ratio. A ratio  $\geq 30$  mg/mmol (0.3 mg/mg) is abnormal.

#### 1.3. Prediction and prevention of pre-eclampsia and associated complications

11. No first or second trimester test or set of tests can reliably predict the development of all cases of pre-eclampsia; however, a combination of maternal risk factors, blood pressure, Placental Growth Factor (PIGF) and uterine artery Doppler can select women who may benefit from 150 mg/day of aspirin to prevent pre-term (before 37 weeks gestation) but not term pre-eclampsia. ISSHP supports first trimester screening for risk of pre-eclampsia when this can be integrated into the local health system, although the cost effectiveness of this approach remains to be established.
12. ISSHP recommends that women with established strong clinical risk factors for pre-eclampsia (i.e., prior pre-eclampsia, chronic hypertension, pre-gestational diabetes, maternal BMI > 30 kg/m<sup>2</sup>, antiphospholipid syndrome and receipt of assisted reproduction) be treated, ideally before 16 weeks but definitely before 20 weeks, with low dose aspirin (defined as 75–162 mg/day, as studied in RCTs).
13. We recommend at this stage against the routine clinical use of 'rule-in' or 'rule-out' tests (specifically PIGF or sFLT-1/PIGF ratio) for pre-eclampsia, which should continue to be evaluated within the context of clinical trials.
14. Women considered at increased risk for pre-eclampsia as above should receive supplemental calcium (1.2–2.5 g/day) if their intake is likely to be low (< 600 mg/day), in addition to aspirin. When intake cannot be assessed or predicted it is reasonable to give calcium.
15. Low molecular weight heparin is not indicated to prevent pre-eclampsia, even with a history of prior early onset pre-eclampsia.
16. Women should exercise during pregnancy to maintain health, appropriate body weight and reduce the likelihood of hypertension.

#### 1.4. Management

17. Regardless of the hypertensive disorder of pregnancy, blood pressure requires urgent treatment in a monitored setting when severe (> 160/110 mmHg); acceptable agents for this include oral nifedipine or intravenous labetalol or hydralazine. Oral labetalol may be used if these treatments are unavailable.
18. Regardless of the hypertensive disorder of pregnancy, blood pressures consistently at or above 140/90 mmHg in clinic or office (or  $\geq 135/85$  mmHg at home) should be treated, aiming for a target diastolic blood pressure of 85 mmHg in the office (and systolic blood pressure of 110–140 mmHg) to reduce the likelihood of developing severe maternal hypertension and other complications such as low platelets and elevated liver enzymes with symptoms. Antihypertensive drugs should be reduced or ceased if diastolic BP falls below 80 mmHg. Acceptable agents include oral methyldopa, labetalol, oxprenolol, nifedipine, and 2nd or 3rd line agents include hydralazine and prazosin.
19. Women with pre-eclampsia should be assessed in hospital when first diagnosed; thereafter, some may be managed as outpatients once it is established that their condition is stable and they can be relied upon to report problems and monitor their blood pressure.
20. Women with pre-eclampsia who have proteinuria and severe hypertension, or hypertension with neurological signs or symptoms, should receive magnesium sulphate (MgSO<sub>4</sub>) for convulsion prophylaxis.
21. Fetal monitoring in pre-eclampsia should include an initial assessment to confirm fetal well-being. In the presence of fetal growth restriction, a recommended schedule for serial fetal surveillance with ultrasound is detailed within these recommendations.
22. Maternal monitoring in pre-eclampsia should include: blood pressure monitoring, repeated assessments for proteinuria if it is not already present, clinical assessment including clonus, and a minimum of twice-weekly blood tests for hemoglobin, platelet count, and tests of liver and renal function, including uric acid, the latter being associated with worse maternal and fetal outcomes.
23. Women with pre-eclampsia should be delivered if they have reached 37 weeks' (and zero days) gestation or if they develop any of the following:
  - a. repeated episodes of severe hypertension despite maintenance treatment with three classes of antihypertensive agents;
  - b. progressive thrombocytopenia;
  - c. progressively abnormal renal or liver enzyme tests;
  - d. pulmonary oedema;
  - e. abnormal neurological features such as severe intractable headache, repeated visual scotomata, or convulsions;
  - f. Non-reassuring fetal status.

#### 1.5. Postpartum care

24. In the early post-partum period, women with pre-eclampsia should be considered at high risk for pre-eclamptic complications for at least 3 days and should have their BP and clinical condition monitored at least every four hours while awake. Antihypertensives administered antenatally should be continued, and consideration should be given to treating any hypertension before day six post-partum with antihypertensive therapy. Thereafter, antihypertensive therapy may be withdrawn slowly over days, but not ceased abruptly. It is important to note that eclamptic seizures may develop for the first time in the early post-partum period.
25. Non-steroidal anti-inflammatory drugs (NSAIDs) for postpartum analgesia should be avoided in women with pre-eclampsia unless other analgesics are not working; this is especially important if they have known renal disease, or pre-eclampsia is associated with

placental abruption, acute kidney injury (AKI), or other known risk factors for AKI (e.g., sepsis, post-partum hemorrhage).

26. All women should be reviewed at 3 months post-partum to ensure that BP, urinalysis, and any laboratory abnormalities have normalised. If proteinuria or hypertension persists then appropriate referral for further investigations should be initiated.
27. There are significant long-term cardiovascular risks for women with chronic hypertension and those who have had gestational hypertension or pre-eclampsia. One initial recommendation may be to aim to achieve pre-pregnancy weight over 12 months and to limit inter-pregnancy weight gain through healthy lifestyle.
28. Annual medical review is advised life-long and all such women should adopt a healthy lifestyle that includes exercise, eating well and aiming for ideal body weight.

## 2. Introduction

World-wide there is disagreement about many aspects of the classification, diagnosis and management of the hypertensive disorders of pregnancy. This lack of consensus hampers our ability to study not only the immediate rates of adverse maternal and fetal outcomes for the various hypertensive disorders in pregnancy, particularly pre-eclampsia, but also the long term health outcomes of women and babies who survive this condition. It also impacts upon research into the pathophysiology of this condition and has almost certainly delayed the development of effective screening tests and treatments, leading to poorer pregnancy outcomes.

One scholarly review of available guidelines has shown broad agreement in the following areas [1]:

1. Definitions of hypertension, proteinuria, chronic hypertension and gestational hypertension;
2. Prevention of pre-eclampsia with low dose aspirin & supplemental calcium (if low calcium intake);
3. Treatment of severe hypertension;
4. Use of MgSO<sub>4</sub> for eclampsia & 'severe' pre-eclampsia;
5. Use of antenatal corticosteroids to enhance fetal lung maturity at < 34 weeks' gestation if delivery is likely within the next 7 days;
6. Delivery for pre-eclampsia at term; and
7. Oxytocin in the third stage of labour.

However, in this analysis there was little or no agreement on:

1. The definition of pre-eclampsia;
2. Target blood pressure when hypertension is not severe;
3. Timing of delivery for women with chronic hypertension, gestational hypertension, or preterm pre-eclampsia;
4. Use of MgSO<sub>4</sub> for pre-eclampsia that is not 'severe'; and
5. Post-partum maternal monitoring.

Following the 2016 World Congress of the International Society for the Study of Hypertension in Pregnancy (ISSHP), it was agreed that a single up-to-date guideline should be available that reflects current evidence, and both the collective expertise of the ISSHP membership and the leadership role that ISSHP would like to take in improving hypertension-related outcomes in pregnancy. Following the Congress, ISSHP charged a small group of clinician researchers to update the last statements from ISSHP 2013 and 2014 [2,3].

This set of recommendations provides practical advice on classification, diagnostic criteria and management for all clinicians, everywhere, who are involved in the management of women with hypertension in pregnancy.

## 3. Classification of the hypertensive disorders of pregnancy

The recommended classification for hypertensive disorders of

pregnancy is as follows:

*Hypertension known before pregnancy or present in the first 20 weeks:*

1. Chronic hypertension
  - a. Essential
  - b. Secondary
2. White-coat hypertension
3. Masked Hypertension

*Hypertension arising de novo at or after 20 weeks:*

1. Transient gestational hypertension
2. Gestational hypertension
3. Pre-eclampsia\* – de novo or superimposed on chronic hypertension

*\*The term 'severe pre-eclampsia' should not be used in clinical practice*

Notes:

- Pre-eclampsia, transient gestational hypertension and gestational hypertension are characterised by the new onset of hypertension (blood pressure  $\geq 140$  mmHg systolic or  $\geq 90$  mmHg diastolic) at or after 20 weeks' gestation [4]; as such, it is important to have normal blood pressure documented either pre-pregnancy or in early pregnancy before there has been much pregnancy-related decrease in blood pressure. Otherwise, a blood pressure first measured after 12 weeks' gestation that is normal may reflect the usual fall in BP from baseline that occurs by the end of the first trimester; in which case there may still be underlying chronic hypertension that has been masked by this first trimester BP fall.
- Transient gestational hypertension is hypertension that arises in the 2nd or 3rd trimester. The hypertension is usually detected in the clinic but then settles with repeated BP readings, such as those taken over the course of several hours in a Day Assessment Unit. This differs from white-coat hypertension that, by definition, must be present from early pregnancy. Transient gestational hypertension is associated with a 40% risk of developing true gestational hypertension or pre-eclampsia in the remainder of the pregnancy [5], a fact that highlights the importance of carefully following-up such women.
- When a woman presents with hypertension in pregnancy at or after 20 weeks' gestation and the earlier blood pressure is unknown, she should be managed in pregnancy as if she has gestational hypertension or pre-eclampsia. Appropriate investigations should be done after pregnancy to determine if she has underlying chronic hypertension. This will generally be apparent because the blood pressure will not have normalised within 3 months post-partum.
- Masked hypertension is another form of hypertension, characterised by blood pressure that is normal at a clinic or office visit but elevated at other times, most typically diagnosed by 24 h ambulatory BP monitoring (ABPM) or automated home blood pressure monitoring (HBPM). Such a diagnosis is generally sought when a patient has unexplained abnormalities consistent with target organ damage from hypertension but no apparent hypertension. Whilst this is a form of chronic hypertension, the prevalence of masked hypertension and its significance in pregnancy are less well-studied; for now, we don't recommend seeking this diagnosis in the absence of the above features (i.e., unexplained chronic kidney disease, left ventricular hypertrophy or retinopathy recognised early in pregnancy).

