Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 27 (2022) 148–169

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice☆

Laura A Magee[a,*], Mark A. Brown[b], David R. Hall[c], Sanjay Gupte[d], Annemarie Hennessy[e], S. Ananth Karumanchi[f], Louise C. Kenny[g], Fergus McCarthy[h], Jenny Myers[i], Liona C. Poon[j], Sarosh Rana[k], Shigeru Saito[l], Anne Cathrine Staff[m,n], Eleni Tsigas[o], Peter von Dadelszen[a]

[a] Department of Women and Children's Health, School of Life Course Sciences, King's College London, UK
[b] Departments of Renal Medicine & Medicine, St. George Hospital & University of New South Wales, Sydney, Australia
[c] Department of Obstetrics & Gynaecology, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa
[d] Secretary General, World Organization Gestosis, Gupte Hospital, Pune, India
[e] School of Medicine, Western Sydney University and South Western Sydney Local Health District, Sydney, Australia
[f] Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, United States
[g] Faculty of Health & Life Sciences, University of Liverpool and INFANT Centre, Cork University Maternity Hospital, Cork, Ireland
[h] Department of Obstetrics and Gynaecology, University College Cork, Cork, Ireland
[i] Maternal & Fetal Health Research Centre, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
[j] Department of Obstetrics and Gynaecology, Chinese University of Hong Kong, Chair of Hypertension in Pregnancy Subcommittee FIGO Pregnancy and NCD Committee, Hong Kong
[k] Department of Obstetrics and Gynecology/Division of Maternal Fetal Medicine, University of Chicago, Chicago, IL, USA
[l] Department of Obstetrics and Gynecology, Graduate School of Medicine and Pharmaceutical Science for Research, University of Toyama, Japan
[m] Faculty of Medicine, University of Oslo, and Division of Obstetrics and Gynaecology, Oslo University Hospital, Oslo, Norway
[n] Global Pregnancy Collaboration (Member, Steering and Executive Committees), USA
[o] Preeclampsia Foundation, USA

ARTICLE INFO

Keywords:
Hypertension
Pregnancy
Pre-eclampsia
Outcome
Maternal
Perinatal

ABSTRACT

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.

Abbreviations: ABPM, ambulatory 24-hour blood pressure monitoring; ACR, albumin:creatinine ratio; AKI, acute kidney injury; ART, assisted reproductive technology; BID, twice daily; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; FGR, fetal growth restriction; FIGO, International Federation of Gynecology and Obstetrics; GPP, good practice point; HBPM, home blood pressure monitoring; HDP, hypertensive disorder of pregnancy; HELLP syndrome, Haemolysis, Elevated Liver enzymes, Low Platelet syndrome; ISSHP, International Society for the Study of Hypertension in Pregnancy; ISUOG, International Society for Ultrasound in Obstetrics and Gynecology; IV, intravenous; LA, long-acting; $MgSO_4$, magnesium sulphate; MR, modified release; NICU, neonatal intensive care unit; PA, prolonged action; PlGF, placental growth factor; QAM, every morning; QID, four times daily; QPM, every evening; OR, odds ratio; PrCr, protein:creatinine ratio; RCT, randomised controlled trial; RR, relative risk; sFlt-1, soluble fms-like tyrosine kinase-1; TID, three times daily; WHO, World Health Organization; XL, extended-release.

☆ This document has been endorsed by World Organization Gestosis and the Japanese Society for the Study of Hypertension in Pregnancy.

* Corresponding author at: Department of Women and Children's Health, School of Life Course Sciences, King's College London, Becket House, 1 Lambeth Palace Road, Room BH.05.11, London SE1 7EU, UK.
E-mail address: laura.a.magee@kcl.ac.uk (L.A. Magee).

https://doi.org/10.1016/j.preghy.2021.09.008
Received 28 September 2021; Accepted 30 September 2021
Available online 9 October 2021

Recommendations

Diagnosis of hypertension and proteinuria

1. Blood pressure (BP) should be measured using standardised technique, including women's position (sitting, feet flat on floor), cuff size ('large' if the mid-upper arm circumference is ≥33 cm), Korotkoff V for the diastolic BP (dBP), and arm used (both, at least initially) (⊕⊕⊕O/Strong).

2. BP taken in pregnancy or postpartum, in any setting, should be measured using a device validated for use in pregnancy and pre-eclampsia (⊕⊕⊕O/Strong).

3. Hypertension should be defined as a systolic BP (sBP) ≥ 140 mmHg and/or dBP ≥ 90 mmHg, based on an average of at least two measurements (⊕⊕⊕⊕, Strong).

4. BP should be repeated to confirm true hypertension; if hypertension is severe (sBP ≥ 160 and/or dBP ≥ 110 mmHg), then repeat within 15 min; otherwise, repeat in at least 4 h or on two consecutive outpatient visits (Good practice point, GPP).

5. Quantitative proteinuria testing for pre-eclampsia should be performed as part of the work-up for women suspected of having pre-eclampsia or at high-risk of developing it (⊕⊕⊕⊕, Strong).

6. Proteinuria should be defined as ≥ 30 mg/mmol urinary protein: creatinine ratio (PrCr) in a spot (random) urine sample, or albumin: creatinine ratio (ACR) ≥ 8 mg/mmol, or ≥ 0.3 g/d in a complete 24-hour urine collection, or ≥ 2 + by urinary dipstick if confirmatory testing is not available (⊕⊕⊕O/Strong).

Classification

7. The hypertensive disorders of pregnancy (HDPs) should be classified according to the criteria presented in Table 1.

8. The ISSHP does not suggest routine testing for secondary causes of hypertension in the absence of clinical clues to these conditions (⊕⊕OO/Strong).

9. Women with white-coat hypertension should undertake regular home BP monitoring (HBPM) (⊕⊕⊕O/Strong).

10. Pre-eclampsia should not be classified as 'mild' or 'severe' in an ongoing pregnancy (⊕⊕⊕O /Strong).

See Table 1 and text.

11. An elevation in BP should not be used to make a diagnosis of pre-eclampsia superimposed on chronic hypertension (⊕⊕OO/Strong).

12. To the assessment of women suspected of having pre-eclampsia (<37 weeks), we recommend adding evaluation of angiogenic imbalance, when available, as a marker of uteroplacental dysfunction to be used in conjunction with other clinical tests. (⊕⊕⊕O/Strong).

Prediction of pre-eclampsia

13. At minimum, women should be screened for clinical risk markers of pre-eclampsia risk at antenatal care booking (GPP).

14. If testing is available, after appropriate counselling, women should be screened at 11–14 weeks for preterm pre-eclampsia risk, using a combination of clinical risk factors, BP, uterine artery pulsatility index, and PlGF, as available, even if they have been already been identified as having clinical 'high-risk' factors (⊕⊕⊕O/Strong).

Prevention of pre-eclampsia

All women in pregnancy

15. Unless there are contraindications, all women should exercise in pregnancy to reduce the likelihood of gestational hypertension and pre-eclampsia (⊕⊕⊕O/Strong).

16. For women with dietary intake of calcium (<900 mg/day), oral calcium supplementation of at least 500 mg/d is recommended (⊕⊕OO/Weak).

17. Women should NOT receive low-molecular-weight heparin*, vitamins C or E, or folic acid for pre-eclampsia prevention (⊕⊕⊕O/Strong).

* *This recommendation relates to use of heparin for pre-eclampsia prevention. and not for other indications, such as thromboprophylaxis in anti-phospholipid antibody syndrome.*

Women at increased risk of pre-eclampsia*

18. Low-dose aspirin is recommended (⊕⊕⊕⊕/Strong), to be taken at bedtime (⊕⊕⊕O/Strong), preferably before 16 weeks and discontinued by 36 weeks (⊕⊕⊕O/Strong).

19. After multivariable screening, aspirin should be given at a dose of 150 mg/night (⊕⊕⊕⊕/Strong).

20. After screening with clinical risk factors and BP, aspirin should be given at a dose of 100–162 mg/d (⊕⊕⊕O/Strong).

Management

Place of care

21. Women with pre-eclampsia or severe hypertension should be assessed and managed in hospital, before carefully-selected cases are considered for outpatient care (GPP).

Antihypertensive therapy

22. Hypertension in pregnancy should be treated with antihypertensive therapy, irrespective of the underlying HDP (⊕⊕⊕O/Strong).

23. Severe hypertension in pregnancy (i.e., sBP ≥ 160 mmHg or dBP ≥ 110 mmHg) requires *urgent* antihypertensive therapy, in a monitored setting (⊕⊕OO/Strong).

24. The target BP for antihypertensive therapy should be a dBP of 85 mmHg, regardless of sBP (⊕⊕⊕⊕/Strong).

25. Non-severe hypertension should be treated with the first-line agents oral methyldopa, labetalol, or nifedipine (⊕⊕⊕O/Strong).

26. Severe hypertension should be treated with the first-line agents oral nifedipine, oral labetalol, intravenous (IV) labetalol, or IV hydralazine (⊕⊕⊕O/Strong).

Plasma volume expansion

27. Plasma volume expansion is not recommended routinely for women with pre-eclampsia. (⊕⊕⊕O/Strong).

Magnesium sulphate

28. Women with eclampsia should receive magnesium sulphate to prevent recurrent seizures (⊕⊕⊕⊕/Strong).

29. Women with pre-eclampsia who have proteinuria and severe hypertension, or hypertension with neurological signs or symptoms, should receive magnesium sulphate for eclampsia prevention (⊕⊕⊕⊕/Strong).

Timed birth

30. Indications for delivery with any HDP at any gestational age (⊕⊕⊕O/Strong) include:

- Abnormal neurological features (such as eclampsia, severe intractable headache or repeated visual scotomata);
- Repeated episodes of severe hypertension despite maintenance treatment with three classes of antihypertensive agents;
- Pulmonary oedema;
- Progressive thrombocytopenia or platelet count $<50 \times 10^9$/L;
- Transfusion of any blood product;
- Abnormal and rising serum creatinine;
- Abnormal and rising liver enzymes;
- Hepatic dysfunction (INR > 2 in absence of DIC or warfarin), haematoma or rupture
- Abruption with evidence of maternal or fetal compromise; or
- Non-reassuring fetal status (including death)

31. A decision to deliver should not be based solely upon the degree of either proteinuria (⊕⊕OO/Strong) or hyperuricaemia (⊕⊕OO/Strong).

(See Table 7 for recommendations according to gestational age.)

Antenatal corticosteroids

32. Do not administer corticosteroids to hasten resolution of Haemolysis Elevated Liver enzyme Low Platelet (HELLP) syndrome (⊕⊕⊕O/Strong)

Postpartum care

33. For women with antepartum hypertension, BP should be monitored at least once on days 3–7 postpartum when it is likely to be highest after birth (GPP).

34. Antihypertensive therapy administered antepartum should be continued after birth. Also, consideration should be given to administering antihypertensive therapy for any hypertension diagnosed before six days postpartum (⊕⊕OO/Weak)

35. The target dBP for postpartum antihypertensive treatment should be 85 mmHg, as antenatally (⊕⊕OO/Weak)

36. Non-steroidal anti-inflammatory drugs (NSAIDs) for postpartum analgesia may be used in women with pre-eclampsia if other analgesics are ineffective, and there is no acute kidney injury (AKI) or other risk factors for it (⊕⊕OO/Weak)

37. Breastfeeding is recommended (⊕⊕⊕O/Strong)

38. Counselling should be provided about the risks of gestational hypertension (at least 4%) or pre-eclampsia (at least 15%) in future pregnancy (GPP)

39. At 3 months postpartum, all women should be reviewed to ensure that BP, urinalysis, and any laboratory abnormalities have normalised. If proteinuria or hypertension persist, then appropriate referral for further investigations should be initiated (GPP).

40. At 6 months postpartum, where possible, all women should be reviewed again, at which point we suggest that BP $\geq$ 120/80 mmHg lead to discussion of lifestyle change (⊕⊕⊕O/Weak)

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

42. We recommend calculating lifetime (not 10-year) cardiovascular risk scores to estimate cardiovascular risk in these women (⊕⊕⊕O/Strong)

43. Annual medical review following hypertensive pregnancy is recommended for the first 5–10 years postpartum (⊕⊕⊕O/Weak)

44. Following hypertensive pregnancy, all women and their offspring should adopt a healthy lifestyle that includes eating well, exercising, aiming for ideal body weight, living smoke-free, and aiming for BP $<$ 120/80 mmHg (⊕⊕⊕⊕/Strong)

1. Introduction

The HDPs are leading causes of maternal and perinatal mortality and morbidity worldwide. >99% of HDP-related maternal deaths occur in under-resourced settings, worldwide, while perinatal death and maternal morbidity remain major challenges for health care providers.

The International Society for the Study of Hypertension in Pregnancy (ISSHP) is committed to providing global leadership through up-to-date, evidence-based guidance for the diagnosis, prediction, prevention, and management of the HDPs. While we recognise that not all guidance can be implemented in all settings even in well-resourced settings, options for management in less-resourced settings are discussed separately. Our guidelines align with the International Federation of Gynecology and Obstetrics (FIGO), and as much as possible, with the World Health Organization (WHO), as the other international organisations providing pregnancy hypertension guidelines.

The current document represents an update of the 2018 guidance following review of intervening published evidence [1,2]. Compared with 2018, we now grade the quality of the evidence and strength of recommendations, although where evidence is lacking, we continue to provide practical advice in the form of 'good practice points' (GPPs). Also, we now outline auditable standards and research recommendations.

Importantly, the 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.

2. Methods

The guideline was developed by maternity care providers, a patient representative, and researchers (from obstetrics, internal medicine, health care administration) who are knowledgeable about the HDP and guideline development. The literature reviewed included the previous (2018) ISSHP guideline, all other national and international pregnancy hypertension guidance and references, updated literature searches covering articles until Dec 2020, and subsequently-published literature known to the authors.

We replicated the search strategy used previously for guideline development [3] (Table S1, restricting articles to those published in English and French). We prioritised randomised controlled trials (RCTs) and systematic reviews (if available) for therapies and evaluated substantive clinical outcomes for mothers (death; serious morbidity, including eclampsia, HELLP (Haemolysis, Elevated Liver enzymes, Low Platelet) syndrome, and other major end-organ complications; severe hypertension; placental abruption; preterm delivery; Caesarean delivery; maternal adverse effects of drug therapies or other interventions; and long-term health) and babies (perinatal death, stillbirth and neonatal death; small for gestational age infants; NICU (neonatal intensive care unit) care; serious neonatal morbidity, and long-term paediatric health and neurodevelopment). All authors graded the quality of the evidence and their recommendations, using GRADE (Level of evidence/Strength of recommendation, Table S1), or designated recommendations as GPPs.

The recommendations are organised into the following sections: classification, diagnosis of hypertension and proteinuria, prediction of pre-eclampsia, prevention of pre-eclampsia, management, and postpartum care. Within each section, any advice specific to a specific hypertensive disorder(s) is highlighted, to avoid repetition inherent in presenting the information for each of chronic hypertension, gestational hypertension, and pre-eclampsia.

This document was reviewed by the Executive Council of the ISSHP and the Preeclampsia Foundation.

3. Recommendations and supporting text

3.1. Diagnosis of hypertension and proteinuria

Recommendations

1. BP should be measured using standardised technique, including women's position (sitting, feet flat on floor), cuff size ('large' if the mid-upper arm circumference is $\geq$ 33 cm), Korotkoff V for the diastolic BP (dBP), and arm used (both, at least initially) (⊕⊕⊕O/Strong).

2. BP taken in pregnancy or postpartum, in any setting, should be measured using a device validated for use in pregnancy and pre-eclampsia (⊕⊕⊕O/Strong).

3. Hypertension should be defined as a systolic BP (sBP) $\geq$ 140 mmHg and/or dBP $\geq$ 90 mmHg, based on an average of at least two measurements (⊕⊕⊕⊕, Strong).

4. BP should be repeated to confirm true hypertension; if hypertension is severe (sBP $\geq$ 160 and/or dBP $\geq$ 110 mmHg), then repeat within 15 min; otherwise, repeat in at least 4 h or on two consecutive outpatient visits (GPP).

5. Quantitative proteinuria testing for pre-eclampsia should be performed as part of the work-up for women suspected of having pre-eclampsia or at high-risk of developing it (⊕⊕⊕⊕, Strong).

6. Proteinuria should be defined as $\geq$ 30 mg/mmol urinary protein: creatinine ratio (PrCr) in a spot (random) urine sample, or albumin: creatinine ratio (ACR) $\geq$ 8 mg/mmol, or $\geq$0.3 g/d in a complete 24-hour urine collection, or $\geq$2+ by urinary dipstick if confirmatory testing is not available (⊕⊕⊕O/Strong).

The definitions of hypertension and proteinuria have not changed since the 2018 guideline.

BP measurement

BP in pregnancy should be measured using the standardised technique, as outside pregnancy. BP should be measured in both arms at least initially, and, thereafter, in the same arm for consistency, choosing the arm with the higher BP.

BP should be measured with a device validated for use in pregnancy and pre-eclampsia (and by extension, for six weeks postpartum) [4]. Mercury sphygmomanometry is no longer available. While aneroid devices are used commonly, they may over- or under-estimate BP [5], and they need to be regularly calibrated. Liquid-crystal sphygmomanometery [6] is the best alternative, but, if unavailable, an automated device validated in pregnancy and pre-eclampsia is preferable; a list of suitable devices is available online [7].

Once BP is found to be elevated in a clinical setting (i.e., clinic/office, obstetrical day unit, or hospital inpatient), and there is no evidence of pre-eclampsia, 'out-of-office' BP monitoring (i.e., at home, by 24-hour ambulatory BP monitoring [ABPM] that takes BP regularly, or in a pharmacy) is advised. This will identify any element of white-coat hypertension, confirm the diagnosis of hypertension, and ideally, thereafter, monitor changes in BP and response to antihypertensive treatment. Also, it is wise to check a woman's home BP device (against a calibrated device in the office) before she begins home BP monitoring (HBPM) and intermittently thereafter. ABPM remains the gold standard for BP assessment, but it is less commonly used, especially in pregnancy because of availability, convenience and women's preferences.

Hypertension

Hypertension in pregnancy continues to be defined as a clinic sBP $\geq$ 140 mmHg and/or a dBP $\geq$ 90 mmHg, with sBP $\geq$ 160 mmHg and/or a dBP $\geq$ 110 mmHg defined as severe hypertension. While the American Heart Association and American College of Cardiology have redefined hypertension outside pregnancy as 130/80 mmHg ('stage 1′ hypertension), with 140/90 as 'stage 2' hypertension, these definitions have not been adopted in pregnancy, even in the United States. While stage 1 may be associated with an increased risk of adverse pregnancy outcomes [8], it has not been shown that implementing a lower diagnostic threshold for hypertension in pregnancy would improve outcomes or be cost-effective [9].

Hypertension should be diagnosed based on at least two readings, averaged to reflect the BP for the visit. If BP values are >10 mmHg different, a third measurement should be taken, and the second and third measurements used.

BP measured out-of-office is generally lower than in the clinic setting among hypertensive women, but there is wide variation [10]. (Use of out-of-office BP values to guide antihypertensive therapy is discussed under 'Management/Antihypertensive therapy', below.)