- Although ISSHP has formerly published a statement documenting ‘severe pre-eclampsia’, we agree with the position of ACOG and others that pre-eclampsia may become a major threat to mother and baby at any stage and classification into ‘mild’ or ‘severe’ disease can be erroneous or misleading to less experienced clinicians. ACOG has eliminated the diagnosis of ‘severe pre-eclampsia’ and instead discusses ‘Pre-eclampsia with or without severe features’, a sensible clinical approach.

#### 4. Diagnosis of the hypertensive disorders of pregnancy

##### What constitutes hypertension in pregnancy?

###### *Hypertension*

- Defined as systolic BP  $\geq 140$  and/or diastolic BP  $\geq 90$  mmHg
- Blood pressure should be repeated to confirm true hypertension
  - o if blood pressure is severe (SBP  $\geq 160$  and/or DBP  $\geq 110$  mmHg) then the blood pressure should be confirmed within 15 min;
  - o for less severe blood pressure, repeated readings should be taken over a few hours.
- Use a liquid crystal sphygmomanometer
  - o If this is unavailable, use a validated and appropriately calibrated automated device

###### Notes:

- Mercury sphygmomanometry is no longer available. The best alternative may be a liquid-crystal sphygmomanometer [6], but these are not yet widely available. Correct cuff size is important, using a ‘large’ cuff if the mid upper arm circumference is above 33 cm.
- Aneroid devices are used commonly for blood pressure measurement, but they may be inaccurate and need to be regularly calibrated. One smaller study found that 50% of aneroid devices had at least one BP reading  $> 10$  mmHg out compared to the same error in only 10% of mercury devices [7].
- Use of an automated device is preferable to use of an aneroid device if the automated device has been shown to be reliable in both pregnancy and pre-eclampsia specifically [8,9]; some devices may be accurate for women with chronic or gestational hypertension in pregnancy but not for women with pre-eclampsia [10]. A list of generally validated home BP monitors, not specific for pregnancy, is available at: <http://bhsoc.org/bp-monitors/bp-monitors/>.

##### What constitutes abnormal Proteinuria in pregnancy?

- Proteinuria should be assessed initially by automated dipstick urinalysis when possible; if not available, careful visual dipstick urinalysis will suffice.
- If positive ( $\geq 1+$ , 30 mg/dl) then spot urine protein/creatinine (PCr) ratio should be performed
- A PCr ratio  $\geq 30$  mg/mmol (0.3 mg/mg) is abnormal
- A negative dipstick test can usually be accepted and further PCr testing is not required at that time
- Proteinuria is **not** required for a diagnosis of pre-eclampsia
- Massive proteinuria ( $> 5$  g/24 h) is associated with more severe neonatal outcomes

###### Notes:

- The gold standard for diagnosing abnormal proteinuria in pregnancy is a 24-h urinary protein  $\geq 300$  mg per day, though this is more a time-honoured value than one with high scientific proof [11]; ideally 24hr creatinine excretion will also be used to assess adequacy of collection as without this, the estimated daily urine protein excretion is often incorrect [12].
- In practice, the 24 h urine protein measurement will mostly be replaced with a spot urine protein/creatinine ratio, a value  $\geq 30$  mg per mmol ( $= 0.26$  mg/mg, usually ‘rounded’ to 0.3 mg/mg) representing significant proteinuria [13–15]; this eliminates the inherent difficulties in undertaking 24-h urine collections and speeds up the process of decision-making.
- 24 h urine collection for proteinuria is still indicated to confirm nephrotic syndrome which has implications for thromboprophylaxis.
- Dipstick testing is not perfect and a small number of proteinuric cases may be missed by a negative dipstick test; a urine PCr below 30 mg/mmol also occasionally gives a false negative result for abnormal 24hr. proteinuria but in such cases the total protein excretion is usually  $< 400$  mg/day [14].
- At present there is insufficient data to recommend using urinary albumin/creatinine ratio but this may change when more research becomes available [13,16], such as the results of DAPPA (Diagnostic Accuracy in Pre-eclampsia using Proteinuria Assessment, RCTN82607486).
- When neither 24 h nor PCr measures of proteinuria are available, dipstick testing provides reasonable assessment of true proteinuria, particularly when values are greater than 1 g per litre i.e. 2+ [15,17].
- There is ongoing debate on the importance of the absolute quantitation of proteinuria. Some believe that the degree of proteinuria provides little additional risk stratification (except in nephrotic syndrome) and it should not be included in considerations of the severity of pre-eclampsia [15,18–20]. Others have shown that massive proteinuria ( $> 5$  g/24 h) is associated with more severe neonatal outcomes and earlier delivery, and a spot Protein/Creat  $> 900$  mg/mmol (or  $> 500$  mg/mmol if age  $> 35$ ) is associated with worse maternal outcomes [21,22]. For this reason some units may choose to continue measuring proteinuria though it is not recommended that a decision to deliver is based upon the degree of proteinuria.
- If proteinuria is diagnosed but subsequent dipstick tests become negative then further quantification tests are appropriate to see whether or not true proteinuria persists.
- In recent years, gestational proteinuria has been recognised as a real entity. It is unclear exactly how many pregnancies are affected by this condition, defined as the new onset of proteinuria in pregnancy without other obvious features of pre-eclampsia or primary renal disease. Women with gestational proteinuria have blood levels of placental growth factor that are intermediate between those of normal pregnancies and pre-eclampsia, prompting consideration that these women have an early form of pre-eclampsia [23].

The recommended approach to management of these women is to consider three possible outcomes.

1. No features of pre-eclampsia develop throughout pregnancy and proteinuria disappears postpartum;
2. Proteinuria turns out to be the first feature of pre-eclampsia which is defined when the blood pressure subsequently rises or other features of pre-eclampsia develop;
3. The proteinuria persists postpartum and ultimately signifies a

primary renal disease which has coincidentally developed in the pregnancy, an unusual event.

It is therefore recommended to monitor these women more frequently than usual for the remainder of their pregnancy, as well as to assess proteinuria at 3 months postpartum.

### 1. Chronic Hypertension

- Chronic hypertension refers to high blood pressure predating the pregnancy or recognised at < 20 weeks' gestation
- In practice, this is often diagnosed for the first time at the first or early second trimester booking visit
- Ideally, this 'office' or 'clinic' hypertension should be confirmed by 24 h. ABPM or HBPM, or at minimum, after repeated measurements over hours at the same visit or on two consecutive antenatal visits, though this latter approach may not always eliminate a diagnosis of 'white-coat' hypertension
- The majority of cases are due to essential hypertension
- Secondary causes are uncommon
- 'White-coat' hypertension refers to elevated office/clinic ( $\geq 140/90$  mmHg) blood pressure but normal blood pressure measured at home or work ( $< 135/85$  mmHg); it is not an entirely benign condition and conveys an increased risk for pre-eclampsia [24]

#### Notes:

- Many women will not have had their blood pressures measured within months before becoming pregnant. In practice therefore, we rely mostly upon the first trimester blood pressure to define normal or high blood pressure.
- Up to one in four patients with elevated clinic or office blood pressure have 'white coat' hypertension. This diagnosis can be avoided in large part by having clinic or office blood pressures recorded by a nurse, rather than a doctor, preferably using repeated blood pressure readings [25]. We recommend that all women have either HBPM monitoring or 24hr ABPM before a diagnosis of true essential hypertension is accepted.
- Normal values for 24 h. ABPM in pregnancy have been determined [26]; before 22 weeks, blood pressure values should be below: 24 h. average 126/76 mmHg; awake average BP 132/79 mmHg; sleep average BP 114/66 mmHg. These values are slightly lower than those used as thresholds for diagnosing hypertension in non-pregnant women.
- Most automated home blood pressure devices are accurate in pregnancy, but about 25% differ from standard sphygmomanometry devices [27]; therefore, all women should have their home blood pressure device checked (against a calibrated sphygmomanometer or automated device validated for use in pregnancy and pre-eclampsia) before using that device. In the absence of severe hypertension ( $\geq 160/110$  mmHg), we suggest relying on average BP over several days rather than acting upon single readings for women monitoring home blood pressure values.
- Most cases of chronic hypertension are due to essential hypertension, usually accompanied by a family history of hypertension and often by overweight or obesity.
- Secondary causes of hypertension are less common; in the age group of women who conceive, the cause is usually an underlying primary renal parenchymal disorder (such as reflux nephropathy or glomerulonephritis) and less commonly, fibromuscular hyperplasia of

the renal arteries or primary hyperaldosteronism. ISSHP does not recommend routine testing for any secondary cause of hypertension in the absence of clinical clues to these conditions.

ISSHP recommends that all women with chronic hypertension in pregnancy have the following tests performed at first diagnosis. This will provide a baseline reference should suspicion arise later in pregnancy of superimposed pre-eclampsia (which will complicate up to 25% of these pregnancies).

- A full blood count (haemoglobin and platelet count)
- Liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH)] and functions tests [international normalised ratio (INR), serum bilirubin, and serum albumin]
- Serum creatinine, electrolytes, and uric acid\*
- Urinalysis & microscopy, as well as PCR or ACR
  - o Renal ultrasound if serum creatinine or any of the urine testing are abnormal

\*Note: Serum uric acid is not a diagnostic criterion for pre-eclampsia, but elevated gestation-corrected uric acid serum levels are associated with worse maternal and fetal outcomes [28–30] and should prompt a detailed assessment of fetal growth, even in women with gestational hypertension. However, uric acid should not be used to determine the timing of delivery.

### 2. Transient Gestational Hypertension

- Transient gestational hypertension is de novo hypertension that develops at any gestation that resolves without treatment during the pregnancy

#### Notes:

- Transient gestational hypertension is not a benign disorder; it is associated with approximately 20% chance of developing pre-eclampsia and a further 20% chance of developing gestational hypertension. Therefore, such women should receive extra monitoring throughout their pregnancy, ideally including home BP measurements.

### 3. Gestational hypertension (gestational hypertension)

- Gestational hypertension is persistent de novo hypertension that develops at or after 20 weeks' gestation in the absence of features of pre-eclampsia

#### Notes:

- Gestational hypertension is not a uniformly benign condition. The risk of complications is dependent on the gestational age at which it develops. Gestational hypertension is important for two reasons:
  - o Pre-eclampsia may develop in 25% of such women, this rate being higher the earlier the presentation [31]; to date, no tests have reliably predicted which women with gestational hypertension will later develop pre-eclampsia [32]
  - o Gestational hypertension, like pre-eclampsia, is also associated



with cardiovascular disease in the long-term [33–36].

#### 4. Pre-eclampsia

- **Pre-eclampsia is gestational hypertension accompanied by one or more of the following new-onset conditions at or after 20 weeks' gestation:**

1. Proteinuria
2. Other maternal organ dysfunction, including:
  - o Acute kidney injury (AKI) (creatinine  $\geq 90 \mu\text{mol/L}$ ; 1 mg/dL)
  - o liver involvement (elevated transaminases e.g. ALT or AST  $> 40 \text{ IU/L}$ ) with or without right upper quadrant or epigastric abdominal pain)
  - o neurological complications (examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata)
  - o haematological complications (thrombocytopenia – platelet count below  $150,000/\mu\text{L}$ , DIC, hemolysis)
3. Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth)

#### Notes:

- Hyperreflexia occurs in many women with pre-eclampsia and resolves post-partum. However, it is a non-specific finding that is often present in otherwise well young women and is highly subject to observer interpretation. Therefore, ISSHP no longer recommends including this in the diagnostic criteria.
- Headaches in pregnancy are multifactorial. However, in the presence of hypertension, a new headache should be considered to be part of pre-eclampsia until proved otherwise; this is a safe clinical approach.
- Proteinuria is not required for a diagnosis of pre-eclampsia but is present in about 75% of cases [19].
- When resources are available, all asymptomatic women with **de novo hypertension** and no dipstick proteinuria should have the following laboratory investigations performed to evaluate maternal organ dysfunction. Without these, it will be impossible to exclude pre-eclampsia. In some countries, this approach will necessitate referral of patients (of whom some will not have pre-eclampsia) from smaller units where same-day laboratory facilities are not available. Local decision-making strategies will be necessary in these areas.
- Hemoglobin, platelet count (and if decreased, tests of coagulation)
- Serum creatinine
- Liver enzymes
- Serum uric acid
- **HELLP:** The combination of all or some of haemolysis elevated liver enzymes and thrombocytopenia is often referred to as the HELLP syndrome. For clinicians familiar with the management of pre-eclampsia, this constellation of abnormalities signifies a more serious part of the spectrum of this disorder. However, it is still considered part of pre-eclampsia and not a separate disorder. ISSHP endorses this approach in order to reduce confusion amongst those less familiar with the multisystem complications that might occur in pre-eclampsia. In other words, women with features of HELLP syndrome should be considered to have pre-eclampsia so that all other features of pre-eclampsia will be sought and addressed.

- Controversy remains as to whether fetal growth restriction in the context of new onset gestational hypertension, without any other maternal feature of pre-eclampsia, should be considered to define pre-eclampsia. The authors' view was that this should apply; given that pre-eclampsia is most commonly of itself a primary placental disorder.
- Although it is probable that pre-eclampsia can be present in some cases without overt hypertension, ISSHP recommends maintaining new onset hypertension in the diagnosis for now.

#### Pre-eclampsia superimposed upon chronic hypertension

- About 25% of women with chronic hypertension will develop superimposed pre-eclampsia. These rates may be higher in women with underlying renal disease.
- This diagnosis is made when a woman with chronic essential hypertension develops any of the above maternal organ dysfunction consistent with pre-eclampsia.
- Rises in blood pressure *per se* are not sufficient to diagnose superimposed pre-eclampsia, as such rises are difficult to distinguish from the usual increase in blood pressure after 20 weeks' gestation.
- In the absence of pre-existing proteinuria, new-onset proteinuria in the setting of a rise in blood pressure is sufficient to diagnose superimposed pre-eclampsia.
- In women with proteinuric renal disease, an increase in proteinuria in the pregnancy is not sufficient *per se* to diagnose superimposed PE.
- Diagnostic biomarkers (particularly PlGF) may assist with diagnosis and prognosis in the future but are not yet recommended for this diagnosis.
- Fetal growth restriction may be part of chronic hypertension *per se* and cannot be used as a diagnostic criterion for superimposed PE.

#### 5. Prediction and prevention of pre-eclampsia

##### a) Predicting the development of pre-eclampsia

- No first or second trimester test or set of tests can reliably predict the development of all cases of pre-eclampsia; however, a combination of maternal risk factors, blood pressure, PlGF and uterine artery Doppler can select women who may benefit in particular from 150 mg/day of aspirin to prevent pre-term but not term pre-eclampsia [37]. ISSHP supports first trimester screening for pre-eclampsia when this can be integrated into the local health system, although the cost effectiveness of this approach remains to be established.
- ISSHP recommends that women with established strong clinical risk factors for pre-eclampsia (i.e., prior pre-eclampsia, chronic hypertension, pre-gestational diabetes, maternal BMI  $> 30 \text{ kg/m}^2$ , antiphospholipid syndrome and receipt of assisted reproduction) be treated, ideally before 16 weeks but definitely before 20 weeks, with 75–162 mg/day aspirin, as studied in RCTs.

Maternal characteristics and history provide strong clues to which women are more at risk of developing pre-eclampsia than others [38], particularly:

- Prior pre-eclampsia
- Chronic hypertension
- Multiple gestation
- Pre-gestational diabetes
- Maternal BMI > 30
- Anti-phospholipid syndrome/SLE
- Assisted reproduction therapies

It may be possible to narrow the risk profile for pre-eclampsia further using a combination of these risk factors, screening of uterine artery Doppler and plasma PlGF. This is an issue for the future.

#### Notes:

Many clinical, ultrasonographic, and laboratory parameters have been explored during early pregnancy as tools for predicting who will later develop pre-eclampsia. These include, amongst others:

- Uterine artery Doppler studies,
- Measurement of angiogenic factors (such as soluble Endoglin, PlGF, Soluble fms-like tyrosine kinase-1 (sFlt-1) and sFlt-1/PlGF ratio) [39],
- Numerous others, such as, plasma pregnancy-associated plasma protein A (PAPP-A), Placental Protein 13 (PP 13), homocysteine, Asymmetric dimethylarginine (ADMA), uric acid and leptin, urinary albumin or calcium [40–44].

Maternal characteristics that are most strongly associated with an increased likelihood of pre-eclampsia include those listed above as well as underlying renal disease or multiple pregnancies.

Other factors less strongly associated with pre-eclampsia include, but are not limited to:

- Advanced maternal age [38],
- Family history of pre-eclampsia [45,46],
- Short duration of sexual relationship (< 6 months) prior to the pregnancy [47,48],
- Primiparity (although pre-eclampsia may occur in subsequent pregnancies even in the absence of pre-eclampsia in the first),
- Primipaternity – both changed paternity [49] and an inter-pregnancy interval greater than 5 years have been associated with an increased risk for pre-eclampsia [50],
- Chronic kidney disease,
- Connective tissue diseases,
- Thrombophilias but Factor V Leiden may be a risk factor for the rarer case of very early onset pre-eclampsia, particularly when associated with severe fetal growth restriction [51].
- One large systematic review demonstrated that parity, pre-eclampsia history, race, chronic hypertension and conception method had an area under the curve (AUC) 0.76 for predicting early onset pre-eclampsia, and that discrimination could be improved with specialised tests [52]. The size of the difference in AUC varied widely between model comparisons in this study, ranging from –0.005 to 0.24 in favour of specialised models. Improvements in discrimination were more modest for models predicting any pre-eclampsia and late-onset pre-eclampsia than for models predicting early onset pre-eclampsia.
- O’Gorman et al. [53] found that the detection rates for preterm and term pre-eclampsia were inferior using NICE (National Institute for Health and Care Excellence) or ACOG clinical criteria alone to first trimester screening using a multivariable approach (that included maternal risk factors, blood pressure, maternal PAPP-A and PlGF, and uterine artery Doppler). At a screen positive rate of 10%, 370 women would have to be screened, and the 37 identified as being at

high risk of pre-eclampsia treated with 150 mg/day of aspirin to prevent one case of pre-term pre-eclampsia. Importantly, the vast majority (~80%) of screen positive women did not have strong clinical risk factors for pre-eclampsia.

- In the ASPRE study [37] almost 27,000 women were screened, 6% were included in final analysis and 48 (about 0.2%) developed pre-term pre-eclampsia. This type of screening added a predictive benefit for pre-term pre-eclampsia above that of clinical predictive factors but the cost-effectiveness of the approach is not yet known. Also, screening must be undertaken clinically in the same way as in ASPRE, although uterine artery Doppler (pulsatility index) is not a difficult procedure to learn.
- An important finding in the ASPRE trial [37] was confirmation that aspirin at a dose of 150 mg at night conferred no greater risk to pregnant women (or their newborns) than placebo.
- **Randomised Controlled Trials of ‘rule in’ and ‘rule out’ tests are needed and must include a co-primary non-inferiority outcome of neonatal morbidity because of the very real risk of earlier delivery in these women.**
  - b) Tests to ‘rule-out’ pre-eclampsia

No test should be used routinely as a ‘rule out’ test at this stage, though PlGF testing may prove useful in selected groups in future studies. Such tests should NOT be employed routinely in clinical practice until further clinical studies are conducted.

#### Notes:

In May 2016, the NICE group published **NICE Diagnostics guidance [DG23]** (<https://www.nice.org.uk/guidance/dg23>) recommending that the Elecsys immunoassay for the sFlt-1/PlGF ratio, or the Triage PlGF test, be used with standard clinical assessment to help rule out proteinuric pre-eclampsia or pre-eclampsia requiring delivery within the next 7 (for the sFlt-1/PlGF ratio) or 14 days (for Triage PlGF), in women with suspected pre-eclampsia between 20 and 34 + 6 weeks’ gestation. This recommendation was based primarily on two multicentre studies of women with a broad definition of suspected pre-eclampsia at < 34 + 6 weeks’ gestation. The PROGNOSIS study [54] found that a sFlt1/PlGF ratio < 38 could reliably rule out development of pre-eclampsia for the next 7 days in women with a wide range of inclusion criteria; this finding may not be of any clinical advantage in centres already established for regular antenatal follow up but may become of use in remote or LMIC areas once further research is conducted. The PELICAN study [55] found that a Triage PlGF value of ≤100 pg/ml or the fifth centile of PlGF concentration for gestational age gave high sensitivity with good precision for identifying women likely to develop pre-eclampsia needing delivery within 14 days of testing, when presenting with suspected pre-eclampsia before 35 weeks’ gestation. PlGF, alone or in combination with sFlt-1, was not recommended to rule-in pre-eclampsia.