Proteinuria

Proteinuria may be detected qualitatively, by urinary dipstick testing (manual or automated), or quantitatively, by PrCr, ACR, or 24-hour urine collection. While testing in pregnancy is focused on detecting the proteinuria of pre-eclampsia, detecting underlying CKD that is associated with adverse pregnancy and long-term outcomes in pregnancy and long-term is important. For CKD detection, a microscopic urinalysis of the urine sediment is an important second component, to detect red or white blood cells and casts. In pregnancy, a third component not covered by these guidelines, is routine screening for asymptomatic bacteriuria by urine culture.

At antenatal care booking, screening for proteinuria may identify early CKD, leading to management in pregnancy to optimise outcomes, and after pregnancy to slow or prevent progression to end-stage kidney disease. However, urinary dipstick testing for proteinuria is a poor test for this purpose. We suggest a case-finding approach in early pregnancy, as advocated outside pregnancy, with proteinuria testing (ideally albuminuria) and microscopic urinalysis for women with dipstick haematuria or CKD risk factors, particularly Aboriginal ethnicity, chronic hypertension (see 'Classification/Chronic hypertension'), diabetes, human immunodeficiency virus or hepatitis C virus infection, sickle cell trait, malignancy, autoimmune disease, nephrolithiasis, recurrent urinary tract infections, or a family history of CKD. Any woman who subsequently has a pregnancy complication associated with CKD, such as pre-eclampsia or FGR, should be evaluated. (See 'Postpartum care'.)

After antenatal care booking, the value of performing dipstick proteinuria screening at all antenatal appointments for low-risk normotensive women has been questioned [11]. Dipstick proteinuria testing has low diagnostic accuracy, being neither sensitive nor specific at the 1 + level [12]. The majority (i.e., at least two-thirds) of women who present with proteinuria without hypertension do not develop pre-eclampsia as pregnancy progresses [13–16]. Furthermore, the costs of screening all women so frequently are substantial [13,15,17]. Undertaking dipstick proteinuria (manual or automated) screening at all antenatal appointments, particularly for women with chronic hypertension or who are normotensive but otherwise at increased risk of pre-eclampsia, is common practice. As such, where resources allow and as suited to local context, proteinuria screening after booking may be undertaken to identify concerns about pre-eclampsia earlier [16].

Quantitative proteinuria testing (by urinary PrCr, ACR, or 24-hour urine collection) should be performed when pre-eclampsia is suspected, including: $\geq$1 + dipstick proteinuria in women with hypertension and rising BP and in women with normal BP, but symptoms or signs suggestive of pre-eclampsia. A PrCr ratio of $\geq$30 mg/mmol (0.3 mg/mg) is considered to be abnormal [18–21], but the test may occasionally give a false negative result, usually at <400 mg/day proteinuria [20]. A 24-hour urine collection offers no advantage [21], and should be reserved to confirm nephrotic syndrome and define the need for thromboprophylaxis. A urinary ACR $\geq$ 8 mg/mmol (71 mg/g) is considered to be abnormal based on its association with a definition of pre-eclampsia that included the need for more intensive monitoring and/or magnesium sulphate [21]. If confirmatory testing for dipstick proteinuria is not available, then dipstick proteinuria of $\geq$2+ (>1g/L) provides a reasonable assessment of true proteinuria [22–23].

Importantly, a decision to deliver should not be based upon the degree of proteinuria alone (see 'Management/Timing of birth', below). Proteinuria is not independently predictive of adverse maternal outcome. While absolute levels of proteinuria correlate with adverse perinatal outcomes [24–28], the predictive value of heavy (4 + dipstick) proteinuria is limited to settings without advanced fetal surveillance capacity. (Please see 'Management/Maternal monitoring and Management/Fetal monitoring' for details.)

3.2. Classification

Recommendations

7. The HDPs should be classified according to the criteria presented in Table 1.

8. The ISSHP does not suggest routine testing for secondary causes of hypertension in the absence of clinical clues to these conditions (⊕⊕OO/Strong).

9. Women with white-coat hypertension should undertake regular HBPM (⊕⊕⊕O/Strong).

10. Pre-eclampsia should not be classified as 'mild' or 'severe' in an ongoing pregnancy (⊕⊕⊕O /Strong).

See Table 1 and text.

11. An elevation in BP should not be used to make a diagnosis of pre-eclampsia superimposed on chronic hypertension (⊕⊕OO/Strong).

12. To the assessment of women suspected of having pre-eclampsia (<37 weeks), we recommend adding evaluation of angiogenic imbalance, when available, as a marker of uteroplacental dysfunction to be used in conjunction with other clinical tests. (⊕⊕⊕O/Strong).

The classification of the HDPs places women into meaningful prognostic groups (Table 1). This classification differs from our 2018 guidance in that women with chronic hypertension can now be diagnosed

Table 1
Classification of the HDPs.

Type of hypertensive disorder	Definition
Pre-pregnancy or at < 20 weeks	
Chronic hypertension	Hypertension detected pre-pregnancy or before 20 weeks' gestation
Essential	Hypertension without a known secondary cause
Secondary	Hypertension with a known secondary cause (e.g., renal disease)
White-coat hypertension	sBP ≥ 140 and/or dBP ≥ 90 mmHg when measured in the office or clinic, and BP < 135/85 mmHg using HBPM or ABPM readings
Masked hypertension	BP that is <140/90 mmHg at a clinic/office visit, but ≥135/85 mmHg at other times outside the clinic/office
≥20 weeks	
Gestational hypertension	Hypertension arising *de novo* at ≥ 20 weeks' gestation in the absence of proteinuria or other findings suggestive of pre-eclampsia
Transient gestational hypertension	Hypertension arising at ≥20 weeks' gestation in the clinic, which resolves with repeated BP readings
Pre-eclampsia*	
De novo	Pre-eclampsia (de novo) is gestational hypertension accompanied by one or more of the following new-onset conditions at ≥20 weeks' gestation: 1. Proteinuria 2. Other maternal end-organ dysfunction, including: • Neurological complications (e.g., eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, or persistent visual scotomata) • Pulmonary oedema • Haematological complications (e.g., platelet count < 150,000/μL, DIC, haemolysis) • AKI (such as creatinine ≥ 90 μmol/L or 1 mg/dL) • Liver involvement (e.g., elevated transaminases such as ALT or AST > 40 IU/L) with or without right upper quadrant or epigastric abdominal pain) 3. Uteroplacental dysfunction (e.g., placental abruption, angiogenic imbalance, fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or intrauterine fetal death).
Superimposed on chronic hypertension	Among women with chronic hypertension, development of new proteinuria, another maternal organ dysfunction(s), or evidence of uteroplacental dysfunction (as above).

ABPM (ambulatory 24-hour BP monitoring), AKI (acute kidney injury), ALT (alanine aminotransferase), AST (aspartate aminotransferase), BP (blood pressure), dBP (diastolic BP), DIC (disseminated intravascular coagulation), HBPM (home BP monitoring), HDPs (hypertensive disorders of pregnancy), sBP (systolic BP).
* Some components of the definition will require use of locally-accepted definitions (such as fetal growth restriction) and clinical judgement. Also, the term 'severe pre-eclampsia' should not be used in clinical practice, as all women with pre-eclampsia are at risk of developing severe features.

with superimposed pre-eclampsia if they have evidence of uteroplacental dysfunction; this was previously excluded from the diagnosis of superimposed pre-eclampsia as a known complication of chronic hypertension.

Chronic hypertension

Chronic hypertension should be confirmed by HBPM or ABPM if at all possible, to exclude white-coat hypertension which is common (as discussed below). If access to the appropriate equipment and instructions is not possible, or women are not willing, then at minimum, elevated BP should be confirmed after repeated measurements over hours at the same visit, or on two consecutive antenatal visits [29].

Chronic hypertension is associated with an excess of adverse maternal and fetal outcomes, including superimposed pre-eclampsia (see below) [30].

Diagnostic testing and ongoing monitoring of women with chronic hypertension are presented in Table 2. Most cases of chronic

Table 2
Chronic hypertension – diagnostic testing and monitoring.

DIAGNOSIS	MONITORING
All women with chronic hypertension should have the following tests performed at first diagnosis in pregnancy, to provide a baseline reference should suspicion arise later in pregnancy of superimposed pre-eclampsia (GPP): • Urine microscopy and urinary protein excretion (ideally, by PrCr or ACR) • Full blood count for platelet count (and haemoglobin); • Serum creatinine; and • Liver enzymes [AST or ALT). Additional testing can be performed if abnormalities are detected, such as other electrolytes, and renal ultrasound if serum creatinine or urinary dipstick testing are abnormal, LDH and a blood film (for schistocytes) if haemolysis is suspected, or 24-hour urine collection (for proteinuria) and serum albumin if nephrotic syndrome is suspected. If resources are limited, prioritise evaluation of urinary protein excretion and serum creatinine.	The frequency of follow-up should be guided by BP level and other individual risks of adverse outcome (GPP).

ACR (albumin:creatinine ratio), ALT (alanine aminotransferase), AST (aspartate aminotransferase), BP (blood pressure), GPP (good practice point), LDH (lactate dehydrogenase), PrCr (protein:creatinine ratio).

hypertension are due to essential hypertension, usually accompanied by a family history of hypertension and often by overweight or obesity. Unless there are clues to a secondary cause of hypertension, the ISSHP does not recommend routine investigations (e.g., renal ultrasound). Chronic hypertension is best managed by 'tight' control of BP (see 'Management/Antihypertensive therapy', below).

White-coat hypertension is common (≈30% of chronic hypertension) and associated with an increased risk of pre-eclampsia [31–32]. HBPM is necessary to manage white-coat hypertension, as it is reasonable to withhold antihypertensive therapy when home BP values are normal. In the absence of severe hypertension (≥160/110 mmHg), we suggest relying on average BP over several days, rather than acting on single readings [33].

Masked hypertension is probably less common in pregnancy, but much less is known about this compared with white-coat hypertension. It is typically diagnosed by HBPM or ABPM that is initiated when there is evidence of hypertensive target organ damage in the mother (e.g., unexplained CKD, or left ventricular cardiac hypertrophy) or uteroplacental dysfunction, but there is no apparent hypertension in clinic.

Gestational hypertension

Transient gestational hypertension resolves with repeated BP measurements, such as those taken over the course of several hours in a Day Assessment Unit. This is not the same as white-coat hypertension, which is associated in early pregnancy with completely normal out-of-office BP measurements. Transient gestational hypertension is associated with a 40% risk of subsequent true gestational hypertension or pre-eclampsia [34], warranting additional monitoring throughout the remainder of pregnancy, ideally including HBPM.

Persistent gestational hypertension is associated with outcomes that are dependent on the gestational age at which hypertension develops after 20 weeks'. About 25% of women who present with gestational hypertension at <34 weeks' will progress to pre-eclampsia and have poorer outcomes [35].

When a woman presents for antenatal care at ≥20 weeks, without knowledge of prior BP values, and she is found to be hypertensive, she should be managed in pregnancy as if she has gestational hypertension or pre-eclampsia, unless, or until the balance of evidence shows

Table 3
Gestational hypertension – diagnostic testing and monitoring.

DIAGNOSIS	ONGOING SURVEILLANCE
Women should undergo testing for pre-eclampsia to rule it out (⊕⊕⊕⊕). Angiogenic markers (if available) could be performed; if normal, the diagnosis of gestational hypertension would be strengthened (⊕⊕⊕O). Fetal ultrasound (where available) should be performed to assess fetal growth, amniotic fluid volume and umbilical artery Doppler (⊕⊕⊕O). If FGR is detected, local/national fetal surveillance guidance should be followed [1] (GPP).	Antenatal contacts should occur at least once weekly (GPP). Proteinuria testing should be performed at each subsequent antenatal visit (⊕⊕⊕O). The risk of adverse maternal outcomes increases with earlier gestational age and/or the onset/worsening of the following features that women should be informed to report between visits, according to the miniPIERS model (https://pre-empt.bcchr.ca/evidence/minipiers).(⊕⊕⊕⊕): • headache/visual disturbances • chest pain/dyspnoea • vaginal bleeding with abdominal pain • sBP (if self-monitoring) • dipstick proteinuria (if self-monitoring) • pulse oximetry (if self-monitoring). Fetal ultrasound should be repeated at least monthly to assess fetal growth, amniotic fluid volume and umbilical artery Doppler (⊕⊕⊕O). If pre-eclampsia is again suspected on clinical grounds, the woman should be re-evaluated for pre-eclampsia (⊕⊕⊕⊕).

FGR (fetal growth restriction), GPP (good practice point), PIERS (Pre-eclampsia Integrated Estimate of Risk Score), sBP (systolic blood pressure).

otherwise.

Diagnostic testing and ongoing monitoring of women with gestational hypertension are presented in Table 3. Where angiogenic marker testing is available, the lack of angiogenic imbalance, as assessed by normal PlGF ($\geq 5^{th}$ centile for gestational age) or normal sFlt/PlGF ratio, suggests that there is no uteroplacental dysfunction. In the absence of other markers of pre-eclampsia (see below), a diagnosis of gestational hypertension can be made. Rarely (<1%), these women will require delivery for pre-eclampsia within the next 7–14 days, although some (up to ≈20%) will evolve into pre-eclampsia at some point [36–38]. Appropriate investigations should be done after pregnancy to determine if she has underlying chronic hypertension; this will generally be apparent because the BP will not have normalised within three months after birth; see 'Postpartum care' for details.

Pre-eclampsia

Pre-eclampsia is the most dangerous of the HDPs; world-wide, each year, pre-eclampsia is responsible for over 500,000 fetal and neonatal deaths and over 70,000 maternal deaths.

While the definition of pre-eclampsia has not changed (Table 1), further clarity has been provided by additional examples of other maternal organ dysfunction (i.e., pulmonary oedema) and uteroplacental dysfunction (i.e., placental abruption, angiogenic imbalance). Given the international target audience, we rely on locally-accepted definitions. 'Other' maternal organ dysfunction includes rarer complications, such as ascites or Bell's palsy.

Pre-eclampsia may develop or be recognised for the first time intrapartum or early postpartum. Superimposed pre-eclampsia may develop in ≈25% of women with chronic hypertension and even more women with underlying renal disease, including those with renal transplants [39]. Pre-eclampsia can deteriorate rapidly and without warning, which is why the ISSHP does not recommend classifying it as non-severe or severe. The HELLP syndrome (full or partial, with only some manifestations, such as elevated liver enzymes and low platelets) is a (serious) manifestation of pre-eclampsia and not a separate disorder.

Among women with chronic hypertension, rises in BP are insufficient to diagnose superimposed pre-eclampsia, as such rises are difficult to distinguish from the usual increase in BP after 20 weeks' gestation. Proteinuria is not mandatory for the diagnosis, but it is commonly present (in up to 75% of cases) [40]. Also, among women with proteinuric renal disease, an increase in proteinuria during pregnancy is insufficient to diagnose superimposed pre-eclampsia. Other manifestations of pre-eclampsia (such as severe headache) are also common in pregnancy, but in the context of new-onset hypertension, it is safest to consider such a woman to have pre-eclampsia and manage accordingly. Elevated serum uric acid corrected for gestational age has been associated with elevated perinatal risk and uteroplacental dysfunction [41–43], but it was not independently predictive of adverse maternal outcome in multivariable modelling [44]. Hyperreflexia is not a diagnostic criterion as it is non-specific, often present in otherwise well young women, and is highly subject to observer interpretation.

Diagnostic testing and ongoing monitoring of women with pre-eclampsia are presented in Table 4.

Angiogenic imbalance

Angiogenic imbalance, as assessed by reduced PlGF (<5th centile for gestational age) or increased sFlt/PlGF ratio (e.g., >38 by the Roche assay), has been actively evaluated for its role in making an earlier diagnosis of pre-eclampsia based on the presence of uteroplacental dysfunction. (For prediction of pre-eclampsia, see 'Prediction' below).

Systematic review (33 studies, 9426 women) has confirmed that angiogenic imbalance shows promise for prediction of adverse maternal and perinatal outcomes, although there is substantial between-study

Table 4
Pre-eclampsia: diagnostic testing and ongoing monitoring.

DIAGNOSIS	ONGOING SURVEILLANCE
Women should undergo comprehensive testing for pre-eclampsia (⊕⊕⊕⊕). Women suspected of having pre-eclampsia superimposed on chronic hypertension should undergo the same testing as for women with de-novo pre-eclampsia (⊕⊕⊕⊕). Maternal testing should include the following components of the fullPIERS model (https://pre-empt.bcchr.ca/evidence/fullpiers), which along with earlier gestational age and the symptoms of chest pain/dyspnoea, identify women at increased risk of adverse maternal outcomes (⊕⊕⊕⊕): • oxygen saturation • platelet count • serum creatinine • AST or ALT Angiogenic markers (if available) could be performed; if there is angiogenic imbalance†, the diagnosis of pre-eclampsia would be strengthened (⊕⊕⊕O). Fetal ultrasound should be performed to assess fetal growth, amniotic fluid volume and umbilical & uterine artery Doppler (⊕⊕⊕O). If FGR is detected, ISUOG fetal surveillance guidance [2] should be followed (GPP).	Women with pre-eclampsia superimposed on chronic hypertension should undergo the same surveillance as for women with de-novo pre-eclampsia (⊕⊕⊕⊕). Once confirmed as significant, proteinuria testing does not need to be repeated (⊕⊕⊕O/Strong). Maternal testing, at least twice weekly, should include re-evaluation of the following components of the fullPIERS model (https://pre-empt.bcchr.ca/evidence/fullpiers) (⊕⊕⊕O): • gestational age • chest pain or dyspnoea • oxygen saturation • platelet count • serum creatinine • AST or ALT Upon admission to delivery suite, women with pre-eclampsia should have a platelet count done, regardless of when this was last performed (GPP). There is insufficient evidence to recommend re-evaluation with angiogenic markers (⊕OOO). Where available, fetal ultrasound should be performed once every two weeks to assess fetal growth, and at least once every two weeks to assess amniotic fluid volume and umbilical artery Doppler (⊕⊕⊕O). We recommend that at <34 weeks when there is fetal growth restriction, Doppler velocimetry of the ductus venosus be performed where available, to assess risk of adverse perinatal outcome (⊕⊕⊕O/Strong). We recommend against use of the biophysical profile to monitor fetuses at risk in hypertensive pregnancy (⊕⊕⊕O/Strong).

ALT (alanine aminotransferase), AST (aspartate aminotransferase), FGR (fetal growth restriction), GPP (good practice point), ISUOG (International Society for Ultrasound in Obstetrics and Gynecology), PIERS (Pre-eclampsia Integrated Estimate of Risk Score).

heterogeneity [45]. For example, among women with 'suspected pre-eclampsia', angiogenic imbalance has high negative predictive value in ruling out: development of proteinuric pre-eclampsia within 7 days, adverse maternal outcomes within 14 days [46], or delivery with pre-eclampsia within 14 days [37–38] when suspected pre-eclampsia is primarily related to hypertension (but not when FGR is a prominent reason [48]). Use of angiogenic markers to guide care may reduce adverse maternal outcomes (5% to 4%) [38], time-to-diagnosis of pre-eclampsia (by an average of 2 days) [38,49], identify women at increased risk of peripartum severe maternal morbidity (including postnatal hypertension) [50], and be cost-saving in the UK [51]. Similar findings are emerging from less-resourced settings [52]. Prediction of adverse outcomes may be improved by combining angiogenic markers with other clinical, routine laboratory, and ultrasonographic data [53–55].

There remain a number of challenges.

- First, the term 'suspected pre-eclampsia' has been used for a broad range of women. Those with new/worsening hypertension who undergo investigations may receive a diagnosis of pre-eclampsia and angiogenic imbalance may aid in identification of uteroplacental dysfunction. Normotensive women with one/more of the symptoms or signs characteristic of pre-eclampsia (e.g., FGR) cannot be diagnosed with pre-eclampsia, but angiogenic imbalance appears to identify those at increased risk of progression to pre-eclampsia. (Normotensive FGR is covered by specific guidance [56].) Other manifestatons are non-specific and overlap with other conditions, such as migraine. As such, the ISSHP advises that 'suspected pre-eclampsia' be used for no more than 24 h to avoid confusion.
- Second, women with 'suspected pre-eclampsia' have often been studied where pre-eclampsia was defined only by gestational hypertension and proteinuria [37,47,57], or women with new dipstick proteinuria did not necessarily undergo confirmatory testing for proteinuria prior to enrolment [36,38]. As such, many women with 'suspected pre-eclampsia' would have already satisfied the current ISSHP broad definition of pre-eclampsia. It is possible that the ability of angiogenic markers to predict 'delivery with pre-eclampsia within 14 days' may have been driven by the fact that many of the women already had pre-eclampsia [36]. Alternatively, angiogenic markers may add further to risk stratification among women who already meet diagnostic criteria for pre-eclampsia [58]. Further work is needed to define the added value of angiogenic markers across gestational ages.
- Third, our understanding about how best to use angiogenic markers is complicated by numerous assays and cut-off values (with PlGF varying with gestational age), and promotion as a test for pre-eclampsia rather than one for uteroplacental dysfunction that underlies many cases of preterm pre-eclampsia, but also other related conditions, like placental FGR [59].
- Finally, we do not know how angiogenic markers add to prediction of adverse outcomes based on routinely-collected data used in models [44,60], although a recent publication suggests that a multivariable approach is important [53]. If reassessment for suspected pre-eclampsia is required, limited data suggested that ≈75% of PlGF results remain similar [61].

These challenges aside, maternal circulating angiogenic markers are increasingly part of investigations for pre-eclampsia, and real-time data from a number of groups support clinical utility as a diagnostic and prognostic tool [53,62]. As such, the ISSHP has moved to incorporate angiogenic markers into investigations as another marker of uteroplacental dysfunction, similar to angiogenic marker dysregulation in FGR, but not as a sole criterion for diagnosing pre-eclampsia. Angiogenic markers may be particularly useful in the face of pre-existing proteinuria, chronic hypertension or CKD [63–64]. As making a diagnosis of pre-eclampsia is such an important clinical decision, all units are encouraged to evaluate patient preferences, resources, outcomes, and costs associated with use of these markers in their own population.

Maternal monitoring

For women with pre-eclampsia, maternal assessment should include BP and proteinuria, as well as the components of the fullPIERS (Pre-eclampsia Integrated Estimate of Risk Score) model that is predictive of adverse maternal outcome in hypertensive pregnancy and pre-eclampsia specifically, when performed at least twice weekly [44,65]. The adverse maternal outcomes are a composite derived from Delphi consensus and similar to the later 14 core maternal outcomes in pre-eclampsia (**Panel**), reflecting one/more of:

- maternal death;
- neurological complications (eclampsia or posterior reversible encephalopathy syndrome; stroke, transient ischaemic attack, or reversible ischaemic neurological deficit; Glasgow coma score <13);
- cardiorespiratory complications (infusion of a third parenteral antihypertensive drug; pulmonary oedema; positive inotropic support; myocardial ischaemia or infarction; oxygen saturation <90%; ≥50% inspired oxygen for more than one hour; intubation other than for Caesarean);
- renal complications (acute renal sufficiency [creatinine >150 μmol/L] with pre-existing renal disease, acute renal failure with pre-existing renal disease [creatinine >200 μmol/L], dialysis;
- hepatic (liver dysfunction or capsule haematoma or rupture);
- haematological (platelet count $< 50 \times 10^9$ per L or transfusion of any blood product);
- placental abruption;
- other (severe ascites, Bell's palsy).

The fullPIERS model includes: gestational age, chest pain/dyspnoea, pulse oximetry, platelet count, serum creatinine, and AST or ALT [44]. By incorporating gestational age into the model, use of fullPIERS model is not restricted to a specific gestational age range, like the PREP model developed for use in pre-eclampsia before 34 weeks [66]. fullPIERS does not include proteinuria; once confirmed as present, proteinuria testing does not need to be repeated. (Please see 'BP and proteinuria' for further details.) An online calculator is available (https://pre-empt.bcchr.ca/evidence/fullpiers).

It is not known how, among women with pre-eclampsia, angiogenic markers (performed once or serially) may add to fullPIERS for prediction of adverse maternal outcomes, or to traditional fetal assessment for prediction of adverse perinatal outcomes. However, there are some promising publications [53,67].

Without ready access to laboratory results, miniPIERS includes: sBP, dipstick proteinuria, parity, gestational age, and symptoms (headache/visual symptoms, chest pain/dyspnoea, abdominal pain with vaginal bleeding); model performance is improved with addition of pulse oximetry [68–69]; an online calculator is available (https://pre-empt.bcchr.ca/evidence/minipiers). With ready access to laboratory results, fullPIERS includes: gestational age, chest pain/dyspnoea, pulse oximetry, platelet count, serum creatinine, and AST or ALT [44]. While clonus reflects central nervous system irritability, the reproducibility of clonus testing (in the maternity setting) and its independent predictive value for adverse outcome is uncertain. Uric acid has been associated with heightened risk of adverse maternal and fetal outcomes, particularly when gestational age corrected, but the test was not independently predictive of adverse maternal outcomes in fullPIERS [41].

Fetal monitoring

Although multiple methods of fetal surveillance are available, there is no strategy of various methods and timings that has been recognised to be superior in hypertensive pregnancy specifically. For the four fetal and four neonatal adverse outcomes in pre-eclampsia, see Panel [70].

While serial FHR monitoring is common practice in hypertensive

pregnancy, the effectiveness of this approach in reducing adverse outcome and the optimal frequency, if any, is undetermined. Where resources are limited, CTGs performed 6-hourly in inpatient women have been used to monitor for placental abruption [71–72].

As the fetus with growth restriction and/or reduced amniotic fluid volume is at particular risk of stillbirth and neonatal mortality and morbidity, ultrasonographic assessment of fetal growth and liquor volume is recommended. Given the shared origins of pre-eclampsia and FGR [73], we recommend that care-providers follow current ISUOG guidance for women with suspected FGR [56]. Doppler ultrasound of the umbilical artery may reduce perinatal death and obstetric intervention in high-risk pregnancies, but the evidence is not definitive [74]; it is important to note that near or at term, a normal umbilical artery Doppler does not exclude fetal compromise. At $\leq 33^{+6}$ weeks in the presence of FGR, the addition of Doppler ultrasound of the ductus venosus may be beneficial, as an absent or reversed a wave is associated with a substantially increased risk for stillbirth [75]; neurodevelopmental outcomes among survivors is improved when timing of birth is based on abnormal ductus venosus Doppler, short-term (computerised) fetal heart rate (FHR) variability, and/or spontaneous FHR decelerations [76–78].

The biophysical profile is not recommended as it can be falsely reassuring in hypertensive and fetal growth-restricted pregnancies, and an abnormal profile is a late finding [79–81].

Without ready access to methods of fetal surveillance beyond FHR monitoring, maternal characteristics (including 4 + dipstick proteinuria) can be used to estimate perinatal risk at ≥32 weeks; before this time, perinatal risk is almost entirely driven by gestational age [82].

4. Prediction of pre-eclampsia

Recommendations

13. At minimum, women should be screened for clinical risk markers of pre-eclampsia risk at antenatal care booking (GPP).

14. If testing is available, after appropriate counselling, women should be screened at 11–14 weeks for preterm pre-eclampsia risk, using a combination of clinical risk factors, BP, uterine artery pulsatility index, and PlGF, as available, even if they have been already been identified as having clinical 'high-risk' factors (⊕⊕⊕O/Strong).

No first or second trimester test or set of tests can reliably predict the development of all cases of pre-eclampsia, and combined first trimester testing (described above) does not predict development of pre-eclampsia at term when most cases develop.

Large-scale epidemiological studies have identified clinical risk factors for pre-eclampsia (Table 5). The strongest are prior pre-eclampsia (RR 8.4, 95% CI 7.1, 9.9) and chronic hypertension (RR 5.1, 95% CI 4.0, 6.5). There is some disagreement as to whether some high-risk factors should be considered moderate-risk, such as obesity and those who have conceived with ART based on risks alone [83]; however, these risk factors are likely to be modifiable by aspirin and addressing by pre-pregnancy weight loss the pre-eclampsia risk associated with obesity could have a substantial impact on pre-eclampsia incidence at the population level [84]. Also, there is a wide spectrum of CKD that was not reflected in the epidemiological studies included in the predictive analyses [84–85].

Clinical measurements, and ultrasonographic and laboratory parameters have been explored during early pregnancy as tools for predicting who will later develop pre-eclampsia [86–87]. According to systematic reviews, well-studied clinical predictors have included demographics, past history, medical conditions, characteristics of current pregnancy (like conception by ART or multifetal pregnancy), physiological variables (like BP), and the social determinants of health (including nutrition). Laboratory measures have included maternal circulating angiogenic proteins (including PlGF, sFlt-1, and soluble endoglin), inflammation (including IFN-γ), lipid metabolism and oxidative stress (including ozone), cardiac function, renal function, coagulation (including genetic thrombophilia testing and anticardiolipin antibodies), and fetoplacental endocrine function (including beta-hCG, pregnancy-associated plasma protein A [PAPP-A], placental protein 13 [PP13], and inhibin A). Ultrasonographic measures have included uterine artery Doppler, placental vascularisation, and single fetal umbilical artery indices. Multivariable, specialised models have outperformed single factors or simple models [88].

Table 5
Clinical risk factors for pre-eclampsia identifiable in early pregnancy (modified from Bartsch et al[3])*.

	'High-risk' factors (any one)	**'Moderate-risk' factors** (two or more)
Prior pregnancy history		
	Prior pre-eclampsia	Prior placental abruption Prior stillbirth Prior fetal growth restriction
Demographics		
	Pre-pregnancy BMI > 30 kg/m^2	Maternal age >40 years
Pre-existing medical conditions		
	Chronic hypertension Pre-gestational diabetes mellitus Chronic kidney disease (inc. kidney transplanted women)† Systemic lupus erythematosus/ antiphospholipid antibody syndrome†	
This pregnancy		
	Assisted reproductive therapy‡	Nulliparity Multifetal pregnancy

BMI (body mass index).
* Women are considered to be at increased risk if they have at one 'high risk' factor or two or more 'moderate risk' factors.
† These have been listed as 'high' (not 'moderate' risk factors[3]) because of the wider spectrum of chronic kidney disease and associated adverse outcomes than evidenced in the included cohort studies [4].
‡ The risk of ART varies with the methods used, being highest among women receiving semen or oocyte donation and following frozen embryo transfer [5].

In the multi-ethnic UK population with an incidence of pre-eclampsia of ≈3%, screening with a 'triple test' (of clinical risk factors plus BP, serum PlGF, and uterine artery Doppler ultrasound) can identify the largest proportion of women (≈80%) who will go on to develop preterm pre-eclampsia [89–90]. Identifying women in this way, and giving them low-dose aspirin, reduces the incidence of preterm (but not term) pre-eclampsia [91]. An online calculator is available on the Fetal Medicine Foundation website [92] and as an app through the App Store. (For recommendations about aspirin, see 'Prevention' below.)

Only ≈10% of women who develop preterm pre-eclampsia have clinical risk factors [83]. However, a large proportion (43.9%) of women with 'strong' clinical risk factors and the majority (70.7%) with 'moderate' ones screen negative by the FMF algorithm, and their risk of pre-eclampsia is substantially lower (i.e., 0.65% and 0.42%, respectively) [83]; 'triple test' screening, where available, should be undertaken with clear objectives in mind, such as women's reassurance, to guide aspirin dosing, or a change in management, including surveillance.

Screening beyond clinical factors should be considered in the context of the available health care resources, and discussed with the woman [83]. The detection rate of maternal factors alone (≈40% of European women and 25% in Asia [93] for preterm pre-eclampsia is inferior to maternal factors plus BP (just under 50%). A combination of maternal risk factors, BP, and uterine artery Doppler can detect just over 75% of women who will develop preterm pre-eclampsia [89]; the addition of PlGF improves detection to 80% [94]. All approaches are poor at

identifying women who go on to develop term pre-eclampsia (≈40% detection) [89–90]. This multivariable approach to screening has also been validated prospectively in mixed-European, Australian, Asian, North and South American populations [93,95–100].

All measurements - clinical, laboratory, or ultrasonographic - should be performed by individuals with adequate training and who undergo ongoing quality assurance assessment. This is a critical point given that some ultrasound departments do not have staff specifically trained in uterine artery Doppler assessment despite performing these tests on a frequent basis.

While the most effective screening strategy involves a number of investigative tools, some consider screening to be complex and expensive; the costs of screening must be weighed against the short-term costs of preterm pre-eclampsia, likely driven by neonatal care unit costs [101], as well as the long-term implications of pre-eclampsia for the mother and offspring. The psychological implications of a false positive screening test for the mother have been raised as a potential concern associated with multivariable screening; however, false positive screening results occurred as frequently with multivariable screening as with clinical criteria, and women who declined to participate in the ASPRE trial were not concerned about being labelled as high risk [102]. It will be important to confirm the cost effectiveness of multivariable screening for pre-eclampsia risk and intervention, contextualised to population, disease prevalence, and models and costs of care. Given the link between prediction and prevention, these issues are discussed further under, 'Prevention', for aspirin.

5. Prevention of pre-eclampsia

All women in pregnancy

Recommendations

15. Unless there are contraindications, all women should exercise in pregnancy to reduce the likelihood of gestational hypertension and pre-eclampsia ((⊕⊕⊕O/Strong).

16. For women with low dietary intake of calcium (<900 mg/day), oral calcium supplementation of at least 500 mg/d is recommended (⊕⊕OO/Weak).

17. Women should NOT receive low-molecular-weight heparin*, vitamins C or E, or folic acid for pre-eclampsia prevention (⊕⊕⊕O/Strong).

** This recommendation relates to use of heparin for pre-eclampsia prevention. And not for other indications, such as thromboprophylaxis in anti-phospholipid antibody syndrome.*

Women at increased risk of pre-eclampsia

Recommendations

18. Low-dose aspirin is recommended (⊕⊕⊕⊕/Strong), to be taken at bedtime (⊕⊕⊕O/Strong), preferably before 16 weeks and discontinued by 36 weeks (⊕⊕⊕O/Strong).

19. After multivariable screening, aspirin should be given at a dose of 150 mg/night (⊕⊕⊕⊕/Strong).

20. After screening with clinical risk factors and BP, aspirin should be given at a dose of 100–162 mg/d (⊕⊕⊕O/Strong).

No treatment to date can prevent pre-eclampsia in all women, but there are approaches that reduce the risk.

5.1. Exercise

In RCTs, exercise reduces the risk of both gestational hypertension (OR 0.61, 95% CI 0.43, 0.85) and pre-eclampsia (OR 0.59, 95% CI 0.37, 0.90) (as well as gestational diabetes by a similar degree) [103–104]. To achieve these reductions, women must undertake at least 140 min per week of moderate-intensity exercise, such as brisk walking, water aerobics, stationary cycling with moderate effort, resistance training, carrying moderate loads, and household chores such as gardening or washing windows. Typically during these activities, a person can talk but not sing, and notices that their heart rate has increased.

Exercise is contraindicated in all women with established pre-eclampsia, and relatively contraindicated in women with gestational hypertension [104], but among those without contraindications, there are no significant adverse effects of exercise in pregnancy.

5.2. Calcium

Calcium administered from 20 weeks' gestation is effective in decreasing pre-eclampsia risk when administered at high (1.5–2.5 g/d) or low dose (<1 g/d) and to women at high or low risk of pre-eclampsia, but only among populations with low baseline intake of calcium (<900 mg/d) [105–106]. Currently, there is no standardised method for assessing dietary intake of calcium among individual women. The bulk of the evidence comes from women at high risk, administered high-dose calcium in low-intake populations, and there is a lack of understanding about how baseline risk, individual calcium intake, and calcium dose administered in pregnancy interact. An ongoing trial in the UK is addressing the question of very high-dose calcium administered to high-risk women in an on average, adequate calcium intake population (CaPE trial, NIHR127325).

In a RCT of 1355 women at high risk of pre-eclampsia based on disease in prior pregnancy, calcium supplementation (vs. placebo) of 500 mg/day before pregnancy and until 20 weeks of the subsequent pregnancy (with an increase in calcium to 1.5 g/d thereafter for all women), reduced the incidence of pre-eclampsia only when compliance with tablets before 20 weeks (45.0%) was at least 80% (RR 0.66, 95% CI 0.44, 0.98), and may have reduced the incidence of pregnancy loss or pre-eclampsia (107/323, 33% vs. 126/310, 41%; RR 0.82, 95% CI 0.66, 1.00) [107]. These data serve to emphasise that low calcium intake should be addressed pre-pregnancy if possible, especially among high-risk women among whom compliance is critical.

Calcium administration should be in addition to aspirin, as indicated.

5.3. Aspirin

Women at increased risk of preterm pre-eclampsia benefit from receiving low-dose aspirin. However, the magnitude of benefit depends on how their risk is identified, the timing of initiation and dose of aspirin administered, and their adherence to aspirin as prescribed.

Method of risk identification

Women identified as being at increased risk of pre-eclampsia based on clinical risk factors alone benefit from receiving low-dose aspirin (75–162 mg/d), but the risk of pre-eclampsia (RR 0.90, 95% CI 0.84, 0.97) or pre-eclampsia with delivery at <34 weeks (RR 0.90, 95% CI 0.83, 0.98) is reduced by only ≈10%, based on an individual participant data meta-analysis (31 trials, 32,217 women) [108]. However, meta-analyses have illustrated that benefit is related to initiation of aspirin before 16 weeks and at higher dosage, and primarily to prevention of preterm and more severe disease [109–111]. Women who book late for antenatal care may still benefit from aspirin started after 16 weeks, although the reduction in pre-eclampsia has been estimated to be non-significant [109].