#### c) Predicting the course of established pre-eclampsia

There are recent studies aiming to predict clinical outcomes for women when they initially present with early features of pre-eclampsia. Measurement of angiogenic factors may play a role in this regard in the future but is still at a research stage [56].

A clinical predictive model, the PIERS model, can predict the likelihood of a composite severe adverse maternal outcome using the following variables gathered from 0 to 48 h. after admission with pre-eclampsia [57,58]:



- gestational age,
- chest pain or dyspnea,
- oxygen saturation,
- platelet count,
- serum creatinine,
- AST.

In practice, pulse oximetry is used infrequently and defaults to an oxygen saturation of 97% in the risk model when oximetry is not available (<https://piers.cfri.ca/PIERSCalculatorH.aspx>).

ISSHP recommends this as a useful adjunct in the initial assessment of women with pre-eclampsia.

#### Notes:

The PREP Collaborative Network published prognostic models that assist predicting the overall risk of women with established pre-eclampsia to experience a complication using logistic regression (PREP-L), and for predicting the time to adverse maternal outcome using a survival model (PREP-S) [59].

The PREP-S model included maternal age, gestation, medical history, systolic blood pressure, deep tendon reflexes, urine protein creatinine ratio, platelets, serum alanine amino transaminase, urea, creatinine, oxygen saturation and treatment with antihypertensives or magnesium sulphate. The PREP-L model included the above except deep tendon reflexes, serum alanine amino transaminase and creatinine (available at <http://stg.pocketapp.co.uk/qmul/#home>).

#### d) Prevention

- Use low dose aspirin (preferably 150 mg/day) started before 16 weeks of pregnancy for women at increased risk for pre-eclampsia, particularly if any of the following conditions exist
  - o previous pre-eclampsia,
  - o pre-existing medical conditions (including chronic hypertension, underlying renal disease, or pre-gestational diabetes mellitus),
  - o antiphospholipid antibody syndrome,
  - o multiple pregnancy,
  - o obesity,
  - o Assisted reproduction pregnancy.
- In the face of low calcium intake (< 600 mg/day), use calcium 1.2–2.5 g per day in women at increased risk.
- Pregnant women should exercise at least 3 days per week for an average 50 min using a combination of aerobic exercise, strength and flexibility training; this has been associated with less weight gain and reduced incidence of hypertensive disorders in pregnancy [60,61]; there are no significant adverse effects of exercise in pregnancy.

- No treatment to date can prevent pre-eclampsia in all women.
- In women considered to be at increased risk for pre-eclampsia on the basis of clinical factors mentioned above, both low dose aspirin and calcium (in the setting of low calcium intake) are recommended for the prevention of pre-eclampsia [62–64].
  - o Aspirin should be given at a dose between 100 and 150 mg per day, started preferably before 16 weeks' gestation, possibly taken at night, and continued until delivery; about 70 women need to be treated to prevent one case of pre-eclampsia, particularly severe pre-eclampsia. Implementation of this practice is associated with improved outcomes [65]; it is possible that initiating aspirin later than 16 weeks' gestation may also be of benefit [66] but we recommend earlier commencement. Recent analyses question: a)

whether aspirin needs be started before 16 weeks or still has benefit if started later, b) the magnitude of effect (ranging from 50% to only 10% risk reduction) and c) what dose is most beneficial, at least 100 mg seeming to be required [67–69].

- o The ASPRE study has demonstrated that the use of 150 mg aspirin at night in women deemed to be high risk for preterm pre-eclampsia on the basis of screening with maternal factors, Doppler and maternal PlGF reduced the incidence of preterm pre-eclampsia from 4.3% to 1.6% in the aspirin group [37].
- o Enoxaparin does not offer any preventative advantage above low dose aspirin even in women at high risk for pre-eclampsia [70].
- Calcium at a dose of at least 1 g/d has been shown to reduce the likelihood of pre-eclampsia in women with low calcium intake. The CAP trial [71] data will be further reported to examine preventative benefits of supplemental calcium in women who are calcium replete (following pre-pregnancy and early pregnancy replacement of 500 mg/d) compared with women who are not replete. This may change future recommendations.
- Exercise using an ACOG program guideline (or aerobic exercise for 50 min, three times per week) in one RCT of 765 women has been associated with reduced gestational hypertension and pre-eclampsia as well as less weight gain and macrosomia [72].
- Supplemental Vitamin C and E are not recommended and may in fact be associated with worse pregnancy outcomes [73].

#### 5.1. Fetal monitoring and management for the hypertensive disorders of pregnancy

- Fetal biometry (bi-parietal diameter together with head circumference, abdominal circumference, and femur length which are computed to produce an estimate of fetal weight), amniotic fluid volume assessment and fetal Doppler waveform analysis should be performed at the first diagnosis of pre-eclampsia.
- In confirmed pre-eclampsia or where there is fetal growth restriction serial evaluation of fetal growth, amniotic fluid volume and umbilical artery Doppler is recommended from 24 weeks' gestation until birth, with fetal growth evaluated no more frequently than at two weekly intervals. Advice should always be sought about ultrasound testing from maternal fetal medicine specialists for earlier gestation cases.
- More frequent ultrasound measurements are needed if there is high umbilical artery resistance or absent or reversed end diastolic flow; in these cases specialised opinion must be sought.
- Prenatal corticosteroids for fetal lung maturation should be given between 24 + 0 and 34 + 0 weeks gestation, but may be given up until 38 + 0 weeks in cases of elective delivery by Caesarean section; multiple steroid courses are not recommended.
- MgSO<sub>4</sub> for fetal neuro-protection should be administered in gestations prior to 32 weeks.

#### Notes:

Pre-eclampsia is, at least in part, a disease of placentation/placental dysfunction and the fetus is potentially vulnerable to the effects of uteroplacental insufficiency, particularly fetal growth restriction and placental abruption.

- In addition to the ideal schedule of a first trimester dating ultrasound and a mid-trimester anomaly scan, fetal biometry, amniotic fluid volume assessment and fetal Doppler waveform analysis

should be performed at the first diagnosis of pre-eclampsia.

- The ideal scanning schedule thereafter is determined by the presence (or absence) of fetal growth restriction at the initial assessment and the gestation at diagnosis.
  - o The American Congress of Obstetricians and Gynecologists (ACOG) and Royal College of Obstetricians and Gynecologists (RCOG) (<https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg31/>) agree that the risk of perinatal morbidity and mortality increases once the estimated fetal weight (EFW) or the abdominal circumference (AC) < 10th centile.
  - o ACOG considers amniotic fluid an “important diagnostic and prognostic parameter in fetuses with IUGR,” whereas the RCOG notes that amniotic fluid assessment has “minimal value in diagnosing” growth restriction. Both guidelines agree that umbilical artery (UA) Doppler is not a reliable screening technique for fetal growth restriction, but is a useful assessment tool once fetal growth restriction is diagnosed.
  - o The Society of Obstetricians and Gynecologists of Canada [74] uses an EFW < 10th centile for diagnosis of small for gestational age and suggests that UA and uterine artery Doppler studies in combination with ultrasound of the placental morphology is useful to establish a more refined diagnosis of fetal growth restriction.
- In confirmed pre-eclampsia, where the maternal condition allows for continuation of pregnancy, serial evaluation of fetal growth, amniotic fluid volume and umbilical artery Doppler is recommended from 26 weeks’ gestation until birth.
- The fetal biometry should be assessed no more frequently than every 2 weeks.
- Criteria for the diagnosis of fetal growth restriction include an EFW < 10th centile on ultrasound based on accurate dating. In particular, an EFW < 3rd centile and/or abnormal UA Doppler, significantly increase the risk of adverse perinatal outcome.
- Once fetal growth restriction is diagnosed, assessment of fetal growth is recommended at two weekly intervals. In addition, amniotic fluid volume and umbilical artery Doppler assessment should be carried out.
- If the umbilical artery Doppler demonstrates increased resistance (Pulsatility Index > 95th centile), the sonographic surveillance should be increased to weekly intervals or more frequently if deemed necessary by the managing clinician.
- If there is absent end-diastolic flow in the umbilical artery (AEDF) prior to 34 weeks’ gestation, daily cardiotocograph (CTG) monitoring, twice weekly UA Doppler and amniotic fluid volume assessment is recommended. These women should be discussed with the team consultant on a daily basis.
- If there is reversed end-diastolic flow in the umbilical artery (REDF) prior to 30 weeks gestation, admission to hospital with daily CTG monitoring, three-times weekly UA Doppler and amniotic fluid volume assessment is recommended; an opinion from a fetal medicine specialist may be sought to determine fetal viability and guide further management.
- In cases of AEDF, delivery should be considered no later than 34 weeks gestation. Earlier delivery may be indicated in cases of poor interval growth, or a deterioration of sonographic variables (Doppler, amniotic fluid).
- In cases of REDF, delivery should be considered no later than 30 weeks gestation. Earlier delivery may be indicated by a deterioration of sonographic variables.
- Prenatal corticosteroids for fetal lung maturation should be considered between 24 + 0 and 34 + 0 weeks gestation, but may be given up until 38 + 0 weeks in cases of elective delivery by Caesarean section. Steroids should be administered in a timed manner. Multiple courses of steroids are not recommended.
- Decisions regarding the optimal timing of delivery need to be made on an individual basis and may require the involvement of an

experienced obstetrician or fetal medicine specialist, in particular in severe, very preterm FGR.

- MgSO<sub>4</sub> for fetal neuroprotection should be administered if delivery is planned prior to 32 weeks gestation.
- Mode of delivery needs to be discussed on an individual basis but Caesarean section is likely when AREDF UA Doppler waveforms are present, or in very preterm gestations.
- If induction of labour is considered in women with abnormal UA Doppler, a continuous CTG should be performed once contractions have started, with a low threshold for Caesarean delivery.
- Cord arterial and venous pH should be recorded for all FGR infants.
- Histopathological examination of the placenta is strongly recommended in all cases where FGR is diagnosed prenatally or at birth to understand the underlying causes and guide management in a subsequent pregnancy [75].