Women identified as being at increased risk of pre-eclampsia (of at least 1%) can be identified by the FMF 'triple test' of multivariable screening and their risk of preterm pre-eclampsia more than halved (OR 0.38, 95% CI 0.20, 0.74) by low-dose aspirin at a dose of 150 mg each night, from 11 to 14 weeks until 36 weeks (or birth, if earlier) [91]. The benefits were even greater when women complied with at least 90% of tablets (71% of women). However, the risk of term pre-eclampsia was unchanged (OR 0.95, 95% CI 0.57, 1.57). No adverse effects of aspirin were reported. However, in subgroup analyses, participants with chronic hypertension may not have benefited from a reduced risk of

preterm pre-eclampsia (aOR 1.29, 95% CI 0.33, 5.12), in contrast to other participants (aOR 0.27, 95% CI 0.12, 0.60; p = 0.055), even among women with excellent adherence to aspirin (p = 0.002) [112]. Until this finding can be replicated, it would be prudent to recommend aspirin to women with chronic hypertension and discuss with them the uncertainties.

The cost-effectiveness of a multivariable screen and treat approach has been demonstrated in Canada [113] and Israel [114], and supported by ASPRE data that estimated that the cost of screening would be outweighed by reduced length of neonatal intensive care unit stay (by US $560 per pregnancy screened) [115]. (Approximately 10% of pregnant women screened are screen-positive.) While multivariable screening has been challenged by analyses demonstrating the cost-effectiveness of universal aspirin prophylaxis in pregnancy for all women [116–117] or all nulliparous women [118], these studies did not all account for likely lower adherence with aspirin, reduced effect size, and a potential increase in complications.

Safety

Low-dose aspirin has been widely regarded as safe in pregnancy, although there are signals of small increases in bleeding risk; aspirin has not been associated with miscarriage. Risks, even at a 75 mg dose, but probably higher with increasing dosage [119] have been reported to include vaginal spotting [118,120], antepartum [121–122], intrapartum [123], and postpartum haemorrhage [118,122–123], postpartum haematoma [123],and importantly, a small (0.06%) absolute increase in neonatal intracranial hemorrhage [123], particularly after vaginal birth [123]. Many risks may be mitigated by discontinuing aspirin by 36 weeks based on the lack of effectiveness for prevention of term pre-eclampsia [124]. Risks of aspirin must be seen in the context of important maternal and perinatal risks of pre-eclampsia occurrence, and should dissuade care-providers from instituting universal aspirin prophylaxis, especially as adverse effects of aspirin have been concentrated in trials targeting low-risk women, even when aspirin was stopped before birth, and in observational studies evaluating universal aspirin prophylaxis.

Dose

The ISSHP recognises that different countries have different formulations of aspirin, and it is not possible to cut enteric-coated tablets. In RCTs, doses of 75–162 mg/day have been studied and there are no head-to-head trials of different aspirin doses. Aspirin at a dose <100 mg is not recommended based on platelet insensitivity to aspirin in up to ≈40% of women, particularly as pregnancy progresses and with higher BMI [125–126]; however, at least some component of non-responsiveness may actually be non-adherence and a lack of exposure of platelets to the aspirin [127]. A dose of 150 mg/day (or 162 mg based on two 81 mg tablets of the available formulation) may be more effective, based on ASPRE [91].

5.4. Other preventative strategies

There is insufficient information at this stage to recommend for or against other preventative strategies, such as oral magnesium, metformin, or statins although several trials are in progress. High-dose folic acid, vitamin C, and vitamin E are not recommended [128].

Low molecular weight heparin (LMWH) has received much attention as a potential preventative strategy for pre-eclampsia and other conditions related to uteroplacental dysfunction. A recent individual patient data meta-analysis including 963 women did not support use of LMWH, given no impact on the primary outcome, a composite of early pre-eclampsia, FGR, and/or pregnancy loss [129]. (These data do not preclude use of LMWH and aspirin for other indications, such as thromboprophylaxis in antiphospholipid antibody syndrome.) Like many other interventions, the hope persists that with improved phenotyping of pre-eclampsia and related placental conditions, future trials will target therapies more effectively in specific groups yielding more positive results.

6. Management

6.1. Place of care

Recommendations

21. Women with pre-eclampsia or severe hypertension should be assessed and managed in hospital, before carefully-selected cases are considered for outpatient care (GPP).

Pre-eclampsia can progress quickly, without warning. The level of BP itself is not a reliable way to stratify immediate risk in pre-eclampsia, because some women may develop serious maternal end-organ or uteroplacental dysfunction at minimally elevated BP. However, when BP elevation is to 160/110 mmHg or above, women require urgent treatment in a monitored setting, given the further elevation in risk of adverse maternal and fetal outcomes [130] and to ensure that antihypertensive is effective in lowering BP. Wherever women with pre-eclampsia receive care, resources should be available to undertake emergent delivery and care for sick mothers and newborns [131]; otherwise, transfer of care should be considered.

Some care outside hospital can be considered for women with non-severe hypertension or pre-eclampsia without maternal end-organ involvement after their initial assessment (Table 1). Models of care could include serial visits to obstetrical day units or home care, but any model should include regular (ideally daily) contact to monitor for disease progression. Women considered for outpatient management should: be informed about concerning symptoms, including when and how to report them and be prepared to do so; be provided with HBPM capability, if possible; live a reasonable distance from hospital; have ready access to maternal and fetal surveillance; and be cared for by an experienced and well-organised team.

6.2. Non-pharmacological therapy

There is insufficient evidence to recommend for or against restricted activity, in hospital or at home, for any HDP. A remotely-published, small trial (218 women) found that for women with gestational hypertension, some bedrest in hospital was superior to unrestricted activity at home [132] which, in a similar trial, was women preferred [133–134]. Concerns about thromboembolism risk should caution practitioners against recommending strict bed rest, due to the potential for harm in the absence of demonstrable benefit.

Uncontrolled hypertension of any type, and pre-eclampsia specifically, are absolute contraindications to exercise [104].

6.3. Antihypertensive therapy

Recommendations

22. Hypertension in pregnancy should be treated with antihypertensive therapy, irrespective of the underlying HDP (⊕⊕⊕O/Strong).

23. Severe hypertension in pregnancy (i.e., sBP ≥ 160 mmHg or dBP ≥ 110 mmHg) requires *urgent* antihypertensive therapy, in a monitored setting (⊕⊕OO/Strong).

24. The target BP for antihypertensive therapy should be a dBP of 85 mmHg, regardless of sBP (⊕⊕⊕⊕/Strong).

25. Non-severe hypertension should be treated with the first-line agents oral methyldopa, labetalol, or nifedipine (⊕⊕⊕O/Strong).

26. Severe hypertension should be treated with the first-line agents oral nifedipine, oral labetalol, IV labetalol, or IV hydralazine (⊕⊕⊕O/Strong).

Target BP

Hypertension associated with chronic hypertension, gestational hypertension, or pre-eclampsia requires treatment to reduce the likelihood

of developing severe maternal hypertension and other complications, such as low platelets and elevated liver enzymes with symptoms based on the findings from the CHIPS trial [29]. While CHIPS enrolled women with chronic or gestational hypertension, almost half of women developed pre-eclampsia and all stayed on their allocated BP control, for an average of two weeks before birth. In the CHIPS trial, severe hypertension was similar to pre-eclampsia in being a surrogate marker for adverse outcomes [135].

While not all national societies have adopted the results of CHIPS, the ISSHP endorses the perspective that, "To manage BP expectantly at <160/110 mmHg, but emergently at ≥160/110 mmHg, is logically inconsistent" [136]. Increasing use of antihypertensive medication in hospitalised women with pre-eclampsia has been associated with a reduced incidence of stroke [137].

The target BP for antihypertensive therapy should be a dBP of 85 mmHg, as in CHIPS [29]. BP control resulted from use of a simple algorithm in which antihypertensive drugs were reduced or ceased if dBP fell to ≤80 mmHg, and increased or started if dBP rose to >85 mmHg or sBP were ≥160 mmHg (regardless of dBP, for safety) (Fig. 1). This simplified focus on dBP resulted in associated control of sBP, achieving a mean BP of 133/85 mmHg between randomisation and delivery.

The approach to hypertension is the same for women with comorbidities associated with hypertension, such as chronic renal disease. The only exception is white-coat hypertension unless women develop BP levels ≥160/110 mmHg in the office/hospital setting.

Among hypertensive women, out-of-office BP is usually lower than office BP, but there is wide variation and no consensus about whether an out-of-office BP target should be 130/80 mmHg (corresponding to an office BP of 135/85 mmHg) or 135/85 mmHg (corresponding to an office BP of 140/90 mmHg) [10]. At present, the ISSHP recommends using similar target BP values for out-of-office and office BP, to minimise the risk of low BP at home. An example of a monitoring strategy is presented in Table 6.

Antihypertensive agents

Antihypertensive therapy is generally safe and benefits outweigh risks.

Initial antihypertensive therapy for non-severe hypertension in pregnancy should be monotherapy from the listed first-line drugs, based on small, randomised trials [138]. The choice of antihypertensive agent should be based on characteristics of the patient, contraindications to a particular drug, and physician and patient preference. Caution should be exercised when using labetalol or other beta-blockers in women with asthma, particularly if not well-controlled, given the slight (about 0.5%) increased risk of status asthmaticus [139]. For women with chronic hypertension, no consistent association has been found between antihypertensive agents and congenital malformations. However, there are lingering concerns that hypertension itself may be associated with an increase in birth defects [140]. Beta-blockers, including labetalol, may increase the risk of neonatal bradycardia and hypoglycaemia, and their use is deemed to warrant newborn blood glucose monitoring in some jurisdictions, such as the UK [141].

No firm conclusions can be drawn with regards to long-term child outcomes given a paucity of relevant high-quality studies designed to examine exposure to antihypertensives [142]. Child outcomes at up to 5 years of age were reassuring following exposure to nifedipine for tocolysis [143].

Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy [144], at least to a mid-range dose; add-on drugs should be from a different drug class chosen from first-line or second-line options [144], Table 7 presents a suggested dosing escalation protocol. Less commonly-used but acceptable second-line antihypertensive agents include other beta-blockers (e.g., metoprolol) [138]. Other potential agents are not usually first line therapies, but are not contraindicated, based on limited trial data (e.g., amlodipine or diltiazem) or unproven concerns about maternal tachycardia when used alone (i.e., oral hydralazine), stillbirth in the setting of pre-eclampsia (i.e., prazosin), or theoretical hazards of reduced maternal circulating volume (i.e., diuretics).

ISSHP recommendations are based on BP values, but there is potential in future to further personalise management, using demographic (Black race) and haemodynamic parameters (lower heart rate and cardiac stroke volume, and higher peripheral vascular resistance). Together, these may identify women who respond better to nifedipine than labetalol [145], a particularly important group more often associated with severe hypertension and FGR, and more likely to respond to a vasodilator (e.g., nifedipine). In contrast, women of non-Black race and with higher heart rate and stroke volume, described as being

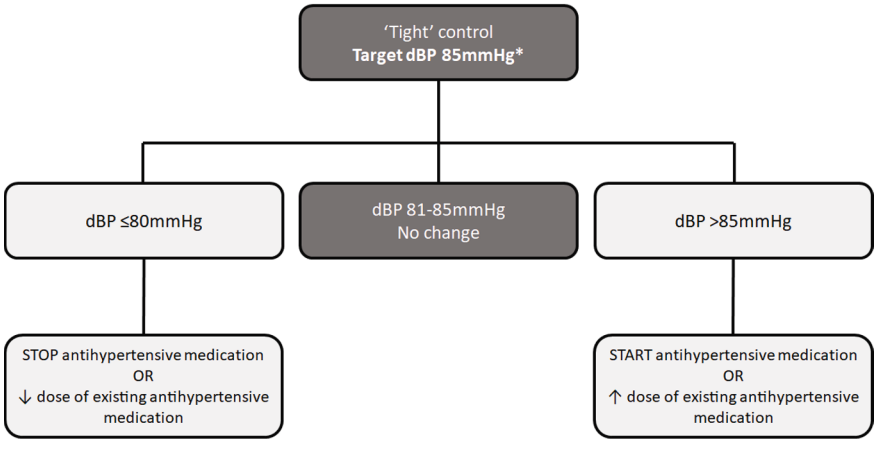

Fig. 1. Algorithm used in the CHIPS trial to achieve BP control (from Magee et al. Ultrasound Obstet Gynecol 2020; 56: 7–10). dBP (diastolic blood pressure), sBP (systolic blood pressure). *If systolic BP (sBP) is ≥160 mmHg, increase dose of existing medication or start new antihypertensive medication to get sBP < 160 mmHg, regardless of diastolic BP. Women require urgent treatment in a monitored setting.

Table 6
Suggested monitoring for hypertensive pregnant women with a target dBP of 85 mmHg (from Magee *et al* 2020 [138], modified from Dougall *et al*. *BMJ Open* 2020;10: e034593. https://doi.org/10.1136/bmjopen-2019-034593).

BP level	**BP** (mmHg)	**Actions**		
	dBP*	**Next BP**	**Contact maternity care provider**	**Ongoing BP monitoring**
Very high	≥105	Sit quietly for 5 min, measure BP again, and send in readings	Contact maternity unit within **4 hours**	Daily
High	90-104		Contact care-provider within **24 hours**	Daily
High-normal	86-89		If repeat BP still high-normal, contact care-provider within **24 hours**	Daily
Normal	81-85	As planned	As planned	As planned
Low-normal	75-80	If not taking BP medication, continue as planned	If not taking BP medication and feeling well, no action required If taking BP medication and repeat BP still low-normal or low, contact care-provider within **24 hours**	As planned if not taking BP medication and feeling well Daily if taking BP medication, or as instructed by care provider if antihypertensive therapy is changed
Low	<75	If taking BP medication, sit quietly for 5 min, measure BP again, and send in readings	Regardless of whether BP medication is being taken, If feeling unwell (such as dizzy), contact care-provider within **4 hours**	

BP (blood pressure), dBP (diastolic blood pressure).
* If at any time, sBP is ≥ 155 mmHg, BP should be considered very high and actions taken accordingly.

Table 7
Maintenance therapy and suggested dose titration of antihypertensive therapy for non-urgent control of hypertension in pregnancy (modified from Magee *et al* 2020) [147].

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

LA (long-acting), MR (modified release), PA (prolonged action), XL (extended release).
* Starting doses are higher than generally recommended for adults given more rapid clearance in pregnancy.
† When a medication is at high (or maximum) dosage, consider using a different medication to treat any severe hypertension that may develop).

"hyperdynamic", were more successfully treated with oral labetalol; in a small observational study (84 women) of as haemodynamic-guided antihypertensive therapy for BP ≥ 140/90 mmHg guided by this model, antihypertensive management was altered for half of women, and the incidence of severe hypertension requiring high dependency unit admission was reduced by 60%, with no increase in FGR [146]. There are no relevant RCTs.

Oral antihypertensives can be given in labour; if BP control is sub-optimal, this may be due to reduced absorption because of gastrointestinal motility and parenteral agents may be needed.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) should not be used in women once pregnant based on fetotoxicity, manifest as fetal renal toxicity and its consequences, including stillbirth; the risk appears to be particularly high with ARBs [147]. For women with chronic hypertension, these medications do not appear to be teratogenic [148–150], and in fact, prior associations with birth defects may have been due to the underlying hypertension itself [151]. As such, it is acceptable to continue ACE inhibitors or ARBs until pregnancy is diagnosed if the drugs are administered for renoprotection, given that the risk of ACE inhibitor and ARB fetotoxicity may be greatest with exposure after 20 weeks [147]. However, as the literature is not uniformly reassuring, with reports of an excess of pregnant complications even when ACE inhibitors and ARBs are stopped in early pregnancy [152], it is prudent to switch to another antihypertensive pre-pregnancy, when clinically possible.

Severe hypertension

No trials have demonstrated that antihypertensive therapy is superior to placebo/no therapy for severe hypertension. However, such trials would be unethical. Severe hypertension is a surrogate marker for adverse maternal and perinatal outcomes [130] and there is consensus that it should be treated. Treatment within 60 min may decrease the incidence of severe maternal morbidity [153]. Advice to lower BP gradually is based on exacerbation of cerebral ischaemia in stroke and an excess of adverse perinatal outcome among women treated with agents that lower BP quickly [154]. Nevertheless, success has been achieved without adverse effects when BP has been lowered within one hour [155].

The most commonly-recommended agents for treatment of severe hypertension are IV labetalol, oral nifedipine, and IV hydralazine. [156] By network *meta*-analysis (51 trials), each of these three medications achieved target BP in a similar number of women (32 trials, 3236 women), although more quickly with nifedipine than IV hydralazine. [157] There was no difference in effectiveness between IV labetalol and either oral nifedipine or IV hydralazine, but more data were needed to compare oral nifedipine and IV hydralazine. A second network meta-analysis restricted to first-line agents (17 trials, 1591 women) found that oral nifedipine more successfully treated severe hypertension than IV hydralazine [158].

A recent, open-label RCT showed that, in low-resource settings, oral nifedipine (PA), labetalol, and methyldopa each successfully treated severe hypertension (without causing maternal or fetal adverse effects) in the majority (at least 75%) of women [159]. However, as single drugs, nifedipine PA and oral labetalol (compared with methyldopa) were less often associated with the need to administer a second agent (1% vs. 3% vs. 19%). While all women with severe hypertension have an obstetric urgency, oral therapy may facilitate earlier treatment while en route to a monitored setting, or more timely treatment in that setting.

Second-line agents include other beta-blockers, other calcium channel blockers, and prazosin. [160]

Local protocols should outline the nature and frequency of maternal and fetal monitoring in hypertensive pregnancy, as well as when to repeat a dose of antihypertensive medication if BP is not well-controlled [161]. To harmonise protocols between medications and minimise the risk of maternal hypotension, a suggested approach is outlined in Table 8. Delayed treatment of severe hypertension has been associated with prior non-severe hypertension, lack of pre-eclampsia symptoms, white race, presentation overnight, having labour-related symptoms, and later gestational age [162].

Antihypertensives, including nifedipine, can be used contemporaneously with magnesium sulphate (for eclampsia prevention or treatment) [163].

6.4. Plasma volume expansion

Recommendations

27. Plasma volume expansion is not recommended routinely for women with pre-eclampsia. (⊕⊕⊕O/Strong).

Data on fluid management in pre-eclampsia are limited. A recent systematic review (6 trials) showed that colloid volume expansion reduced maternal BP, but no other benefits or harms were demonstrated [164], unlike the largest trial in which multiple adverse effects were demonstrated (i.e., Caesarean delivery, reduced pregnancy prolongation, and more frequent pulmonary oedema) [165]. For women with pre-eclampsia, total fluid intake in labour is usually restricted to ≈80 mL/hour to minimise the risk of pulmonary oedema without increasing the risk of acute kidney injury [166].

6.5. Magnesium sulphate

Recommendations

28. Women with eclampsia should receive magnesium sulphate to prevent recurrent seizures (⊕⊕⊕⊕/Strong).

Table 8
Suggested dose titration of antihypertensive therapy for urgent control of hypertension in pregnancy* (from Magee *et al* 2020) [164].

	Caution	T0	T 30 min	T 60 min	T 90 min	T 120 min	T 150 min	T 180 min
Labetalol (oral)	▪ Contra-indicated with uncontrolled asthma or heart failure ▪ May cause neonatal bradycardia and neonatal hypoglycaemia and warrants newborn screening in some jurisdictions	200 mg	–	200 mg	–	200 mg	–	Use alternative from a different drug class†
Labetalol (IV intermittent)		10–20 mg	20–40 mg‡	40–80 mg	40–80 mg [29]	40–80 mg	40–80 mg§	
Labetalol (IV infusion)		0.5–2 mg/min	→	→	→	→	→†	
Nifedipine (oral tablet or capsule, either of which to be swallowed whole, NOT bitten or punctured)	▪ May cause maternal headache and tachycardia	10 mg	10 mg	–	10 mg	–	10 mg	
Methyldopa (oral)	▪ Onset of action may be delayed	1000 mg	–	–	–	–		
Hydralazine (IV)	▪ May increase risk of maternal hypotension, and maternal and fetal tachycardia	5 mg	5–10 mg	5–10 mg¶	5–10 mg¶			

* When severe hypertension has resolved, switch to routine oral medication.
† If nifedipine or hydralazine were the initial drug used, choose oral labetalol or oral methyldopa as the alternative.
‡ Double the initial dose of labetalol IV.
§ Do not exceed the maximum dose of IV labetalol, which is 300 mg total in a treatment course.
¶ Do not exceed the maximum dose of IV hydralazine of 20 mg.

29. Women with pre-eclampsia who have proteinuria and severe hypertension, or hypertension with neurological signs or symptoms, should receive magnesium sulphate for eclampsia prevention (⊕⊕⊕⊕/Strong).

There is clear evidence that magnesium sulphate halves both the incidence and recurrence of eclampsia [167–168]. The number-needed-to-treat (NNT) is ≈100 to prevent one seizure. However, it is controversial whether all women with pre-eclampsia should receive magnesium sulphate, due to an elevated risk of Caesarean delivery, more maternal adverse effect risks, and higher costs (i.e., US$23,000 to prevent one seizure if administered to all women with pre-eclampsia) [169]. As the NNT is lower (≈50), it is reasonable in well-resourced settings to restrict magnesium sulphate use to women with 'severe' pre-eclampsia as defined by the Magpie trial: 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). Each unit should have a consistent policy concerning their use of magnesium sulphate and the monitoring of women and babies receiving this therapy.

The dosing regimens used in the Eclampsia and Magpie trials are recommended, as outlined in Table 9, along with a protocol for monitoring and treatment of toxicity. There are a few points worthy of particular discussion. First, magnesium sulphate comes in different concentrations and ampoules of different volume, and some sites have the drug pre-mixed for administration; if mixing is required, this should be done according to local protocols. Second, while alternative magnesium sulphate regimens (using lower doses or being more restricted in duration) have been evaluated, data are currently insufficient to inform clinical practice [170]. Unless there is renal impairment, standard doses should be used until further evidence is published on the effectiveness of administration that is reduced in dose or abbreviated in duration. Finally, magnesium sulphate may be administered while women at preterm gestational ages are being considered for expectant care; if investigations reveal that they do not require immediate birth, it is reasonable to stop magnesium sulphate and re-evaluate its need when timed birth is considered or there is spontaneous onset of labour.

When not indicated for seizure prophylaxis or treatment, administration of magnesium sulphate for fetal neuroprotection should be considered when delivery is imminent at $\leq 33^{+6}$ weeks [171].

Table 9
Magnesium sulphate dosing and monitoring (modified from Brown *et al.* 2018) [2]

Dosing [168,171]		
	IV administration	**Combined IV and IM administration***
Loading dose	4 g $MgSO_4$ IV in 100 mL normal saline, infused over 20 min using an infusion device	4 g $MgSO_4$ IV in 100 mL normal saline, infused over 20 min using an infusion device *and* 5 g IM into EACH buttock (for a total of 10 g)
Maintenance	1 g/hr IV in normal saline, using an infusion device	5 g IM into ONE buttock every 4 hrs
Duration	Until 24 hrs after last eclamptic seizure or birth, whichever is later	
Monitoring		
	Observations	**Signs of toxicity‡**
Maternal‖		
Upon completion of loading dose	Reflexes	Decreased or absent
Every 30 min	BP	Lower
	Heart rate	Lower or cardiac arrythmias
	Respiratory rate	<12/min for 15 min
	Pulse oximetry (if available)	O_2 saturation < 94% for 15 min
Every hr	Urine output§	<30 mL/hr for 4 hrs¶
	Reflexes	Decreased or absent
Symptoms‖	–	Central nervous system (e.g., excessive drowsiness, slurred speech)
	–	Neuromuscular (e.g., muscle weakness)
Fetal		
≥26 wks	Continuous cardiotocography	
<26 wks	Intermittent fetal heart rate auscultation every 30 min	

*Administration can be switched to IV dosing by starting 1 g/hr (without a loading dose) when the next dose of IM $MgSO_4$ is due.
‖If toxicity is suspected, cease the $MgSO_4$ infusion and take blood for serum Mg level. If toxicity is clear, administer calcium gluconate 10% (10 mL in 100 mL normal saline IV over 10 min).
‡Monitoring of serum Mg levels is not necessary unless there is decreased renal function or signs of toxicity.
§Foley catheterisation is recommended.
¶Decreased urine output is included because it increases the risk of toxicity.
‖Symptoms of toxicity should be distinguished from well-known side effects, which include: flushing of the skin, a metallic taste in the mouth, sweating, nausea and vomiting, heaviness in the chest, palpitations, and lowering of the BP initially.

6.6. Timed birth

Recommendations

30. Indications for delivery with any HDP at any gestational age (⊕⊕⊕O/Strong) include:

- Abnormal neurological features (such as eclampsia, severe intractable headache or repeated visual scotomata);
- Repeated episodes of severe hypertension despite maintenance treatment with three classes of antihypertensive agents;
- Pulmonary oedema;
- Progressive thrombocytopenia or platelet count $<50 \times 10^9$/L;
- Transfusion of any blood product;
- Abnormal and rising serum creatinine;
- Abnormal and rising liver enzymes;
- Hepatic dysfunction (INR > 2 in absence of DIC or warfarin), haematoma or rupture
- Abruption with evidence of maternal or fetal compromise; or
- Non-reassuring fetal status (including death)

Recommendations

31. A decision to deliver should not be based solely upon the degree of either proteinuria (⊕⊕OO/Strong) or hyperuricaemia (⊕⊕OO/Strong).

(See Table 10 for recommendations according to gestational age.)

Indications for planned birth, regardless of gestational age, apply to 'complicated' pre-eclampsia (i.e., involving end-organ complications that are associated with a heightened risk of maternal or perinatal death) [172]. At present, angiogenic imbalance (i.e., maternal blood levels of sFLt-1 and/or PlGF) in itself is not an indication for delivery. If timing allows, delivery should occur in a perinatal centre capable of caring for sick mothers and newborns.

Recommendations for timing of delivery based on gestational age are presented in Table 10.

Pre-viability, expectant care of pre-eclampsia is associated with very high perinatal mortality (>80%), as well as frequent maternal complications (in 27–71% of cases) that may include death [173–174]. Termination of pregnancy should be discussed and patient values considered, along with transfer of care to a referral hospital.

From viability to 33^{+6} weeks, the limited evidence favours expectant care when there is no clear indication for birth. By systematic review (6 trials, 748 women), interventionist (vs. expectant) care was associated with earlier gestational age at birth by ≈10 days (mean −9.91 days, 95% CI −16.37, −3.45), similar maternal outcomes (but very wide CIs), but more neonatal morbidity (i.e., intraventricular haemorrhage [RR 1.94,

Table 10
Recommendations for timing of birth.

Gestational age	Pre-eclampsia	Gestational hypertension	Chronic hypertension
Pre-viability	Termination of pregnancy should be discussed (⊕⊕OO/Weak)		
Viability to 33^{+6} weeks	Expectant management should be considered, but only in hospitals where very preterm infants and sick mothers can be cared for (⊕⊕⊕O/Weak)	Expectant care is recommended unless there is an indication for birth ((⊕⊕OO/Strong)	Expectant care is recommended unless there is an indication for birth (⊕OOO/Strong)
34^{+0} to 36^{+6} weeks	At 34^{+0}-36^{+6} weeks, initiation of delivery should be discussed as it decreases maternal but increases neonatal risk, particularly where antenatal corticosteroids are not prescribed (⊕⊕⊕O/Strong)		
≥37^{+0} weeks	Initiation of delivery is recommended (⊕⊕⊕⊕/Strong)	Women who reach 40^{+0} weeks should be offered delivery (⊕⊕OO/Strong) Women at 37^{+0} –39^{+6} weeks may be offered delivery (⊕⊕OO/Weak)	Women who reach 40^{+0} weeks should be offered delivery (⊕⊕OO/Strong) Initiation of delivery may be offered at 38^{+0} to 39^{+6} weeks (⊕⊕OO/Weak)

95% CI 1.15, 3.29], hyaline membrane disease [RR 2.30, 95% CI 1.39, 3.81], and ventilation [RR 1.50, 95% CI 1.11, 2.02]), despite fewer babies being SGA (RR 0.38, 95% CI 0.24, 0.61) [175].

At 34^{+0}-36^{+6} weeks, there are maternal benefits of delivery but also neonatal risks, particularly where antenatal corticosteroids are not routinely administered at this gestational age. In the PHOENIX trial (UK) in which expectant care was associated with more neonatal unit admission, but not more neonatal respiratory illness, most (60%) women had received antenatal steroids [176], whereas in the HYPITAT II trial in which immediate delivery was associated with more neonatal respiratory distress syndrome, only 1% of women had received steroids [177]. An individual patient data meta-analysis suggested that neonatal risk may not be increased from 36^{+0} weeks, also consistent with subgroup analyses in PHOENIX [176,178]. Nevertheless, child neurodevelopment to the age of 5 years appears to be similar after either interventionist or expectant care [179].

RCT data for 50 women with chronic hypertension suggests that initiation of delivery at 37^{+0} weeks is associated with an excess of neonatal morbidity [180].

At term (≥37^{+0} weeks), women with pre-eclampsia should be offered birth based on the results of the HYPITAT trial [181]. The 2/3 of women in HYPITAT who had gestational hypertension at term experienced no reduction in poor maternal outcome (OR 0.81, 95% CI 0.63, 1.03), raising questions about whether these women benefit from timed birth [182]. Women with preterm gestational hypertension [183] or those with chronic hypertension [184–185] may benefit from timed birth at 38^{+0}-39^{+6} weeks, based on observational data; there is one ongoing trial (ISRCTN77258279).

Decision aids and risk communication strategies should be used to support patient education and truly *informed* consent.

6.7. Antenatal corticosteroids

Recommendations

32. Do not administer corticosteroids to hasten resolution of HELLP syndrome (⊕⊕⊕O/Strong)

Antenatal corticosteroids, in a single course, should be administered to women with HDPs in line with recommendations for any woman at $<34^{+0}$ weeks who is at risk of birth within the next 7 days, to reduce neonatal death and neonatal morbidity, respiratory distress, and intraventricular haemorrhage [186]. This is true in all settings where gestational age can be accurately assessed [187]. A single repeat course of steroids can be administered prior to 34 weeks if the woman remains pregnant at least 7 days (WHO) to 14 days (ACOG) after the initial course, and she remains at high risk of preterm birth within the next 7 days [188]. Corticosteroids can be administered between 34^{+0} and 36^{+6} weeks in women with pre-eclampsia or gestational hypertension at risk for delivery, among women with singleton pregnancies who have not received steroids before and are non-diabetic [189].

Steroids should not be specifically administered for HELLP syndrome. While they may transiently improve platelet count and other laboratory values in HELLP, they have not been proven to reduce adverse outcomes and they have common adverse effects, such as hyperglycaemia and further elevation of BP [190–191].

6.8. Novel therapies

Currently, there is no treatment for pre-eclampsia other than timed birth. Many therapies are being (e.g., statins, metformin) evaluated, at various gestational ages or stages of disease, for their theoretically positive effects on the pathogenesis of pre-eclampsia, particularly angiogenic imbalance and maternal systemic endothelial dysfunction and/or inflammation. A major barrier to progress is limited safety data, but this is being addressed by repurposing drugs acceptable for use in pregnancy, as well as novel nanoparticle delivery systems adapted from oncology [192].

7. Postpartum care

Recommendations

33. For women with antepartum hypertension, BP should be monitored at least once on days 3–7 postpartum when it is likely to be highest after birth (GPP).

34. Antihypertensive therapy administered antepartum should be continued after birth. Also, consideration should be given to administering antihypertensive therapy for any hypertension diagnosed before six days postpartum (⊕⊕OO/Weak)

35. The target dBP for postpartum antihypertensive treatment should be 85 mmHg, as antenatally (⊕⊕OO/Weak)

36. Non-steroidal anti-inflammatory drugs (NSAIDs) for postpartum analgesia may be used in women with pre-eclampsia if other analgesics are ineffective, and there is no AKI or other risk factors for it (⊕⊕OO/Weak)

37. Breastfeeding is recommended (⊕⊕⊕O/Strong)

38. Counselling should be provided about the risks of gestational hypertension (at least 4%) or pre-eclampsia (at least 15%) in future pregnancy (GPP)

39. At 3 months postpartum, all women should be reviewed to ensure that BP, urinalysis, and any laboratory abnormalities have normalised. If proteinuria or hypertension persist, then appropriate referral for further investigations should be initiated (GPP).

40. At 6 months postpartum, where possible, all women should be reviewed again, at which point we suggest that BP ≥ 120/80 mmHg lead to discussion of lifestyle change (⊕⊕⊕O/Weak)

41. Following hypertensive pregnancy, particularly pre-eclampsia, counselling should be provided about the heightened health risks for the mother (particularly cardiovascular) and the offspring (⊕⊕⊕O/

Strong)

42. We recommend calculating lifetime (not 10-year) cardiovascular risk scores to estimate cardiovascular risk in these women (⊕⊕⊕O/Strong)

43. Annual medical review following hypertensive pregnancy is recommended for the first 5–10 years postpartum (⊕⊕⊕O/Weak)

44. Following hypertensive pregnancy, all women and their offspring should adopt a healthy lifestyle that includes eating well, exercising, aiming for ideal body weight, living smoke-free, and aiming for BP < 120/80 mmHg (⊕⊕⊕⊕/Strong)

7.1. Short-term considerations

Women may develop pre-eclampsia or pre-eclampsia complications (including eclampsia) for the first time postpartum; therefore, BP measurement and control should be offered to all women postpartum. BP peaks around days 3–7 after delivery, following redistribution of extravascular fluid [193]. As the highest BP values may occur after women leave the monitored inpatient setting, and postpartum hypertension may be the commonest indication for postnatal hospital readmission [194], it is important to have in place a BP monitoring and treatment plan.

Antihypertensive therapy should target a similar BP goal as before delivery. First, there are no fetal concerns postpartum, by definition. Second, approximately half of strokes and half of eclampsia occur after birth [195]. Third, most antihypertensive agents (including the ACE inhibitors captopril, enalapril, and quinapril) are acceptable for use in breastfeeding; up-to-date information can be obtained in LactMed @NIH (www.ncb.nlm.nih.gov) [196]. A caveat is that many practitioners shy away from use of methyldopa, based on unsubstantiated concerns that it may increase the risk of postnatal mental health problems [182]. Very limited data suggest similar efficacy in BP-lowering between agents [197]. Fourth, good BP control in the months following a hypertensive pregnancy may result in less aortic stiffness [198] and lower BP [199] (and therefore, cardiovascular risk) long-term; a recent randomised controlled trial [199] found that self-management of postnatal hypertension to achieve good BP control in the first six weeks postpartum was associated with lower dBP at six months postpartum, when almost all (>95%) of the women were taking no antihypertensive treatment. Finally, following pre-eclampsia, breastfeeding is associated with lower long-term maternal hypertension in observational studies [200–201].

NSAIDs may be used for postpartum analgesia if other analgesia is ineffective following hypertensive pregnancy as long as BP is controlled and there is no AKI or risk factors for AKI, including CKD, sepsis, or postpartum haemorrhage. When NSAIDs are prescribed, women with pre-eclampsia should have close monitoring of their BP, including home BP monitoring when possible. A case series of six women initially raised concerns that postpartum use of NSAIDs following hypertensive pregnancy may increase the risk of hypertensive urgency [202]. However, subsequently-published literature has been reassuring. Retrospective cohort studies (involving 538 women, mostly with pre-eclampsia) have suggested that NSAIDs do not increase postpartum BP, antihypertensive dose or dose escalation, maternal complications, readmission rates, or opioid use [203–205]. Two RCTs of ibuprofen vs. acetaminophen for postpartum analgesia have been reassuring, finding either no increase in hypertension to six weeks postpartum [206] or an increase in BP ≥ 150/100 mmHg but no increase in the incidence of severe hypertension [207].

7.2. Risks in a future pregnancy

If a hypertensive disorder of pregnancy recurs in subsequent pregnancy, women with a history of gestational hypertension tend to have gestational hypertension (25%) rather than pre-eclampsia (4%), whereas women with prior pre-eclampsia may develop either gestational hypertension (15%) or pre-eclampsia (15%) [208–209]. All of these women have an increased risk of subsequent SGA babies, even if their BP remains normal. Recurrence risks will be further modified by the presence of any additional risk factors, such as earlier-onset or more complicated pre-eclampsia (which at its most extreme, can be associated with recurrence in up to 50% of women).

7.3. Long-term health risks

The long-term risks of pre-eclampsia, and gestational hypertension, are now well-established [210]. These women have greater propensity to developing cardiovascular disease risk factors (like hypertension), diabetes mellitus (a cardiovascular disease 'equivalent'), cardiovascular disease (including stroke or death) [211–212], in addition to venous thromboembolic disease (VTE), vascular dementia, and CKD.

How best to decrease these cardiovascular risks is a challenge, related to suboptimal engagement of women, high attrition, and a lack of evidence that shows that intervention following hypertensive pregnancy reduces long-term events. However, many risk factors for long-term cardiovascular and metabolic disease are modifiable and related to healthy lifestyle (i.e., healthy eating and physical activity) and good control of risk factors (i.e., smoking cessation, achieving a normal BMI and BP) [213].

Following hypertensive pregnancy, all women should be offered lifestyle advice according to international guidelines (e.g. https://www.heartfoundation.org.au and Diet and Physical Activity Guidelines for Americans 2018, available from https://health.gov/dietaryguidelines/ and https://health.gov/paguidelines/).

There is no evidence-based schedule of assessments for women following hypertensive pregnancy, but the following has been proposed and presented in a 'My Health Beyond Pregnancy' tool [214]:

- 6–12 weeks postpartum: for a simple cardiovascular screening with a general practitioner or obstetrician, to assess cardiovascular risk based on risk factors, physical activity and at minimum, BP. Of note, values that we use to define normal BP in the community are derived from older and often male populations; ongoing studies will define a new 'normal' range of BP for young women who have not had pre-eclampsia. Lifestyle advice should be offered.
- 6 months postpartum: BP should be < 120/80 mmHg [215]; if higher than this, then women should be alerted to the fact that their BP is abnormal and encouraged to increase lifestyle measures to lower BP.
- 1 year post-partum: for a similar visit to the 6–12 week postpartum visit, with additional testing of LDL, triglycerides and total cholesterol, fasting blood glucose, HbA1c, high sensitivity C-reactive protein (CRP), and urinary albumin:creatinine ratio. Also, even with an elevated lifetime risk of cardiovascular disease, young women may have low 10-year cardiovascular risk scores using well-established risk tools, and may be overlooked as being at high risk on that basis [216]. Therefore, we do not recommend a sole reliance on such tools to predict cardiovascular risk in these women. Lifestyle advice should be offered. Referral to specialists and drug therapy for hyperlipidaemia, abnormal glucose metabolism or high BP should follow local/national guidelines for primary prevention of cardiovascular disease.
- Annual medical review with a general practitioner for women at highest risk (such as those with a family history of cardiovascular disease or those with recurrent preterm pre-eclampsia), particularly during the first 5–10 years after hypertensive pregnancy when cardiovascular risk factors and disease appear most frequently [217].