## 6. Management principles for the hypertensive disorders of pregnancy

### 6.1. Chronic essential hypertension

- Use antihypertensives to maintain blood pressure in the range 110–140/80–85 mmHg.
- Acceptable initial anti-hypertensives include labetalol, oxprenolol, methyldopa, nifedipine, diltiazem; prazosin and hydralazine are usually used as 2nd or 3rd line agents [76].
- Home blood pressure monitoring is a very useful adjunct to clinic visits if available; about ¾ home BP devices are accurate [27] so we recommend checking device accuracy against a sphygmomanometer for each woman.
- The key risks of chronic essential hypertension are
  - o super-imposed PE,
  - o fetal growth restriction,
  - o accelerated maternal hypertension.
- Therefore, monitor for developing pre-eclampsia using urinalysis at each visit along with clinical assessment, and blood tests (Hb, platelet count, liver transaminases, uric acid and creatinine) at 28 and 34 weeks as a minimum.
- Assess fetal wellbeing with ultrasound from 26 weeks’ gestation and thereafter at 2–4 weekly intervals if fetal biometry is normal and more frequently in the presence of suspected fetal growth restriction (see above).
- Indications for delivery are similar to those of pre-eclampsia (see below); if no such indication arises delivery at 39 weeks appears optimum [77].

#### Notes:

- The CHIPS trial [78] enrolled mostly chronic hypertensive women; targeting a DBP of 85 mmHg was associated with reduced likelihood of developing accelerated maternal hypertension and no demonstrable adverse outcome for babies compared with targeting higher DBP. Therefore, current evidence supports controlling BP to these levels.

### 6.2. Chronic hypertension due to renal disease

Management of this group is complex and beyond the scope of this document but is discussed in detail elsewhere [79,80]. General principles include:

- Maternal and fetal outcomes are generally worse than the general population even when chronic kidney disease (CKD) is mild [81]
- Control of maternal BP is important to pregnancy and long-term maternal renal outcome
- Monitoring for superimposed pre-eclampsia and for adequate fetal growth is important
- Early dialysis with an aggressive dialysis prescription of about 36 h. per week appears to convey the best outcome for those with progressive renal disease in pregnancy [82]

### 6.3. White-coat hypertension (Fig. 3)

- Where a diagnosis of white coat hypertension is confirmed, pregnant women can be managed with regular home blood pressure assessments and antihypertensives can be avoided, at least up to office blood pressure levels of 160/110 mmHg.
- There are limited studies on the outcome of these pregnancies but it appears that up to half will develop true gestational hypertension or pre-eclampsia [24]; it is possible that the risk of pre-eclampsia is twice that of the normal pregnant population, though this needs to be confirmed. The important messages around white coat hypertension are as follows:
  - it is reasonable to withhold antihypertensive therapy in this group,
  - blood pressure should continue to be monitored regularly at home,
  - Increased surveillance is required throughout pregnancy to detect the emergence of pre-eclampsia.
    - o In areas where home blood pressure assessments are not available, maternal blood pressure should be checked regularly, preferably weekly, by a health care worker; this is probably best done by someone other than a doctor to reduce the likelihood of a white-coat effect.

### 6.4. Gestational hypertension

The key principles of management of gestational hypertension are:

1. Control blood pressure to levels of 110–140/85 mmHg, as above
2. Monitor for development of pre-eclampsia
3. Monitor fetal growth, especially if maternal uric acid is elevated
4. Delivery can be delayed until 39 + 6 weeks provided blood pressure can be controlled, fetal monitoring is reassuring and pre-eclampsia has not developed

#### Notes

- By definition, gestational hypertension is not a benign disorder as at least a quarter of such cases will progress to become pre-eclampsia [31].
- There is no specific test or set of tests that allow prediction of which women with gestational hypertension will develop pre-eclampsia at the time they are diagnosed with gestational hypertension, although

the risk is highest among those who present with gestational hypertension at < 34 weeks [32].

- Women with gestational hypertension require assessment in hospital if they develop pre-eclampsia or severe hypertension  $\geq 160/110$  mmHg.
- The optimum time for delivery remains uncertain for women with gestational hypertension and no features of pre-eclampsia. A large retrospective study concluded an optimum time of 38–39 weeks [83] but this will need to be clarified with future randomised trials.

### 6.5. Pre-eclampsia

#### 6.5.1. Ante-natal

ISSHP endorses the following key management points:

1. Regardless of the hypertensive disorder of pregnancy, blood pressure requires urgent treatment in a monitored setting when  $\geq 160/110$  mmHg; acceptable agents for this include oral nifedipine or intravenous labetalol or hydralazine.
2. Regardless of the hypertensive disorder of pregnancy, we recommend that blood pressures consistently at or above 140/90 mmHg be treated aiming for a target diastolic blood pressure of 85 mmHg (and systolic blood pressure at least below 160 mmHg; some Units target 110–140 mmHg) to reduce the likelihood of developing severe maternal hypertension and possibly other complications such as low platelets and elevated liver enzymes with symptoms. Antihypertensive drugs should be reduced or ceased if diastolic BP falls below 80 mmHg. Acceptable agents include oral methyldopa, labetalol, oxprenolol, nifedipine, with 2nd or 3rd line agents hydralazine and prazosin.
3. Women with pre-eclampsia should all be assessed in hospital when first diagnosed; thereafter some may be managed as outpatients once it is established that their condition is stable and they can be relied upon to report problems and monitor their blood pressure.
4. Women with pre-eclampsia who have proteinuria and severe hypertension, or hypertension with neurological signs or symptoms, should receive  $\text{MgSO}_4$  for convulsion prophylaxis.
5. Plasma volume expansion is not recommended routinely in women with pre-eclampsia.
6. Fetal monitoring in pre-eclampsia should include assessment of fetal biometry, amniotic fluid (AFI) and umbilical artery Doppler with ultrasound at first diagnosis and thereafter at 2 weekly intervals if the initial assessment was normal and more frequent AFI and Doppler in the presence of fetal growth restriction.
7. Maternal monitoring in pre-eclampsia should include: BP monitoring, repeated assessments for proteinuria if not already present, clinical assessment including clonus, and twice weekly blood tests for Hb, platelet count, liver transaminases, creatinine and uric acid. Evaluation should be performed at least twice weekly (and again in response to a change in clinical status) in most women with pre-eclampsia.
8. There should be no attempt to diagnose 'mild' vs. 'severe' pre-eclampsia clinically as all cases may become emergencies, often rapidly.
  - Women with pre-eclampsia should be delivered if they have reached 37 weeks' gestation or they develop any of the following: repeated episodes of severe hypertension despite maintenance treatment with three classes of antihypertensive agents; progressive thrombocytopenia; progressively abnormal renal or liver enzyme tests; pulmonary

oedema; abnormal neurological features such as severe intractable headache, repeated visual scotomata, or convulsions; or non-reassuring fetal status. *Neither the serum uric acid nor the level of proteinuria* should be used as an indication for delivery.

9. In low resource settings, all women with pre-eclampsia should receive  $\text{MgSO}_4$  for convulsion prophylaxis, typically a loading dose of 4 g iv or 10 g intramuscular (imi), followed by 5 g imi every 4 h or an infusion of 1 g/h. until delivery and for at least 24 h. post-partum.
10. In other centres women should receive  $\text{MgSO}_4$  if they have severe hypertension ( $\geq 160/110$  mmHg) and proteinuria or if there are premonitory signs of eclampsia such as severe headaches, repeated visual scotomata, or clonus.
11. ISSHP does not advocate for any clinical distinction between mild and severe pre-eclampsia in usual clinical practice. Instead, all cases of pre-eclampsia should be treated in the knowledge that the condition can change rapidly and that world-wide, this remains a major cause of maternal mortality.
  - a. Distinctions between early and late onset, and mild and severe pre-eclampsia, may be useful for research purposes [3]. However, for **clinical purposes**, the condition should be considered as one that is at any time capable of being severe and life-threatening for mother and baby [84].
  - b. There are clinical findings that warrant closer attention; examples include ongoing or recurring severe headaches, visual scotomata, nausea/vomiting, epigastric pain, oliguria and severe hypertension as well as progressive derangements in laboratory tests such as rising creatinine or liver transaminases or falling platelet count, or failure of fetal growth or abnormal Doppler findings. These women should be followed in a centre with maternal high dependency or intensive care unit capacity for mother and baby.
12. Delivery should be effected depending on gestational age and maternal and fetal status, as follows:
  - a. Women with onset of pre-eclampsia at  $\geq 37$  weeks' gestation should be delivered.
  - b. Women with onset of pre-eclampsia between 34 and 37 weeks' gestation **should** be managed with an expectant conservative approach, as below.
  - c. Women with onset of pre-eclampsia at  $< 34$  weeks' gestation **should** be managed with a conservative (expectant) approach at a centre with Maternal and Fetal Medicine expertise.
  - d. Women with pre-eclampsia with a fetus at the limits of viability (generally before 24 weeks gestation) should be counselled that termination of pregnancy may be required.
  - e. Delivery is necessary when one or more of the following indications emerge:
    - i. Inability to control maternal blood pressure despite using 3 or more classes of antihypertensives in appropriate doses.
    - ii. Maternal pulse oximetry  $< 90\%$ .
    - iii. Progressive deterioration in liver function, creatinine, haemolysis or platelet count.
    - iv. Ongoing neurological features such as severe intractable headache, repeated visual scotomata, or eclampsia.
    - v. Placental abruption.
    - vi. Reversed end-diastolic flow in the umbilical artery Doppler velocimetry, a non-reassuring CTG, or still-birth.