The offspring of women with hypertensive pregnancy appear to be at increased risk of cardiovascular disease and CKD. Consideration should be given to monitoring them for hypertension. Parents should encourage healthy lifestyle for their offspring to mitigate their increased cardiovascular disease risk [218–219].

8. Application of these guidelines to less health developed countries

Less health developed countries have variably robust public and private health systems; private health care in the Western Cape, South Africa, differs greatly from maternity care in a refugee camp in northern Syria. In settings with overburdened and fragile health systems, where most maternal-newborn care is provided by non-experts, the question arises about how best to interpret and implement these recommendations.

In our opinion, all health systems should prioritise the provision of all elements of the Implementation Package (see below). Some practical points are expanded here.

- Regular antenatal care, in addition to adequate obstetric support, is important to reduce maternal and offspring mortality and morbidity.
- Access to the low-cost and validated Microlife CRADLE VSA BP device would provide accurate BP readings in pregnant and hypertensive pregnant women [220].
- The Fetal Medicine Foundation model is more accurate than clinical risk factor assessment in identifying women at risk of preterm pre-eclampsia, and aspirin (which is ubiquitous) reduces that risk.
- In countries with limited formularies, effective antihypertensives may include beta-blockers that are not usually prescribed in more-developed country settings (e.g., propranolol, metoprolol). Methyldopa is generally the cheapest antihypertensive medication that has been rigorously evaluated in both non-severe and severe pregnancy hypertension. Methyldopa, nifedipine (as a tocolytic), hydralazine and amlodipine are on the WHO List of Essential Medicines (2019) [221].
- The broad definition of pre-eclampsia should be used, especially where cost and access to toileting can limit the use of dipstick screening for proteinuria.
- The miniPIERS model can identify risk of adverse outcomes using clinical symptoms and signs in hypertensive pregnant women, especially with the addition of accurate pulse oximetry.
- Magnesium sulphate is on the WHO List of Essential Medicines (2019). However, supply chains can be unreliable and public health system provision is not uniform.
- Measurement of BP in hypertensive women on postpartum days 3–6 may require task-sharing to community health workers, as achieved in the Community-Level Interventions for Pre-eclampsia Trials [222].

9. How our guidance compares with other international and national guidance

The ISSHP has the shortest cycle for guideline update in keeping with our commitment to regular updates, in order to reduce confusion and promote discussion about the most recent pregnancy hypertension research.

Compared with a previous systematic review of pregnancy hypertension guidelines (2014) [223], there has been an increase in the number of clinical practice guidelines (from 13 to 15) with all those published within the last 10 years having been updated in part or in whole [156]. Table 11 indicates that there remains broad agreement in a number of areas, and where there is disagreement, consensus is building.

The key areas in which these guidelines differ are: incorporation of angiogenic markers into the assessment of pre-eclampsia risk (i.e., 1st trimester screening) and assessment of suspected pre-eclampsia (after 20–24 gestational weeks) as a marker of uteroplacental dysfunction, and detailed advice about titration of antihypertensive therapy dose and polytherapy.

Guidelines focused on under-resourced settings include those of WHO 2011 and FIGO. IMPAC 2016 also provides pregnancy hypertension guidance, although it is a compilation of decision algorithms to guide practice, rather than a clinical practice guideline *per se*.

Table 12 presents an implementation package.

Table 13 presents research recommendations.

Table 11
Areas of agreement and disagreement in clinical practice guidelines for the hypertensive disorders of pregnancy.

Areas of agreement	Areas of disagreement
Definitions of hypertension, proteinuria, chronic hypertension, gestational hypertension, and pre-eclampsia	The definition of 'severe' pre-eclampsia and use of the term.
Prevention of pre-eclampsia with low dose aspirin & supplemental calcium (if low calcium intake)	Target blood pressure when hypertension is not severe
Treatment of severe hypertension	Timing of delivery for women with chronic hypertension, gestational hypertension, or preterm pre-eclampsia
Use of magnesium sulphate for eclampsia & 'severe' pre-eclampsia	Use of magnesium sulphate for fetal neuroprotection when pre-eclampsia is not 'severe'
Use of antenatal corticosteroids to enhance fetal lung maturity at <34 weeks' gestation if delivery is likely within the next 7 days	Post-partum maternal monitoring
Delivery for pre-eclampsia at term	
Oxytocin as an element of the active management of the third stage of labour	

Table 12
Implementation priorities.

Measure BP with a device validated for use in pregnancy and postpartum
Assess the risk of pre-eclampsia at antenatal care booking and prescribe aspirin for women identified as being at increased risk.
Treat hypertension (BP ≥ 140/90 mmHg) with antihypertensive therapy, antepartum and postpartum
Define pre-eclampsia according to gestational hypertension with maternal, fetal, or placental complications, and not just by new proteinuria
Assess the risk of adverse maternal outcomes in hypertensive women using the fullPIERS or miniPIERS models
Deliver women with complicated pre-eclampsia regardless of gestational age (see 'Management/Timing of birth')
Time delivery from 37 weeks for women with uncomplicated pre-eclampsia
Use magnesium sulphate to treat eclampsia or pre-eclampsia with proteinuria and severe hypertension, or any hypertension with neurological signs or symptoms
Measure BP postpartum, at least once on days 3–7 after hypertensive pregnancy
BP (blood pressure), PIERS (Pre-eclampsia Integrated Estimate of Risk Score)

Table 13
Research recommendations.

Evaluate whether routine proteinuria screening in normotensive women is associated with improved outcomes
Assess whether self-monitoring of BP reduces adverse pregnancy outcomes among women with pregnancy hypertension, or those at high risk of pre-eclampsia
Incorporate women's views into decisions about personalised risk stratification for pre-eclampsia and associated prophylaxis with aspirin
Determine the cost-effectiveness of using a broad ISSHP definition of pre-eclampsia, rather than a restrictive one based only on new hypertension and proteinuria
Investigate whether haemodynamic-guided antihypertensive therapy can achieve maternal BP control and optimise perinatal outcomes
Establish whether angiogenic markers add prognostic value to the broad definition of pre-eclampsia or either the fullPIERS or miniPIERS modes for prediction of adverse short- and long-term maternal outcomes in pre-eclampsia
Establish mechanisms to engage women in cardiovascular risk reduction following hypertensive pregnancy

10. Future directions

The ISSHP aims to update these recommendations every two years. We invite feedback to info@isshp.org.

11. Contributions

The first and second authors (LAM and MB) drafted the initial document following contributions from all co-authors that collectively represent the Executive and Council of the ISSHP (LAM, MAB, DRH, AH, SAK, LCC, FM, SR, SS, PvD, AS). Further input was sought from additional authors (JM, SG, LP, AS) who have expertise in the long-term cardiovascular follow-up, management of hypertensive disorders in critical regions or less-resourced settings and/or represent other important international organisations (NICE, UK; Global Pregnancy Collaboration; World Gestosis; and FIGO).

Funding

There were no sources of funding for this manuscript.

Declaration of Competing Interest

The following authors had no disclosures: Magee LA, Brown MA, Gupta S, Hall DR, Hennessy A, McCarthy FP, and Saito S.

Kenny LC is a minority shareholder in Metabolomic Diagnostics, a company which has licenced intellectual property pertaining to biomarkers for the prediction of pre-eclampsia.

Karumanchi SA disclosed patents on biomarkers held by Harvard hospitals, and is a consultant to Thermofisher Scientific, Roche, and Aggamin LLC.

Myers JE has led research studies related to the implementation of angiogenic markers for the diagnosis of pre-eclampsia, received industry funding from Alere and Roche to fund biomarker tests, and is a member of the NICE Diagnostic Assessment Panel.

Poon LC has received in-kind contributions from PerkinElmer Inc., Thermo Fisher Scientific and Roche Diagnostics and reports serving as consultant to Roche Diagnostics.

Rana S reports serving as consultant to Thermo Fisher Scientific and Roche Diagnostics.

Staff A has received compensation from Roche Diagnostics for Advisory Board service in 2018 regarding preeclampsia screening, and reagents for sFlt-1 and PlGF biomarker analyses from Roche Diagnostics (Rotkreuz, Switzerland).

von Dadelszen P has received speaker's fees and grants-in-aid from Alere Incorporated.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2021.09.008.

References

[1] M.A. Brown, L.A. Magee, L.C. Kenny, et al., Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice, Hypertension 72 (2018) 24–43.
[2] M.A. Brown, L.A. Magee, L.C. Kenny, et al., The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice, Pregnancy Hypertens. 13 (2018) 291–310.
[3] L.A. Magee, A. Pels, M. Helewa, E. Rey, P. von Dadelszen, Canadian Hypertensive Disorders of Pregnancy Working G. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy, Pregnancy Hypertens 4 (2014) 105–145.
[4] N.A. Bello, E. Miller, K. Cleary, R. Wapner, D. Shimbo, A.T. Tita, Out of office blood pressure measurement in pregnancy and the postpartum period, Curr. Hypertens. Rep. 20 (2018) 101.
[5] J.J. Waugh, M. Gupta, J. Rushbrook, A. Halligan, A.H. Shennan, Hidden errors of aneroid sphygmomanometers, Blood Press Monit 7 (2002) 309–312.
[6] G.K. Davis, L.M. Roberts, G.J. Mangos, M.A. Brown, Comparisons of auscultatory hybrid and automated sphygmomanometers with mercury sphygmomanometry in hypertensive and normotensive pregnant women: parallel validation studies, J Hypertens 33 (2015) 499–505, discussion-6.
[7] STRIDEBP. STRIDE-BP: Validated BP monitors in pregnancy. https://stridebp.org/bp=monitors Accessed 02 Jan 2021.
[8] M. Reddy, D.L. Rolnik, K. Harris, et al., Challenging the definition of hypertension in pregnancy: a retrospective cohort study, Am. J. Obstet. Gynecol. 222 (606) (2020) e1–e21.
[9] J.N. Bone, L.A. Magee, J. Singer, et al., Blood pressure thresholds in pregnancy for identifying maternal and infant risk: a secondary analysis of Community-Level Interventions for Pre-eclampsia (CLIP) trial data, Lancet Glob. Health 9 (2021) e1119–e1128.
[10] K.L. Tucker, C. Bankhead, J. Hodgkinson, et al., How do home and clinic blood pressure readings compare in pregnancy? Hypertension 72 (2018) 686–694.
[11] C.R. Green, J.M. Blake, G.D. Carson, L. Po, A.R.H. Brown, C.L. Friedman, Choosing wisely: SOGC's top 10 recommendations, J. Obstet. Gynaecol. Can. 40 (2018) 716–722.
[12] J.T. Henderson, J.H. Thompson, B.U. Burda, A. Cantor, Preeclampsia screening: evidence report and systematic review for the US preventive services task force, JAMA 317 (2017) 1668–1683.
[13] W.H. Chung, W.W.K. To, Outcome of pregnancy with new onset proteinuria and progression to pre-eclampsia: a retrospective analysis, Pregnancy Hypertens. 12 (2018) 174–177.
[14] N. Murray, C.S. Homer, G.K. Davis, J. Curtis, G. Mangos, M.A. Brown, The clinical utility of routine urinalysis in pregnancy: a prospective study, Med. J. Aust. 177 (2002) 477–480.
[15] T. Yamada, M. Obata-Yasuoka, H. Hamada, et al., Isolated gestational proteinuria preceding the diagnosis of preeclampsia - an observational study, Acta Obstet. Gynecol. Scand. 95 (2016) 1048–1054.
[16] R. Akaishi, T. Yamada, M. Morikawa, R. Nishida, H. Minakami, Clinical features of isolated gestational proteinuria progressing to pre-eclampsia: retrospective observational study, BMJ Open 4 (2014), e004870.
[17] L.A. Magee, S. Sharma, E. Sevene, et al., Population-level data on antenatal screening for proteinuria; India, Mozambique, Nigeria, Pakistan, Bull. World Health Organ. 98 (2020) 661–670.
[18] T.J. Cade, P.C. de Crespigny, T. Nguyen, J.R. Cade, M.P. Umstad, Should the spot albumin-to-creatinine ratio replace the spot protein-to-creatinine ratio as the primary screening tool for proteinuria in pregnancy? Pregnancy Hypertens. 5 (2015) 298–302.
[19] A.M. Cote, M.A. Brown, E. Lam, et al., Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review, BMJ 336 (2008) 1003–1006.
[20] P.J. Saudan, M.A. Brown, T. Farrell, L. Shaw, Improved methods of assessing proteinuria in hypertensive pregnancy, Br. J. Obstet. Gynaecol. 104 (1997) 1159–1164.
[21] J. Waugh, R. Hooper, E. Lamb, et al., Spot protein-creatinine ratio and spot albumin-creatinine ratio in the assessment of pre-eclampsia: a diagnostic accuracy study with decision-analytic model-based economic evaluation and acceptability analysis, Health Technol. Assess. 21 (2017) 1–90.
[22] T.J. Cade, S.A. Gilbert, A. Polyakov, A. Hotchin, The accuracy of spot urinary protein-to-creatinine ratio in confirming proteinuria in pre-eclampsia, Aust. N. Z. J. Obstet. Gynaecol. 52 (2012) 179–182.
[23] L.K. Phelan, M.A. Brown, G.K. Davis, G. Mangos, A prospective study of the impact of automated dipstick urinalysis on the diagnosis of preeclampsia, Hypertens. Pregnancy 23 (2004) 135–142.
[24] T. Lei, T. Qiu, W. Liao, et al., Proteinuria may be an indicator of adverse pregnancy outcomes in patients with preeclampsia: a retrospective study, Reprod. Biol. Endocrinol. 19 (2021) 71.
[25] X. Xu, Y. Wang, H. Xu, Y. Kang, Q. Zhu, Association between proteinuria and maternal and neonatal outcomes in pre-eclampsia pregnancy: a retrospective observational study, J. Int. Med. Res. 48 (2020), 300060520908114.
[26] A. Tanacan, E. Fadiloglu, M.S. Beksac, The importance of proteinuria in preeclampsia and its predictive role in maternal and neonatal outcomes, Hypertens Pregnancy 38 (2019) 111–118.
[27] J.P. Guida, M.A. Parpinelli, F.G. Surita, M.L. Costa, The impact of proteinuria on maternal and perinatal outcomes among women with pre-eclampsia, Int. J. Gynaecol. Obstet. 143 (2018) 101–107.
[28] M. Jayaballa, S. Sood, I. Alahakoon, S. Padmanabhan, N.W. Cheung, V. Lee, Microalbuminuria is a predictor of adverse pregnancy outcomes including preeclampsia, Pregnancy Hypertens. 5 (2015) 303–307.
[29] L.A. Magee, P. von Dadelszen, E. Rey, et al., Less-tight versus tight control of hypertension in pregnancy, N. Engl. J. Med. 372 (2015) 407–417.
[30] K. Bramham, B. Parnell, C. Nelson-Piercy, P.T. Seed, L. Poston, L.C. Chappell, Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis, BMJ 348 (2014), g2301.
[31] M.A. Brown, G. Mangos, G. Davis, C. Homer, The natural history of white coat hypertension during pregnancy, BJOG 112 (2005) 601–606.
[32] A. Rodrigues, C. Barata, I. Marques, M.C. Almeida, Diagnosis of White Coat Hypertension and pregnancy outcomes, Pregnancy Hypertens. 14 (2018) 121–124.
[33] G.S. Stergiou, K. Kario, A. Kollias, et al., Home blood pressure monitoring in the 21st century, J. Clin. Hypertens. (Greenwich) 20 (2018) 1116–1121.
[34] T. Lee-Ann Hawkins, M.A. Brown, G.J. Mangos, G.K. Davis, Transient gestational hypertension: Not always a benign event, Pregnancy Hypertens. 2 (2012) 22–27.
[35] P. Saudan, M.A. Brown, M.L. Buddle, M. Jones, Does gestational hypertension become pre-eclampsia? Br. J. Obstet. Gynaecol. 105 (1998) 1177–1184.
[36] L.C. Chappell, S. Duckworth, P.T. Seed, et al., Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study, Circulation 128 (2013) 2121–2131.
[37] H. Zeisler, E. Llurba, F. Chantraine, et al., Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia, N. Engl. J. Med. 374 (2016) 13–22.