#### Notes:

- The level of blood pressure itself is not a reliable way to stratify immediate risk in pre-eclampsia because some women may develop serious organ dysfunction such as renal impairment or neurological complications at relatively mild levels of hypertension. Hence, decisions to admit and monitor should be based upon having developed pre-eclampsia regardless of the initial BP levels.
- Blood pressures at or above 160/110 mmHg are thought to be surrogate markers for the risk of stroke, as well as a reflection of increased severity of the overall condition of pre-eclampsia [85]. In the follow-up of women in the CHIPS trial, the development of severe hypertension was associated with significantly greater likelihood of adverse outcomes for both the baby (i.e., low birth weight, prematurity, death and morbidity requiring neonatal unit care) and the mother (i.e., thrombocytopenia, abnormal liver enzymes with symptoms and longer hospital stay). Among women who were managed at the higher blood pressure target (of 'less tight' control), severe hypertension was also associated with significantly more serious maternal complications [85].
- There is no universal agreement in clinical practice guidelines as to what blood pressure level should be maintained when anti-hypertensives are instituted for non-urgent indications in pregnancy. However, all guidelines were published prior to publication of the CHIPS Trial results [78]. The Canadian guidelines recommend 130–155/90–105 mmHg in the absence of co-morbid conditions [86], and the NICE guidelines recommend keeping BP below 150 mmHg systolic and between 80 and 100 mmHg diastolic [87]. The USA SMFM decided not to endorse the finding of the CHIPS trial [88]. Yet, as pointed out editorially "To manage BP expectantly at  $< 160/110$  mmHg but emergently at  $\geq 160/110$  mmHg is logically inconsistent" [89]. ISSHP endorses an approach that seeks to reduce the likelihood of developing severe maternal hypertension, namely commencing antihypertensives to treat any persistent non-severe hypertension, well before BPs of 160/110 mmHg are reached. This recommendation applies to all hypertensive disorders of pregnancy. CHIPS enrolled women with chronic (75%) or gestational (25%) hypertension, but superimposed pre-eclampsia developed in almost half of women, and they continued to receive the blood pressure treatment to which they were randomised for two subsequent weeks prior to delivery.
- The target blood pressure for antihypertensive therapy in the 'tight' control arm of CHIPS was a diastolic blood pressure of 85 mmHg, and a systolic blood pressure  $< 160$  mmHg.
- Each unit should have a protocol (based on national or international recommendations) that documents their recommended target blood pressure and regular audit of associated pregnancy outcomes is recommended.
- There is clear evidence that  $\text{MgSO}_4$  prevents eclampsia, approximately halving the rate; overall approximately 100 women need  $\text{MgSO}_4$  to prevent one seizure [90]. ISSHP recommends that, especially because the cost benefit is greatest, all pre-eclamptic women in LMICs should receive  $\text{MgSO}_4$ . In highly specialised centres, and in high income settings where the costs of administering  $\text{MgSO}_4$  are higher, selective use in women with pre-eclampsia is reasonable. In the landmark Magpie Trial, women with pre-eclampsia were given  $\text{MgSO}_4$  if they had severe hypertension and at least 3+ of proteinuria, or slightly lower measurements (150/100 mmHg and least 2+ of proteinuria) in the presence of at least two signs or symptoms of "imminent eclampsia" (which was not defined but is taken to mean headache, visual symptoms, or clonus) [91]. ISSHP recommends that each unit has a consistent policy concerning their use of  $\text{MgSO}_4$  that incorporates appropriate monitoring, recognition of the risks of  $\text{MgSO}_4$  infusions, and assessment of maternal and fetal outcomes. The dosing regimens used in the Eclampsia and Magpie trials should be used.



- The duration of MgSO<sub>4</sub> use post-partum remains contentious; one recent study in Latin America found that women who had received at least 8 g of MgSO<sub>4</sub> before delivery had no additional benefit of continuing the magnesium for a further 24 h. post-partum [92]. This approach needs to take into consideration the known incidence of eclampsia post-partum. As such, either approach is reasonable but until further studies confirm these findings in other populations, we recommend continuing MgSO<sub>4</sub> for 24 h. post-partum. Each Unit should develop their own protocols for post-partum magnesium.

#### 6.5.2. Intra-partum

- Oral anti-hypertensives should be given at the start of labour
- Treat hypertension urgently with oral nifedipine or either iv labetalol or hydralazine if blood pressure rises  $\geq 160/110$  mmHg
- Total fluid intake should be limited to 60–80 ml/h

Notes:

- Reduced gastrointestinal motility may decrease absorption of anti-hypertensives following oral administration. Therefore, intravenous (ivi) antihypertensives may be needed to control blood pressure, particularly if it becomes severe.
- Fluid balance should aim for euolemia as at all other times. Pre-eclamptic women have capillary leak [93] but may have either reduced or increased cardiac output [94,95]. To ensure euolemia, insensible losses should be replaced (30 ml/h) along with anticipated urinary losses (0.5–1 ml/kg/h). We suggest not using more than 80–100 ml/h. to avoid risks of pulmonary oedema. There is no rationale to ‘run dry’ a pre-eclamptic woman as she is already at risk of acute kidney injury.

#### 6.5.3. Post-partum

- Monitor blood pressure at least 4–6 hourly during the day for at least 3 days post-partum.
- Pre-eclampsia may develop de novo intra- or early post-partum [96]; such cases should be managed as above and a careful assessment for retained products should be made; these cases often take longer to settle post-partum.
- Monitor general well-being and neurological status as per pre-delivery; eclampsia may occur post-partum.
- Repeat Hb, Platelets, Creatinine, liver transaminases the day after delivery then 2nd daily until stable if any of these were abnormal before delivery.
- Anti-hypertensives should be restarted after delivery and tapered slowly only after days 3–6 postpartum unless blood pressure becomes very low ( $< 110/70$  mmHg) or the woman becomes symptomatic in the meantime.
- Most women can be discharged by day 5 post-partum, especially when they are able to monitor their blood pressure at home.
- Avoid NSAIDs in women with pre-eclampsia if possible, especially in the setting of AKI, and use alternative pain relief.

Notes:

- There is controversy as to whether NSAIDs are harmful or not in this setting. Certainly some women develop severe hypertension from NSAIDs [97] but other observational studies suggest the risk is small, if any [98,99]. NSAIDs are very effective analgesics. Until

prospective randomised trials are conducted on this issue, we recommend using alternative analgesia as a first choice for women who have pre-eclampsia.

#### 6.5.4. Short-term follow-up

- Women with pre-eclampsia should be reviewed within one week if still requiring anti-hypertensives at discharge from hospital.
- All women should be reviewed 3 months post-partum by which time blood pressure, urinalysis, and all laboratory tests should have normalised.
- Further investigation is required for persistent abnormalities, including a work-up for secondary causes of persistent severe hypertension or underlying renal disease with persistent proteinuria.
- Assessment should also include a clinical check for depression, anxiety or PTSD symptoms [100].

#### 6.5.5. Long-term follow-up

All women with chronic hypertension, gestational hypertension or pre-eclampsia require lifelong follow-up because of their increased cardiovascular risk. We recommend:

- Advice to women with gestational hypertension or pre-eclampsia that they have increased risks of cardiovascular disease, death, stroke [33,101,102], diabetes, venous thromboembolic disease (VTE) and CKD compared with women who have had normotensive pregnancies [103].
- Advice to women with pre-eclampsia that they have approximately a 15% risk for developing pre-eclampsia again and a further 15% risk for gestational hypertension in a future pregnancy [104,105] and that they should receive low-dose aspirin in another pregnancy.
- Advice to women with gestational hypertension that they have approximately a 4% risk for developing pre-eclampsia and a further 25% risk for gestational hypertension in a future pregnancy [104,105].
- Advice to women with gestational hypertension or pre-eclampsia that they have increased risks of SGA babies in another pregnancy even if pre-eclampsia does not recur.
- Regular follow-up with a general practitioner to monitor BP and periodic measurement of fasting lipids and blood sugar.
- Adopt healthy lifestyle with maintenance of ideal weight and regular aerobic exercise.

Notes

- The long-term risks of pre-eclampsia, and gestational hypertension, are now well established, though some believe these risks are confined to those who remain hypertensive and behave as chronic hypertensives [106].
- It is probable that in the long-term these women have some degree of underlying metabolic syndrome and higher blood pressure than women who did not have hypertensive pregnancies [107,108].
- The values we use to define ‘normal’ blood pressure are derived from older and often male populations; ongoing studies will define a new ‘normal’ range of blood pressure for young women who have not had pre-eclampsia, thereby permitting a reassessment of whether a woman who has had pre-eclampsia truly has normal blood



pressure when followed up 6 months or more post-partum [109].

- Even with an elevated lifetime risk of cardiovascular disease, young women may have low 10-year cardiovascular risk scores using well-established tools, and may be overlooked as being at high risk on that basis.
- Ongoing clinical studies may provide more specific information on how best to manage formerly pre-eclamptic women.

## 7. Application of these ISSHP recommendations to low resource countries

### 7.1. General recommendations

- The recommendations described in this document are for an ideal setting. In some instances, it may not be possible to adopt all of these recommendations. Health systems in low and middle-income countries (LMICs) may have to consider the minimum required to reach as many women as possible.
- It is recommended that there is ongoing review and update of national and facility clinical guidelines, pre-service educational material and in-service training materials to ensure that all documents reflect these ISSHP recommendations so as to improve outcomes for women and babies.
- In circumstances where the documented goals of this guideline are not attainable in their entirety, physicians should work pragmatically towards them as far as the local resources allow.
- It is the responsibility of managing physicians to advocate for the use of effective interventions whether they practice in well- or under-resourced settings.
- The distances between community clinics and referral hospitals are often large and transport problems exist. For this reason patients diagnosed with pre-eclampsia should be referred as soon as possible to a centre with an appropriate level of care and managed as in-patients.
- The effectiveness of referral systems is in many low- and middle-income countries is less than optimal and many rural areas are without centres that can provide basic obstetric and neonatal services. Women diagnosed with pre-eclampsia in such settings should be advised to re-locate immediately to areas with better health care services, especially where they have family members if possible.
- Communities should put strategies in place for transport from clinics or primary healthcare centres to referral centres.
- All health care facilities should regularly review and update facility and community health worker referral pathways for women with pre-eclampsia.
- All women with a hypertensive disorder of pregnancy require delivery in a centre that provides emergency obstetric and neonatal care, while women with maternal complications require delivery in a centre capable of providing maternal critical care. Those with pregnancies at the limit of viability require the highest available level of neonatal support.
- Antihypertensive agents for treatment of moderate and severe hypertension and  $MgSO_4$  to prevent or treat eclampsia must be available at community level centres and clinics so that patients can be stabilised and referred safely.
- Women with pre-eclampsia in LMICs may have a limited comprehension of the nature and risks of the disease. A South African study showed that a structured information sheet (in addition to verbal counselling by a physician) improved patients' understanding and knowledge in a limited way but did not alleviate their anxiety [110]. Better understanding of the disease will lead to greater acceptance of advantageous treatment options and prime the patient for life-long care of her health.
- A key issue is the supply of  $MgSO_4$  which is rarely in stock; there are challenges with out of stock, challenges with the distribution system, the drug often being stuck at district level and then sitting

there without getting to the health care facility. Priority should be given to provision of such stock.

### 7.2. Antenatal care

The 2016 WHO guidelines on routine antenatal care (ANC) ([http://www.who.int/reproductivehealth/publications/maternal\\_perinatal\\_health/anc-positive-pregnancy-experience/en/](http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/)) recommends several health systems interventions to increase use of antenatal services and improve the quality of care delivered. Recommendations include:

- Midwife-led continuity of care throughout the antenatal, intra-partum, and postnatal periods;
- A minimum of 8 antenatal care contacts;
- Women-held case notes;
- Promotion of health-related behaviours and distribution of nutrition supplements;
- Recruitment and retention of health workers in rural and remote areas (where one out of 20 people do not have access to essential health services); and
- Community mobilisation to improve communication and support to pregnant women.

### 7.3. Prevention of hypertensive disorders in pregnancy

- Prophylactic use of aspirin – use low dose aspirin for women with:
  - o one or more of the major risk factors for pre-eclampsia
    - (Prior pre-eclampsia, Chronic hypertension, Pre-gestational diabetes, Maternal BMI > 30, chronic kidney disease, Anti-phospholipid syndrome)
  - o or two or more of minor risk factors
    - (advanced maternal age, family history of pre-eclampsia, short duration of sexual relationship (< 6 months) prior to the pregnancy, primiparity, primipaternity – both changed paternity and an interval greater than 5 years have been associated with an increased risk for pre-eclampsia, connective tissue disorders)
- preferably starting before 16 weeks' gestation, until 37 weeks, using 100–150 mg daily

Calcium supplements 1200 mg daily if dietary calcium intake is low in the local population.

### Notes

- Knowledge of prophylactic use of aspirin, and calcium where dietary intake is low, is very poor in district and health centres, even among doctors (Landscape analyses in Nigeria and Bangladesh – Ending Eclampsia – Population Council [www.endingeclampsia.org](http://www.endingeclampsia.org)).
- The main challenge is to identify women at risk of developing pre-eclampsia to receive aspirin and calcium supplementation before 16 weeks. Women in LMIC do not usually seek care much before 20 weeks. Therefore, community based messaging and education is required.
- There is a need to ensure time and counselling skills in order that women take aspirin and calcium:
  - Confirm aspirin and calcium dosing and timing as per these international recommendations.
  - Ensure aspirin prophylaxis is included in all national guidelines and protocols.

- Consider group based counselling and task shifting so that lower level health care workers can provide aspirin and calcium to women in areas where there is known calcium deficiency or a high prevalence of pre-eclampsia and for women with risk factors for pre-eclampsia as above.
- Antiphospholipid antibody syndrome is not commonly diagnosed in LMIC or routinely seen as a risk factor; in any case enoxaparin is not widely available.
- Health managers and facilities must estimate the expected number of pregnancies per annum and budget and procure aspirin and calcium in a timely manner to prevent stock-outs and thereby ensure women benefit from these simple preventative measures.

#### 7.4. Early detection and diagnosis

- Aim to test the blood pressure and proteinuria at every visit.
- In many contexts (due to frequent stock outs) urine can only be tested for protein if BP is raised and/or women present with symptoms such as headache, visual disturbance, epigastric pain.
- For proteinuria the use of visual dipstick testing according to the manufacturer's specification is acceptable.
- Each ANC unit should have as a minimum a dedicated sphygmomanometer and urine dipsticks for detecting proteinuria.
- Health care providers must be trained on how to measure blood pressure correctly using the appropriate technique.

Laboratory tests to rule out end-organ complications of pre-eclampsia are often not available at primary or even secondary level health facilities. Diagnosis will need to be made initially on the basis of B, symptoms and proteinuria until transfer to a tertiary facility.

#### Notes:

- Clear protocols are required in each unit, utilising the ISSHP recommendations for diagnosis and management.
- Confusion remains on definitions of hypertension and knowledge gaps persist across providers at both secondary and primary facilities, including when to initiate anti-hypertensives. These ISSHP recommendations should be publicised across low and middle income countries as the standards to be sought.
- In LMIC settings home blood pressure monitoring is unlikely. Women should be encouraged to attend for a minimum of eight ANC visits, attend more frequently if they develop warning symptoms or signs of pre-eclampsia or blood pressure was raised on prior visits. They must 'know their blood pressure numbers' and understand the importance of knowing what their BP should be, both before and after delivery. This requires ongoing education aiming towards women understanding the significance of having a raised BP.
- In LMIC settings visual dipstick for proteinuria is used, not automated measurement. Often due to resource constraints, dipstick is only done if blood pressure is raised (above 140/90 mmHg). It is important for local groups to lobby for consistent supply.
- The gold standard continues to be the 24-h. urine protein measurement in LMIC. Quantifying with spot urine protein/creatinine ratio is rarely available but efforts should be made to ensure urine creatinine measurement is available thereby enabling spot P/Cr to be done. This should be a priority given the challenges and potentially dangerous time delays inherent in doing 24 h. urine collections. Though it is unlikely to be done at primary health care level, health providers should work to ensure this is available in the

tertiary hospital setting.

- Women in LMICs are usually referred to tertiary hospitals to receive all tests. However, many women do not go due to costs related to transport and to treatment. A signs and symptoms-based model (miniPIERS) is available to identify women at low risk of complications, and this should be explored for use at primary and secondary care levels.

#### 7.5. Fetal monitoring

In some LMICs in tertiary facilities first and mid-trimester ultrasound, fetal biometry, amniotic fluid volume and fetal Doppler studies take place.

Fundal height measurements may also take place every 2 weeks.

However, the recent WHO ANC guidelines suggest that the following should not be continued due to insufficient evidence:

- Routine daily fetal movement counting
- Symphysis-fundal height measurement
- Routine antenatal cardiotocography
- Although recommended before 24 weeks, ultrasound should only be performed where capacity exists; Units should consider costs and maintenance of ultrasound equipment over the cost of ensuring sphygmomanometers are widely available to measure blood pressure, which can provide greater recognition of women with pre-eclampsia.

#### 7.6. Management of hypertensive disorders of pregnancy

- Aim to maintain blood pressure 110–140/85 mmHg.
  - o Typically Methyldopa and Nifedipine are used and both are acceptable.
- Women with pre-eclampsia should all be assessed **in hospital** when first diagnosed; thereafter some may be managed as outpatients once it is established that their condition is stable and they can be relied upon to report problems and monitor their blood pressure.
- Laboratory tests are not always available at primary or even secondary level health facilities; when transfer to a higher level of care is not available, clinical decisions must be made using BP measures, fundal height assessment, symptoms, and urine dipstick testing when available.
- At first referral level antihypertensive therapy and magnesium sulphate should be adjusted or continued as appropriate and women should be triaged for appropriate referral to tertiary-level care, including those eligible for expectant care and those at high risk of, or with severe maternal morbidity.
- One protocol for treatment of acute severe hypertension is described in Fig. 1; others may be developed by individual Units as desired.
- Treatment and prevention of eclampsia is achieved ideally with the protocol of intravenous magnesium (Fig. 2) which is that used in the MAGPIE trial; when this is not possible the 'Pritchard regimen' (also used in the MAGPIE trial) can be used as follows:
  - o 4 g is administered as an intravenous dose and 5 g in one buttock and another 5 g in the other buttock. These together constitute the loading dose (14 g). Thereafter, 5 g is administered every 4 h for 24 h. in alternate buttocks as maintenance dose.
- At gestational age less than 34 weeks repeatedly weigh the relative benefits and risks of continuation of pregnancy against progression of maternal disease, using the recommendations for timing of delivery in this document, viz.:

- o repeated episodes of severe hypertension despite maintenance treatment with three classes of antihypertensive agents;
- o progressive thrombocytopenia;
- o progressively abnormal renal or liver enzyme tests;
- o pulmonary oedema;
- o abnormal neurological features such as severe intractable headache, repeated visual scotomata, or convulsions;
- o Non-reassuring fetal status.
- Prenatal corticosteroids for fetal lung maturation should be given between 24 + 0 and 34 + 0 weeks gestation, but may

be given up until 38 + 0 weeks in cases of elective delivery by Caesarean section; multiple steroid courses are not recommended.

Notes:

- Task shifting guidelines for both MgSO<sub>4</sub> and antihypertensive treatment should be available in each Unit so that lower level providers can initiate treatment with a loading dose and refer.
- o Task shifting policies vary on whether lower level providers can prescribe antihypertensives to keep blood pressure in the range

Severe Hypertension	SBP $\geq$ 160 and/or DBP $\geq$ 110 mmHg
Administer <b>10mg nifedipine tablet orally</b>	
Monitor and record BP every 15 minutes Perform continuous CTG monitoring	
If after 45 minutes severe hypertension persists:	
Give second dose of <b>10mg nifedipine orally</b>	
Monitor BP every 15 minutes until BP stabilises	
If after another 45 min (90 min from first dose), severe hypertension persists:	
Commence <b>IV management</b> as below (should be commenced prior to transfer if delay in transfer occurs)	
Dilute 20mg hydralazine in 20mL of water for injection	
Administer <b>5mg (5mL) Hydralazine</b> as an IV bolus	
Monitor and record BP every 10 minutes Perform continuous CTG monitoring	
If after 20 minutes severe hypertension persists:	
Administer second dose of <b>5mg (5mL) Hydralazine</b> as an IV bolus	
If after another 20 minutes, severe hypertension persists:	
Administer third dose of <b>5mg (5mL) Hydralazine</b> as an IV bolus	

If severe hypertension persists after 3 boluses of IV hydralazine:

Draw 10mL out of a 500mL normal saline bag, mix the 10mL with 80mg hydralazine powder and then load it back into bag to make 500mL bag
Commence <b>hydralazine infusion</b> via infusion pump Commence infusion at <b>30mL/hr</b> i.e. 5mg/hr
Increase infusion by 10mL every 30 minutes to a maximum of 90mL/hr. (i.e. 15mg/hr.), aiming for SBP 140 –160mmHg and DBP 90-100mmHg

Fig. 1. Management of severe Hypertension with oral Nifedipine and/or intravenous Hydralazine.