[38] K.E. Duhig, J. Myers, P.T. Seed, et al., Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial, Lancet 393 (2019) 1807–1818.
[39] G.B. Majak, A.V. Reisaeter, M. Zucknick, et al., Preeclampsia in kidney transplanted women; Outcomes and a simple prognostic risk score system, PLoS ONE 12 (2017), e0173420.
[40] C.S. Homer, M.A. Brown, G. Mangos, G.K. Davis, Non-proteinuric pre-eclampsia: a novel risk indicator in women with gestational hypertension, J. Hypertens. 26 (2008) 295–302.
[41] J.R. Livingston, B. Payne, M. Brown, et al., Uric acid as a predictor of adverse maternal and perinatal outcomes in women hospitalized with preeclampsia, J. Obstet. Gynaecol. Can. 36 (2014) 870–877.
[42] T.L. Hawkins, J.M. Roberts, G.J. Mangos, G.K. Davis, L.M. Roberts, M.A. Brown, Plasma uric acid remains a marker of poor outcome in hypertensive pregnancy: a retrospective cohort study, BJOG 119 (2012) 484–492.
[43] A. Ryu, N.J. Cho, Y.S. Kim, E.Y. Lee, Predictive value of serum uric acid levels for adverse perinatal outcomes in preeclampsia, Medicine (Baltimore) 98 (2019), e15462.
[44] P. von Dadelszen, B. Payne, J. Li, et al., Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model, Lancet 377 (2011) 219–227.
[45] S. Lim, W. Li, J. Kemper, A. Nguyen, B. Mol, M. Reddy, Biomarkers and the prediction of adverse outcomes in preeclampsia: a systematic review and meta-analysis, Obstet. Gynecol. (2020).
[46] S. Rana, C.E. Powe, S. Salahuddin, et al., Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia, Circulation 125 (2012) 911–919.
[47] X. Bian, A. Biswas, X. Huang, et al., Short-term prediction of adverse outcomes using the sFlt-1 (Soluble fms-Like Tyrosine Kinase 1)/PlGF (placental growth factor) ratio in asian women with suspected preeclampsia, Hypertension 74 (2019) 164–172.
[48] D. Hayes-Ryan, A.S. Khashan, K. Hemming, et al., Placental growth factor in assessment of women with suspected pre-eclampsia to reduce maternal morbidity: a stepped wedge cluster randomised control trial (PARROT Ireland), BMJ 374 (2021), n1857.
[49] A.S. Cerdeira, J. O'Sullivan, E.O. Ohuma, et al., Randomized interventional study on prediction of preeclampsia/eclampsia in women with suspected preeclampsia, Hypertension 74 (4) (2019 Oct) 983–990.
[50] J. Lopes Perdigao, S. Chinthala, A. Mueller, et al., Angiogenic factor estimation as a warning sign of preeclampsia-related peripartum morbidity among hospitalized patients, Hypertension 73 (2019) 868–877.
[51] NICE. PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio). Diagnostics guidance [DG23] 2016.
[52] R. Soundararajan, S.C. Suresh, A. Mueller, et al., Real life outpatient biomarker use in management of hypertensive pregnancies in third trimester in a low resource SeTting: ROBUST study, Pregnancy Hypertens. 23 (2021) 97–103.
[53] L.A. Droge, F.H. Perschel, N. Stutz, et al., Prediction of preeclampsia-related adverse outcomes with the sFlt-1 (Soluble fms-Like Tyrosine Kinase 1)/PlGF (placental growth factor)-ratio in the clinical routine: a real-world study, Hypertension 77 (2021) 461–471.
[54] M.Y. Tan, D. Wright, L. Koutoulas, R. Akolekar, K.H. Nicolaides, Comparison of screening for pre-eclampsia at 31–34 weeks' gestation by sFlt-1/PlGF ratio and a method combining maternal factors with sFlt-1 and PlGF, Ultrasound Obstet. Gynecol. 49 (2017) 201–208.
[55] I. Dragan, T. Georgiou, N. Prodan, R. Akolekar, K.H. Nicolaides, Screening for pre-eclampsia using sFlt-1/PlGF ratio cut-off of 38 at 30–37 weeks' gestation, Ultrasound Obstet. Gynecol. 49 (2017) 73–77.
[56] C.C. Lees, T. Stampalija, A. Baschat, et al., ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction, Ultrasound Obstet. Gynecol. 56 (2020) 298–312.
[57] H. Zeisler, E. Llurba, F.J. Chantraine, et al., Soluble fms-like tyrosine kinase-1 to placental growth factor ratio: ruling out pre-eclampsia for up to 4 weeks and value of retesting, Ultrasound Obstet. Gynecol. 53 (2019) 367–375.
[58] L. Lai, A. Syngelaki, K.H. Nicolaides, P. von Dadelszen, L.A. Magee, Impact of new definitions of preeclampsia at term on identification of adverse maternal and perinatal outcomes. Am. J. Obstet. Gynecol. 2021 May;224(5):518.e1-518.e11. https://doi.org/10.1016/j.ajog.2020.11.004. Epub 2020 Nov 6.
[59] S. Rana, S.D. Burke, S.A. Karumanchi, Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders, Am. J. Obstet. Gynecol. (2020).
[60] S. Thangaratinam, J. Allotey, N. Marlin, et al., Prediction of complications in early-onset pre-eclampsia (PREP): development and external multinational validation of prognostic models, BMC Med. 15 (2017) 68.
[61] K.E. Duhig, L.M. Webster, A. Sharp, et al., Diagnostic accuracy of repeat placental growth factor measurements in women with suspected preeclampsia: a case series study, Acta Obstet. Gynecol. Scand. 99 (2020) 994–1002.
[62] A. Dathan-Stumpf, V. Czarnowsky, V. Hein, T. Andraczek, H. Stepan, Real-world data on the clinical use of angiogenic factors in pregnancies with placental dysfunction, Am. J. Obstet. Gynecol. (2021).
[63] K. Bramham, P.T. Seed, L. Lightstone, et al., Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease, Kidney Int. 89 (2016) 874–885.
[64] U. Perni, C. Sison, V. Sharma, et al., Angiogenic factors in superimposed preeclampsia: a longitudinal study of women with chronic hypertension during pregnancy, Hypertension 59 (2012) 740–746.
[65] U.V. Ukah, B. Payne, H. Karjalainen, et al., Temporal and external validation of the fullPIERS model for the prediction of adverse maternal outcomes in women with pre-eclampsia, Pregnancy Hypertens. 15 (2019) 42–50.
[66] S. Thangaratinam, J. Allotey, N. Marlin, et al., Development and validation of Prediction models for Risks of complications in Early-onset Pre-eclampsia (PREP): a prospective cohort study, Health Technol. Assess. 21 (2017) 1–100.
[67] S. Rana, S.A. Karumanchi, M.D. Lindheimer, Angiogenic factors in diagnosis, management, and research in preeclampsia, Hypertension 63 (2014) 198–202.
[68] B.A. Payne, J.A. Hutcheon, J.M. Ansermino, et al., A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) multi-country prospective cohort study, PLoS Med. 11 (2014), e1001589.
[69] B.A. Payne, J.A. Hutcheon, D. Dunsmuir, et al., Assessing the incremental value of blood oxygen saturation (SpO(2)) in the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) Risk Prediction Model, J Obstet. Gynaecol. Can. 37 (2015) 16–24.
[70] J. Duffy, A.E. Cairns, D. Richards-Doran, et al. A core outcome set for pre-eclampsia research: an international consensus development study. BJOG 2020; 127:1516-26. doi: 10.111/471-0528.16319.
[71] D.R. Hall, H.J. Odendaal, G.F. Kirsten, J. Smith, D. Grove, Expectant management of early onset, severe pre-eclampsia: perinatal outcome, BJOG 107 (2000) 1258–1264.
[72] H.J. Odendaal, D.R. Hall, D. Grove, Risk factors for and perinatal mortality of abruptio placentae in patients hospitalised for early onset severe pre-eclampsia – a case controlled study, J. Obstet. Gynaecol. 20 (2000) 358–364.
[73] S.J. Benton, L.M. McCowan, A.E. Heazell, et al., Placental growth factor as a marker of fetal growth restriction caused by placental dysfunction, Placenta 42 (2016) 1–8.
[74] Z. Alfirevic, T. Stampalija, T. Dowswell, Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev 2017;6:CD007529.
[75] J. Caradeux, R.J. Martinez-Portilla, T.R. Basuki, T. Kiserud, F. Figueras, Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis, Am. J. Obstet. Gynecol. 218 (2018). S774–S82 e21.
[76] G.H.A. Visser, C.M. Bilardo, J.B. Derks, et al., Fetal monitoring indications for delivery and 2-year outcome in 310 infants with fetal growth restriction delivered before 32 weeks' gestation in the TRUFFLE study, Ultrasound Obstet. Gynecol. 50 (2017) 347–352.
[77] C.M. Bilardo, K. Hecher, G.H.A. Visser, et al., Severe fetal growth restriction at 26–32 weeks: key messages from the TRUFFLE study, Ultrasound Obstet. Gynecol. 50 (2017) 285–290.
[78] T. Frusca, T. Todros, C. Lees, C.M. Bilardo, T. Investigators, Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe, Am. J. Obstet. Gynecol. 218 (2018) S783–S789.
[79] B.A. Payne, P.M. Kyle, K. Lim, et al., An assessment of predictive value of the biophysical profile in women with preeclampsia using data from the fullPIERS database, Pregnancy Hypertens. 3 (2013) 166–171.
[80] O.M. Turan, S. Turan, S. Gungor, et al., Progression of Doppler abnormalities in intrauterine growth restriction, Ultrasound Obstet. Gynecol. 32 (2008) 160–167.
[81] R.J. Snijders, L.S. Ribbert, G.H. Visser, E.J. Mulder, Numeric analysis of heart rate variation in intrauterine growth-retarded fetuses: a longitudinal study, Am. J. Obstet. Gynecol. 166 (1992) 22–27.
[82] B.A. Payne, H. Groen, U.V. Ukah, et al., Development and internal validation of a multivariable model to predict perinatal death in pregnancy hypertension, Pregnancy Hypertens. 5 (2015) 315–321.
[83] L.C. Poon, D.L. Rolnik, M.Y. Tan, et al., ASPRE trial: incidence of preterm pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm, Ultrasound Obstet. Gynecol. 51 (2018) 738–742.
[84] E. Bartsch, K.E. Medcalf, A.L. Park, J.G. Ray, High Risk of Pre-eclampsia Identification G. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ 2016;353:i1753.
[85] J.J. Zhang, X.X. Ma, L. Hao, L.J. Liu, J.C. Lv, H. Zhang, A systematic review and meta-analysis of outcomes of pregnancy in CKD and CKD outcomes in pregnancy, Clin. J. Am. Soc. Nephrol. 10 (2015) 1964–1978.
[86] R. Townsend, A. Khalil, Y. Premakumar, et al., Prediction of pre-eclampsia: review of reviews, Ultrasound Obstet. Gynecol. 54 (2019) 16–27.
[87] K. Giannakou, E. Evangelou, S.I. Papatheodorou, Genetic and non-genetic risk factors for pre-eclampsia: umbrella review of systematic reviews and meta-analyses of observational studies, Ultrasound Obstet. Gynecol. 51 (2018) 720–730.
[88] Z. Al-Rubaie, L.M. Askie, J.G. Ray, H.M. Hudson, S.J. Lord, The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review, BJOG 123 (2016) 1441–1452.
[89] N. O'Gorman, D. Wright, L.C. Poon, et al., Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations, Ultrasound Obstet. Gynecol. 49 (2017) 756–760.

[90] M.Y. Tan, D. Wright, A. Syngelaki, et al., Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE, Ultrasound Obstet. Gynecol. 51 (2018) 743–750.
[91] D.L. Rolnik, D. Wright, L.C. Poon, et al., Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia, N. Engl. J. Med. 377 (2017) 613–622.
[92] https://fetalmedicine.org/research/assess/preeclampsia/first-trimester. Accessed 2020 Dec 29.
[93] P. Chaemsaithong, R.K. Pooh, M. Zheng, et al., Prospective evaluation of screening performance of first-trimester prediction models for preterm preeclampsia in an Asian population, Am. J. Obstet. Gynecol. 221 (650) (2019) e1–e16.
[94] M.Y. Tan, L.C. Poon, D.L. Rolnik, et al., Prediction and prevention of small-for-gestational-age neonates: evidence from SPREE and ASPRE, Ultrasound Obstet. Gynecol. 52 (2018) 52–59.
[95] R.B. Skrastad, G.G. Hov, H.G. Blaas, P.R. Romundstad, K.A. Salvesen, Risk assessment for preeclampsia in nulliparous women at 11–13 weeks gestational age: prospective evaluation of two algorithms, BJOG 122 (2015) 1781–1788.
[96] M. Guizani, J. Valsamis, V. Dutemeyer, et al., First-trimester combined multimarker prospective study for the detection of pregnancies at a high risk of developing preeclampsia using the fetal medicine foundation-algorithm, Fetal Diagn. Ther. 43 (2018) 266–273.
[97] B. Mosimann, C. Pfiffner, S. Amylidi-Mohr, L. Risch, D. Surbek, L. Raio, First trimester combined screening for preeclampsia and small for gestational age – a single centre experience and validation of the FMF screening algorithm, Swiss Med. Wkly. 147 (2017), w14498.
[98] J. Sonek, D. Krantz, J. Carmichael, et al., First-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume, Am. J. Obstet. Gynecol. 218 (126) (2018) e1–e13.
[99] F.J. Park, C.H. Leung, L.C. Poon, P.F. Williams, S.J. Rothwell, J.A. Hyett, Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy, Aust. N Z J. Obstet. Gynaecol. 53 (2013) 532–539.
[100] G.A.R. Lobo, P.M. Nowak, A.P. Panigassi, et al., Validation of Fetal Medicine Foundation algorithm for prediction of pre-eclampsia in the first trimester in an unselected Brazilian population, J. Matern Fetal Neonatal Med. 32 (2019) 286–292.
[101] R.J. Ahmed, A. Gafni, E.K. Hutton, et al., The cost implications of less tight versus tight control of hypertension in pregnancy (CHIPS Trial), Hypertension (Dallas, Tex) 2016 (68) (1979) 1049–1055.
[102] A.V. Nikcevic, Z. Dodd, J. Prior, N. O'Gorman, L.C. Poon, K.H. Nicolaides, Reasons for accepting or declining participation in the ASPRE trial: a qualitative study with women at high risk of preterm pre-eclampsia, Prenat Diagn. 39 (2019) 1127–1135.
[103] M.H. Davenport, S.M. Ruchat, V.J. Poitras, et al., Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis, Br. J. Sports Med. 52 (2018) 1367–1375.
[104] M.F. Mottola, M.H. Davenport, S.M. Ruchat, et al. No. 367-2019 Canadian Guideline for Physical Activity throughout Pregnancy. J. Obstet. Gynaecol. Can. 2018;40:1528-37.
[105] G.J. Hofmeyr, S. Manyame, N. Medley, M.J. Williams, Calcium supplementation commencing before or early in pregnancy, for preventing hypertensive disorders of pregnancy. Cochrane Database Syst Rev 2019;9:CD011192.
[106] G.J. Hofmeyr, J.M. Belizan, P. von Dadelszen, Calcium And Pre-eclampsia Study Group, Low-dose calcium supplementation for preventing pre-eclampsia: a systematic review and commentary, BJOG 121 (2014) 951–957.
[107] G.J. Hofmeyr, A.P. Betran, M. Singata-Madliki, et al., Prepregnancy and early pregnancy calcium supplementation among women at high risk of pre-eclampsia: a multicentre, double-blind, randomised, placebo-controlled trial, Lancet 393 (2019) 330–339.
[108] L.M. Askie, L. Duley, D.J. Henderson-Smart, L.A. Stewart, P.C. Group, Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data, Lancet 369 (2007) 1791–1798.
[109] E. Bujold, S. Roberge, Y. Lacasse, et al., Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis, Obstet. Gynecol. 116 (2010) 402–414.
[110] S. Roberge, K. Nicolaides, S. Demers, J. Hyett, N. Chaillet, E. Bujold, The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis, Am. J. Obstet. Gynecol. 216 (110–20) (2017), e6.
[111] S. Roberge, P. Villa, K. Nicolaides, et al., Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis, Fetal Diagn. Ther. 31 (2012) 141–146.
[112] D.L. Rolnik, K.H. Nicolaides, L.C. Poon, Prevention of preeclampsia with aspirin, Am. J. Obstet. Gynecol. (2020), https://doi.org/10.1016/j.ajog.2020.08.045. S0002-9378(20)30873-5, Online ahead of print. PMID: 32835720.
[113] D. Ortved, T.L. Hawkins, J.A. Johnson, J. Hyett, A. Metcalfe, Cost-effectiveness of first-trimester screening with early preventative use of aspirin in women at high risk of early-onset pre-eclampsia, Ultrasound Obstet. Gynecol. 53 (2019) 239–244.
[114] A. Shmueli, H. Meiri, R. Gonen, Economic assessment of screening for pre-eclampsia, Prenat. Diagn. 32 (2012) 29–38.
[115] D. Wright, D.L. Rolnik, A. Syngelaki, et al., Aspirin for evidence-based preeclampsia prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit, Am. J. Obstet. Gynecol. 218 (612) (2018) e1–e6.
[116] E.F. Werner, A.K. Hauspurg, D.J. Rouse, A cost-benefit analysis of low-dose aspirin prophylaxis for the prevention of preeclampsia in the United States, Obstet. Gynecol. 126 (2015) 1242–1250.
[117] D. Mallampati, W. Grobman, D.J. Rouse, E.F. Werner, Strategies for prescribing aspirin to prevent preeclampsia: a cost-effectiveness analysis, Obstet. Gynecol. 134 (2019) 537–544.
[118] F. Mone, J.F. O'Mahony, E. Tyrrell, et al., Preeclampsia prevention using routine versus screening test-indicated aspirin in low-risk women, Hypertension 72 (2018) 1391–1396.
[119] L. Duley, S. Meher, K.E. Hunter, A.L. Seidler, L.M. Askie, Antiplatelet agents for preventing pre-eclampsia and its complications, Cochrane Database Syst. Rev. 2019 (2019).
[120] K.A. Ahrens, R.M. Silver, S.L. Mumford, et al., Complications and safety of preconception low-dose aspirin among women with prior pregnancy losses, Obstet. Gynecol. 127 (2016) 689–698.
[121] T.T. Xu, F. Zhou, C.Y. Deng, G.Q. Huang, J.K. Li, X.D. Wang, Low-dose aspirin for preventing preeclampsia and its complications: a meta-analysis, J. Clin. Hypertens. (Greenwich) 17 (2015) 567–573.
[122] F.M. Liu, M. Zhao, M. Wang, H.L. Yang, L. Li, Effect of regular oral intake of aspirin during pregnancy on pregnancy outcome of high-risk pregnancy-induced hypertension syndrome patients, Eur. Rev. Med. Pharmacol. Sci. 20 (2016) 5013–5016.
[123] R. Hastie, S. Tong, A.K. Wikstrom, A. Sandstrom, S. Hesselman, L. Bergman, Aspirin use during pregnancy and the risk of bleeding complications: a Swedish population-based cohort study, Am. J. Obstet. Gynecol. (2020).
[124] S. Roberge, E. Bujold, K.H. Nicolaides, Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis, Am. J. Obstet. Gynecol. 218 (287–93) (2018), e1.
[125] N. Caron, G.E. Rivard, N. Michon, et al., Low-dose ASA response using the PFA-100 in women with high-risk pregnancy, J. Obstet. Gynaecol. Can. 31 (2009) 1022–1027.
[126] K. Navaratnam, A. Alfirevic, Z. Alfirevic, Low dose aspirin and pregnancy: how important is aspirin resistance? BJOG 123 (2016) 1481–1487.
[127] K. Navaratnam, A. Alfirevic, A. Jorgensen, Z. Alfirevic, Aspirin non-responsiveness in pregnant women at high-risk of pre-eclampsia, Eur. J. Obstet. Gynecol. Reprod. Biol. 221 (2018) 144–150.
[128] S.W. Wen, R.R. White, N. Rybak, et al., Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial, BMJ 362 (2018), k3478.
[129] M.A. Rodger, J.C. Gris, J.I.P. de Vries, et al., Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials, Lancet 388 (2016) 2629–2641.
[130] L.A. Magee, P. von Dadelszen, J. Singer, et al., The CHIPS randomized controlled trial (control of hypertension in pregnancy study): is severe hypertension just an elevated blood pressure? Hypertension (Dallas tex) 2016 (68) (1979) 1153–1159.
[131] CMQCC. Improving Health Care Response to Preeclampsia: A California Toolkit to Transform Maternity Care (California Maternal Quality Care Collaborative). https://www.cmqcc.org/resources-tool-kits/toolkits/preeclampsia-toolkit 2014.
[132] C.A. Crowther, A.M. Bouwmeester, H.M. Ashurst, Does admission to hospital for bed rest prevent disease progression or improve fetal outcome in pregnancy complicated by non-proteinuric hypertension? Br. J. Obstet. Gynaecol. 99 (1992) 13–17.
[133] K.Y. Leung, T.K. Sum, C.Y. Tse, K.W. Law, M.Y. Chan, Is in-patient management of diastolic blood pressure between 90 and 100 mm Hg during pregnancy necessary? Hong Kong Med. J. 4 (1998) 211–217.
[134] S. Meher, E. Abalos, G. Carroli, Bed rest with or without hospitalisation for hypertension during pregnancy, Cochrane Database Syst. Rev. (2005). CD003514.
[135] A. Pels, B.W.J. Mol, J. Singer, et al., Influence of gestational age at initiation of antihypertensive therapy: secondary analysis of CHIPS trial data (control of hypertension in pregnancy study), Hypertension 71 (2018) 1170–1177.
[136] T.R. Easterling, Post-control of hypertension in pregnancy study (CHIPS): what is the optimal strategy to manage hypertension during pregnancy? Hypertension 68 (2016) 36–38.
[137] K.L. Cleary, Z. Siddiq, C.V. Ananth, et al., Use of antihypertensive medications during delivery hospitalizations complicated by preeclampsia, Obstet. Gynecol. 131 (2018) 441–450.
[138] E. Abalos, L. Duley, D.W. Steyn, C. Gialdini, Antihypertensive drug therapy for mild to moderate hypertension during pregnancy, Cochrane Database Syst. Rev. 10 (2018). CD002252.
[139] W.A. Booker, C. Gyamfi-Bannerman, J.-J. Sheen, et al., Maternal outcomes by race for women aged 40 years or older, Obstet. Gynecol. 132 (2018) 404–413.
[140] B.T. Bateman, K.F. Huybrechts, M.A. Fischer, et al., Chronic hypertension in pregnancy and the risk of congenital malformations: a cohort study, Am. J. Obstet. Gynecol. 212 (337) (2015) e1–e14.
[141] Identification and Management of Neonatal Hypoglycaemia in the Full Term Infant (2017). A BAPM Framework for Practice. https://www.bapm.org/resources/40-identification-and-management-of-neonatal-hypoglycaemia-in-the-full-term-infant-2017 2017.
[142] C.A. Fitton, M.F.C. Steiner, L. Aucott, et al., In-utero exposure to antihypertensive medication and neonatal and child health outcomes: a systematic review, J. Hypertens. 35 (2017) 2123–2137.
[143] T. van Winden, J. Klumper, C.E. Kleinrouweler, et al., Effects of tocolysis with nifedipine or atosiban on child outcome: follow-up of the APOSTEL III trial, BJOG 127 (2020) 1129–1137.