<b>For intravenous infusion:</b>
Loading dose: use 4g (8mL) MgSO <sub>4</sub> in 100mL Normal Saline
<b>Administer IVI at 300 mL/hr via infusion device (i.e. over 20 minutes)</b>
Maintenance dose: Remove 20 mL solution from 100 mL normal saline infusion bag and discard. Add 10g MgSO <sub>4</sub> (4 amps = 20 mL) to the bag.
<b>Infuse at 10mL/hr (1g/hr)</b>
Maintain infusion for 24 hrs. post-natally

#### Observations and care during MgSO<sub>4</sub> infusion:

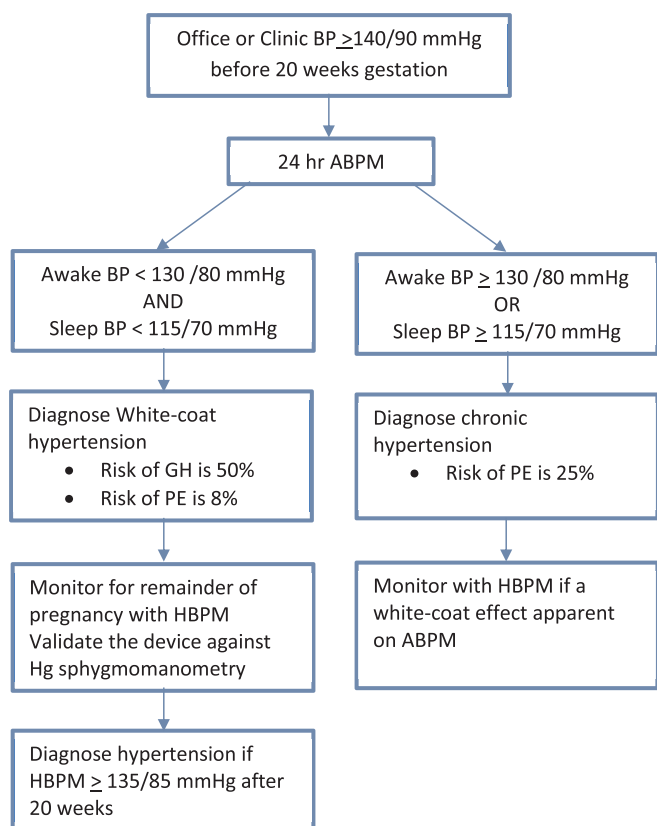
- Continuous CTG monitoring if  $\geq 26$  weeks gestation (if  $< 26$  weeks gestation, perform 30 minutely auscultation)
- Maternal observations:
  - Respiratory rate (and pulse oximetry if available) every 30 min.
  - BP 30 minutely
  - Maternal pulse hourly
  - Urine output hourly
  - Reflexes at the completion of the loading dose and then every 2 hours

<b>For intra-muscular magnesium</b>
<b>Loading dose:</b> 4 gm is administered as an intravenous dose Then 5 gm in one buttock and another 5 gm in the other buttock.
<b>These together constitute the loading dose (14 gm).</b>
<b>Maintenance dose:</b> Thereafter, 5 gm is administered in alternate buttocks every 4 hours for 24 hr.

#### Management of MgSO<sub>4</sub> toxicity

- Measurement of serum MgSO<sub>4</sub> levels is not necessary unless signs of toxicity
- Signs of MgSO<sub>4</sub> toxicity:
  - Respiratory rate  $< 10/\text{min}$  or SaO<sub>2</sub>  $< 92\%$
  - Muscle Paralysis
  - Reflexes absent
- If toxicity suspected:
  - Cease the infusion, take blood for MgSO<sub>4</sub> level
- Treatment of MgSO<sub>4</sub> toxicity:
  - Administer calcium gluconate 10%, 10mL in 100 mL normal saline IVI over 10-20 minutes

**Fig. 2.** One protocol for use of Magnesium Sulphate for eclampsia treatment or prophylaxis. Check the concentration of Mg carefully to ensure a match with the doses below. Different countries may have different strength Mg concentrations.



**Fig. 3.** Clinical application of ABPM in early pregnancy to diagnose and manage white-coat hypertension. Hypertension is diagnosed if either systolic or diastolic BP is elevated, awake or sleep. ABPM = ambulatory blood pressure monitoring; GH = gestational hypertension; PE = pre-eclampsia; HBPM = home blood pressure monitoring (from Ref. [114]).

110–140/85 mmHg. A change in practice should be explored so that asymptomatic women without proteinuria or other evidence of pre-eclampsia could receive antihypertensives from lower level providers.

- Task-shifting policies may only allow administration of intramuscular  $\text{MgSO}_4$ . In such cases a woman should receive a loading dose of IM 5 mg  $\text{MgSO}_4$  in each buttock and refer. It is better to initiate treatment with this dose than refer without any  $\text{MgSO}_4$ .
- Clear protocols are required in each unit, utilising these ISSHP recommendations.
- In LMIC, oxprenolol, diltiazem and prazosin are not readily available and are costly; methyldopa and nifedipine are more readily available and either can be used as a first line treatment.
- Regular blood work up at 28 and 34 weeks may not happen if a woman is not near a tertiary facility. Ultrasound is also not always available. Mostly workers use serial fundal height check.
- Ensure every health facility/unit has clear clinical protocols for  $\text{MgSO}_4$  use; this is a key education priority. One study demonstrated that use of  $\text{MgSO}_4$  for prevention and treatment of eclampsia varied widely and was largely inconsistent with current international guidelines.
- There is often poor knowledge of how to monitor for  $\text{MgSO}_4$  toxicity; this is a key area for education; the protocols in Fig. 2. can be used.

### 7.7. Chronic hypertension in pregnancy

- In LMIC, oxprenolol, diltiazem and prazosin are not readily available and costly; methyldopa and nifedipine are more readily available and either can be used as a first line treatment.
- Where resources are limited and the combination of chronic hypertension and obesity are prevalent, the recommended tests may be reduced to haemoglobin, platelet count, serum creatinine, urinalysis and appropriate quantification of urinary protein as baseline reference.
- Community based blood pressure measurement and protein dipsticks should be made available for women at first point of care – either by community based health worker or at primary health care level living far from tertiary/hospitals facilities.
- Task shifting policies vary on whether lower level providers can prescribe antihypertensives to keep blood pressure in the range 110–140/85 mmHg. A change in practice should be explored so that asymptomatic women with chronic hypertension without evidence of pre-eclampsia could receive antihypertensives from lower level providers on an outpatient basis.

### 7.8. Postnatal care

- Blood pressure should be recorded shortly after birth and if normal again within 6 h.
  - Postnatal blood pressure should be controlled as per ISSHP recommendations
- In LMIC blood tests are usually done twice in the week after birth if abnormal before delivery.
- All women should have BP recorded and defer discharge for at least 24 h or until vital signs are normal and/or treated or referred. Any woman with an obstetric complication and/or newborn with complications should stay in the hospital until both are stable.
- WHO recommendations include:
  - stay in the facility for at least 24 h,
  - Check up within 48–72 h of the birth and again at 7–14 days and at six weeks post-partum. A home visit within the first week is recommended for those who did not deliver in a health facility.
- All women should be reminded of the danger signs of pre-eclampsia following birth including headaches, visual disturbances, nausea, vomiting, epigastric or hypochondrial pain, feeling faint or convulsions.

#### Notes:

- Discharge and follow up should occur at tertiary facility; referral to a physician at hospital is advised if hypertensive or renal problems persist. Every woman should have details/documents to provide to the primary health care (PHC) facility for close follow up.
- It is important to counsel/provide education on postpartum contraception and family planning regarding limiting/spacing of next pregnancy. Family planning counselling should start in the ANC and be offered to each woman before she leaves the facility and again when advised to come back at six weeks for infant immunisation and family planning consultation. Any family planning method that the



woman wants to receive is acceptable if based on comprehensive counselling (and is available in the particular country setting).

- In many LMIC women go home within 6–24 h after birth. This should be discouraged after a pre-eclampsy pregnancy. Even in busy units with heavy pressure on post-natal beds women with pre-eclampsia should not be discharged early.
- It is an important opportunity at the time of discharge to reinforce the importance of early antenatal care in the next pregnancy due to risks of recurrent pre-eclampsia.

### 7.9. What do other guidelines say?

ISSHP acknowledges the expertise and rigorous approach that has been undertaken in the development of several key guidelines including:

- NICE 2010 [87]
- SOMANZ 2014 [111]
- Canadian 2014 [112]
- ACOG 2013 [113]
- The key areas in which these guidelines differ are:
  1. the requirement for proteinuria in the diagnosis of pre-eclampsia (NICE)
  2. the level at which routine antihypertensive treatment of blood pressure is mandatory and the target blood pressure thereafter (although all were published before the CHIPS Trial results were available)
  3. when MgSO<sub>4</sub> should be administered

Other guidelines include those of WHO 2011 and IMPAC 2016. WHO 2011 Recommendations for prevention and treatment of pre-eclampsia and eclampsia 2011. [http://www.who.int/reproductivehealth/publications/maternal\\_perinatal\\_health/9789241548335/en/](http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548335/en/). IMPAC 2016 (although this is actually incorrect and should be for Managing Complications in Pregnancy and Childbirth (MCPC)): [http://www.who.int/maternal\\_child\\_adolescent/documents/managing-complications-pregnancy-childbirth/en/](http://www.who.int/maternal_child_adolescent/documents/managing-complications-pregnancy-childbirth/en/).

Adopting the management recommendations of any of these guidelines is entirely justified though one aim of the ISSHP is to see a single set of flexible and regularly updated guidelines throughout the world so as to reduce confusion around diagnosis and management of women with hypertension in pregnancy.

Importantly, ISSHP recommends that each unit has a specific policy as to management guidelines that are to be followed so that there is uniform practice within each unit. In addition, each unit should strive to record and evaluate their maternal and fetal outcomes to ensure that their policies and guidelines remain appropriate at all times.

### 7.9. Guideline process

The first author drafted the initial document and sought further input from all co-authors; these authors were chosen as being expert members of the ISSHP executive (authors 1–7) with additional authors who had expertise and experience in the management of pre-eclampsia in low resource countries (authors 7–10). Relevant literature up to April 2017 was included with an emphasis on more recent publications; the document was revised again after the publication of the ASPRE trial in August 2017. The first version was circulated by email to all members in March 2017 and eight subsequent versions emanated following email discussions to achieve consensus amongst the group. The document was then sent to all members of ISSHP Council for further comment and those who responded are listed in the acknowledgements below. The final version was concluded on December 28th 2017 then amended after reviewers' comments by March 1st 2018.

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