[144] S. Butalia, F. Audibert, A.M. Cote, et al., Hypertension Canada's 2018 guidelines for the management of hypertension in pregnancy, Can. J. Cardiol. 34 (2018) 526–531.
[145] D. Stott, M. Bolten, M. Salman, D. Paraschiv, A. Douiri, N.A. Kametas, A prediction model for the response to oral labetalol for the treatment of antenatal hypertension, J. Hum. Hypertens. 31 (2017) 126–131.
[146] D. Stott, I. Papastefanou, D. Paraschiv, K. Clark, N.A. Kametas, Serial hemodynamic monitoring to guide treatment of maternal hypertension leads to reduction in severe hypertension, Ultrasound Obstetrics Gynecol. 49 (2017) 95–103.
[147] C. Weber-Schoendorfer, A. Kayser, T. Tissen-Diabate, et al., Fetotoxic risk of AT1 blockers exceeds that of angiotensin-converting enzyme inhibitors: an observational study, J. Hypertens. 38 (2020) 133–141.
[148] B. Ahmed, D.T. Tran, H. Zoega, S.E. Kennedy, L.R. Jorm, A. Havard, Maternal and perinatal outcomes associated with the use of renin-angiotensin system (RAS) blockers for chronic hypertension in early pregnancy, Pregnancy Hypertens. 14 (2018) 156–161.
[149] A. Walfisch, A. Al-maawali, M.E. Moretti, C. Nickel, G. Koren, Teratogenicity of angiotensin converting enzyme inhibitors or receptor blockers, J. Obstet. Gynaecol. 31 (2011) 465–472.
[150] B.T. Bateman, E. Patorno, R.J. Desai, et al., Angiotensin-converting enzyme inhibitors and the risk of congenital malformations, Obstet. Gynecol. 129 (2017) 174–184.
[151] S.C. Fisher, A.R. Van Zutphen, M.M. Werler, et al., Maternal antihypertensive medication use and congenital heart defects: updated results from the national birth defects prevention study, Hypertension 69 (2017) 798–805.
[152] M. Bullo, S. Tschumi, B.S. Bucher, M.G. Bianchetti, G.D. Simonetti, Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review, Hypertension 60 (2012) 444–450.
[153] M. Gupta, N. Greene, S.J. Kilpatrick, Timely treatment of severe maternal hypertension and reduction in severe maternal morbidity, Pregnancy Hypertens. 14 (2018) 55–58.
[154] L.A. Magee, C. Cham, E.J. Waterman, A. Ohlsson, P. von Dadelszen, Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis, BMJ 327 (2003) 955–960.
[155] A. Hennessy, C.E. Thornton, A. Makris, et al., A randomised comparison of hydralazine and mini-bolus diazoxide for hypertensive emergencies in pregnancy: the PIVOT trial, Aust. N. Z. J. Obstet. Gynaecol. 47 (2007) 279–285.
[156] G. Scott, T.E. Gillon, A. Pels, P. von Dadelszen, L.A. Magee, Guidelines-similarities and dissimilarities: a systematic review of international clinical practice guidelines for pregnancy hypertension, Am. J. Obstet. Gynecol. (2020), https://doi.org/10.1016/j.ajog.2020.08.018. S0002-9378(20)30846-2, Online ahead of print. PMID: 32828743.
[157] K. Sridharan, R.P. Sequeira, Drugs for treating severe hypertension in pregnancy: a network meta-analysis and trial sequential analysis of randomized clinical trials, Br. J. Clin. Pharmacol. 84 (2018) 1906–1916.
[158] S. Alavifard, R. Chase, G. Janoudi, et al., First-line antihypertensive treatment for severe hypertension in pregnancy: A systematic review and network meta-analysis, Pregnancy Hypertens. 18 (2019) 179–187.
[159] T. Easterling, S. Mundle, H. Bracken, et al., Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial, Lancet 394 (2019) 1011–1021.
[160] L. Duley, S. Meher, L. Jones, Drugs for treatment of very high blood pressure during pregnancy, Cochrane Database System. Rev. (2013). CD001449.
[161] M.J. Miller, P. Butler, J. Gilchriest, A. Taylor, M.A. Lutgendorf, Implementation of a standardized nurse initiated protocol to manage severe hypertension in pregnancy, J. Matern Fetal Neonatal Med. 33 (2020) 1008–1014.
[162] A. Kantorowska, C.J. Heiselman, T.A. Halpern, et al., Identification of factors associated with delayed treatment of obstetric hypertensive emergencies, Am. J. Obstet. Gynecol. 223 (250) (2020) e1–e11.
[163] L.A. Magee, S. Miremadi, J. Li, et al., Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia, Am. J. Obstet. Gynecol. 193 (2005) 153–163.
[164] T. Pretorius, G. van Rensburg, R.A. Dyer, B.M. Biccard, The influence of fluid management on outcomes in preeclampsia: a systematic review and meta-analysis, Int. J. Obstet. Anesth. 34 (2018) 85–95.
[165] W. Ganzevoort, A. Rep, G.J. Bonsel, et al., A randomised controlled trial comparing two temporising management strategies, one with and one without plasma volume expansion, for severe and early onset pre-eclampsia, BJOG 112 (2005) 1358–1368.
[166] C.E. Thornton, P. von Dadelszen, A. Makris, J.M. Tooher, R.F. Ogle, A. Hennessy, Acute pulmonary oedema as a complication of hypertension during pregnancy, Hypertens. Pregnancy 30 (2011) 169–179.
[167] L. Duley, Magnesium sulphate in eclampsia. Eclampsia Trial Collaborative Group, Lancet 352 (1998) 67–68.
[168] D. Altman, G. Carroli, L. Duley, et al., Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial, Lancet 359 (2002) 1877–1890.
[169] J. Simon, A. Gray, L. Duley, G. Magpie Trial Collaborative, Cost-effectiveness of prophylactic magnesium sulphate for 9996 women with pre-eclampsia from 33 countries: economic evaluation of the Magpie Trial, BJOG 113 (2006) 144–151.
[170] J.J. Pratt, P.S. Niedle, J.P. Vogel, et al., Alternative regimens of magnesium sulfate for treatment of preeclampsia and eclampsia: a systematic review of non-randomized studies, Acta Obstet. Gynecol. Scand. 95 (2016) 144–156.
[171] L.A. Magee, D.A. De Silva, D. Sawchuck, A. Synnes, P. von Dadelszen, No. 376-magnesium sulphate for fetal neuroprotection, J. Obstet. Gynaecol. Can. 41 (2019) 505–522.
[172] M. Knight, K. Bunch, D. Tuffnell, et al. (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care – Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2015-17. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2019.
[173] B.M. Sibai, J.R. Barton, Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications, Am. J. Obstet. Gynecol. 196 (514) (2007) e1–e9.
[174] W. Ganzevoort, B.M. Sibai, Temporising versus interventionist management (preterm and at term), Best Pract. Res. Clin. Obstet. Gynaecol. 25 (2011) 463–476.
[175] D. Churchill, L. Duley, J.G. Thornton, M. Moussa, H.S. Ali, K.F. Walker. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. Cochrane Database Syst Rev 2018;10:CD003106.
[176] L.C. Chappell, P. Brocklehurst, M.E. Green, et al., Planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial, Lancet 394 (2019) 1181–1190.
[177] K. Broekhuijsen, G.J. van Baaren, M.G. van Pampus, et al., Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial, Lancet (london, england) 385 (2015) 2492–2501.
[178] T.P. Bernardes, E.F. Zwertbroek, K. Broekhuijsen, et al., Delivery or expectant management for prevention of adverse maternal and neonatal outcomes in hypertensive disorders of pregnancy: an individual participant data meta-analysis, Ultrasound Obstet Gynecol 53 (2019) 443–453.
[179] E.F. Zwertbroek, J. Zwertbroek, K. Broekhuijsen, et al., Neonatal developmental and behavioral outcomes of immediate delivery versus expectant monitoring in mild hypertensive disorders of pregnancy: 5-year outcomes of the HYPITAT II trial, Eur. J. Obstet. Gynecol. Reprod. Biol. 244 (2020) 172–179.
[180] H.O. Hamed, M.A. Alsheeha, A.M. Abu-Elhasan, A.E. Abd Elmoniem, M. M. Kamal, Pregnancy outcomes of expectant management of stable mild to moderate chronic hypertension as compared with planned delivery, Int. J. Gynaecol. Obstet. 127 (2014) 15–20.
[181] C.M. Koopmans, D. Bijlenga, H. Groen, et al., Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial, Lancet 374 (2009) 979–988.
[182] Hypertension in pregnancy: diagnosis and management. 2019. at https://www.nice.org.uk/guidance/ng133.).
[183] M.O. Cruz, W. Gao, J.U. Hibbard, What is the optimal time for delivery in women with gestational hypertension? Am. J. Obstet. Gynecol. 207 (214) (2012) e1–e6.
[184] M. Ram, H. Berger, M. Geary, et al., Timing of delivery in women with chronic hypertension, Obstet. Gynecol. 132 (2018) 669–677.
[185] J.A. Hutcheon, S. Lisonkova, L.A. Magee, et al., Optimal timing of delivery in pregnancies with pre-existing hypertension, BJOG 118 (2011) 49–54.
[186] E. McGoldrick, F. Stewart, R. Parker, S.R. Dalziel, Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst. Rev., 2020;12:CD004454.
[187] A.H. Jobe, M.W. Kemp, B. Kamath-Rayne, A.F. Schmidt, Antenatal corticosteroids for low and middle income countries, Semin Perinatol. 43 (2019) 241–246.
[188] American College of O, Gynecologists', Committee on Obstetric P, Society for Maternal- Fetal M, Committee Opinion No.677: Antenatal Corticosteroid Therapy for Fetal Maturation, Obstet. Gynecol. 128 (2016) e187–e194.
[189] C. Gyamfi-Bannerman, E.A. Thom, S.C. Blackwell, et al., Antenatal Betamethasone for Women at Risk for Late Preterm Delivery, N Engl J Med 374 (2016) 1311–1320.
[190] D.M. Woudstra, S. Chandra, G.J. Hofmeyr, T. Dowswell, Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy, Cochrane Database Syst. Rev. (2010). CD008148.
[191] A. Takahashi, N. Kita, Y. Tanaka, et al., Effects of high-dose dexamethasone in postpartum women with class 1 haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, J. Obstet. Gynaecol 39 (2019) 335–339.
[192] N. de Alwis, N.K. Binder, S. Beard, et al., Novel approaches to combat preeclampsia: from new drugs to innovative delivery, Placenta 102 (2020) 10–16.
[193] ACOG Practice Bulletin No, 203: Chronic Hypertension in Pregnancy, Obstet. Gynecol. 133 (2019) e26–e50.
[194] S.H. Nasab, H.N. Moussa, M.A. Alrais, BM. Sibai, Postpartum readmissions: what we can learn from numbers? [18K]. Obstetr. Gynecol. 2018;131:1235. 10.097/01.AOG.0000533520.08596.85.
[195] K.A. Douglas, C.W. Redman, Eclampsia in the United Kingdom, BMJ 309 (1994) 1395–1400.
[196] Drugs and Lactation Database (LactMed) [Internet]. National Library of Medicine (US), 2006-. at https://www.ncbi.nlm.nih.gov/books/NBK501922/?term=lactmed.).
[197] A.E. Cairns, L. Pealing, J.M.N. Duffy, et al., Postpartum management of hypertensive disorders of pregnancy: a systematic review, BMJ Open 7 (2017), e018696.
[198] W. Ying, J.M. Catov, P. Ouyang, Hypertensive disorders of pregnancy and future maternal cardiovascular risk, J. Am. Heart Assoc. 7 (2018), e009382.

[199] A.E. Cairns, K.L. Tucker, P. Leeson, et al., Self-management of postnatal hypertension: the SNAP-HT Trial, Hypertension (Dallas, tex) 2018 (72) (1979) 425–432.
[200] E. Bonifacino, E.B. Schwartz, H. Jun, C.B. Wessel, J.A. Corbelli, Effect of lactation on maternal hypertension: a systematic review, Breastfeed Med. 13 (2018) 578–588.
[201] H. Kirkegaard, M. Bliddal, H. Stovring, et al., Breastfeeding and later maternal risk of hypertension and cardiovascular disease – the role of overall and abdominal obesity, Prev. Med. 114 (2018) 140–148.
[202] A. Makris, C. Thornton, A. Hennessy, Postpartum hypertension and nonsteroidal analgesia, Am J Obstet. Gynecol. 190 (2004) 577–578.
[203] O.A. Viteri, J.A. England, M.A. Alrais, et al., Association of nonsteroidal antiinflammatory drugs and postpartum hypertension in women with preeclampsia with severe features, Obstet. Gynecol. 130 (2017) 830–835.
[204] H.B. Anastasio, L.E. Campbell, A. Buermeyer, et al., Nonsteroidal antiinflammatory drug administration and postpartum blood pressure in women with hypertensive disorders of pregnancy, Obstet. Gynecol. 132 (2018) 1471–1476.
[205] S.W. Wasden, E.S. Ragsdale, S.T. Chasen, D.W. Skupski, Impact of non-steroidal anti-inflammatory drugs on hypertensive disorders of pregnancy, Pregnancy Hypertens. 4 (2014) 259–263.
[206] N.R. Blue, C. Murray-Krezan, S. Drake-Lavelle, et al. Effect of ibuprofen vs acetaminophen on postpartum hypertension in preeclampsia with severe features: a double-masked, randomized controlled trial. Am. J. Obstetr. Gynecol. 2018;218: 616.e1-.e8.
[207] P. Vigil-De Gracia, V. Solis, N. Ortega, Ibuprofen versus acetaminophen as a post-partum analgesic for women with severe pre-eclampsia: randomized clinical study, J. Matern. Fetal Neona 30 (2017) 1279–1282.
[208] M.F. van Oostwaard, J. Langenveld, E. Schuit, et al., Recurrence of hypertensive disorders of pregnancy: an individual patient data metaanalysis, Am. J. Obstet. Gynecol. 212 (624) (2015) e1–e17.
[209] M.A. Brown, C. Mackenzie, W. Dunsmuir, et al., Can we predict recurrence of pre-eclampsia or gestational hypertension? BJOG 114 (2007) 984–993.
[210] K. Khosla, S. Heimberger, K.M. Nieman, et al., Long-term cardiovascular disease risk in women after hypertensive disorders of pregnancy: recent advances in hypertension, Hypertension 78 (2021) 927–935.
[211] L.H. Theilen, A. Fraser, M.S. Hollingshaus, et al., All-cause and cause-specific mortality after hypertensive disease of pregnancy, Obstet. Gynecol. 128 (2016) 238–244.
[212] J. Tooher, C. Thornton, A. Makris, R. Ogle, A. Korda, A. Hennessy, All hypertensive disorders of pregnancy increase the risk of future cardiovascular disease, Hypertension (Dallas, tex) 2017 (70) (1979) 798–803.
[213] J.W. Rich-Edwards, J.J. Stuart, G. Skurnik, et al., Randomized trial to reduce cardiovascular risk in women with recent preeclampsia, J. Womens Health (Larchmt) 28 (2019) 1493–1504.
[214] My Health Beyond Pregnancy. 2021. at https://preeclampsia.org/beyondpregnancy.).
[215] M.A. Brown, L. Roberts, A. Hoffman, et al., Recognizing cardiovascular risk after preeclampsia: the P4 study, J. Am. Heart Assoc. 9 (2020), e018604.
[216] K. Moe, M. Sugulle, R. Dechend, A.C. Staff, Risk prediction of maternal cardiovascular disease one year after hypertensive pregnancy complications or gestational diabetes mellitus, Eur. J. Prev. Cardiol. 27 (2020) 1273–1283.
[217] J.J. Stuart, L.J. Tanz, S.A. Missmer, et al., Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development: an observational cohort study, Ann. Intern. Med. 169 (2018) 224–232.
[218] S.M. Goffin, J.G.B. Derraik, K.M. Groom, W.S. Cutfield, Maternal pre-eclampsia and long-term offspring health: is there a shadow cast? Pregnancy Hypertens. 12 (2018) 11–15.
[219] I.V. Alsnes, L.J. Vatten, A. Fraser, et al., Hypertension in pregnancy and offspring cardiovascular risk in young adulthood: prospective and sibling studies in the HUNT study (nord-trondelag health study) in Norway, Hypertension (Dallas, Tex) 2017 (69) (1979) 591–598.
[220] H.L. Nathan, N. Vousden, E. Lawley, et al., Development and evaluation of a novel Vital Signs Alert device for use in pregnancy in low-resource settings, BMJ Innov. 4 (2018) 192–198.
[221] WHO, World Health Organization Model List of Essential Medicines, 21st List., World Health Organization, Geneva, 2019.
[222] P. von Dadelszen, Z.A. Bhutta, S. Sharma, et al., The community-level interventions for pre-eclampsia (CLIP) cluster randomised trials in Mozambique, Pakistan, and India: an individual participant-level meta-analysis, Lancet 396 (2020) 553–563.
[223] T.E. Gillon, A. Pels, P. von Dadelszen, K. MacDonell, L.A. Magee, Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines, PLoS ONE 9 (2014), e113715.