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Peripartum management of hypertension. A position paper of the ESC Council on Hypertension and the European Society of Hypertension

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Abstract:	<p>Hypertensive disorders are the most common medical complications in the peripartum period associated with a substantial increase in morbidity and mortality. Hypertension in the peripartum period may be due to the continuation of pre-existing or gestational hypertension, de novo development of pre-eclampsia or it may be also induced by some drugs used for analgesia or suppression of postpartum haemorrhage. Women with severe hypertension and hypertensive emergencies are at high risk of life threatening complications, therefore, despite the lack of evidence-based data, based on expert opinion, antihypertensive treatment is recommended. Labetalol intravenously and metyldopa orally are then the two most frequently used drugs. Short-acting oral nifedipine is suggested to be used only if other drugs or iv access are not available. Induction of labor is associated with improved maternal outcome and should be advised for women with gestational hypertension or mild pre-eclampsia at 37 weeks' gestation. This position paper provides the first interdisciplinary approach to the management of hypertension in the peripartum period based on the best available evidence and expert consensus</p>

Prof. Stefan Agewall, MD, FESC

Editor in Chief

European Heart Journal – Cardiovascular Pharmacotherapy

24 November 2019,

Dear Professor Agewall,

I am submitting a manuscript entitled “Peripartum Management of Hypertension. A position paper of the ESC Council on Hypertension and the European Society of Hypertension” on behalf of all the co-authors to be considered for publication in the European Heart Journal – Cardiovascular Pharmacotherapy.

As stated in the title, it is a joint effort of the ESC Council on Hypertension and the European Society of Hypertension. The proposal for this position paper was previously approved by the ESC and the manuscript has been recently approved by the CPG.

I hereby confirm the manuscript has not been submitted to any other journal.

Thank you very much for considering our manuscript for publication.

With my best regards,

Prof. Renata Cífková, MD, PhD, FESC

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Peripartum management of hypertension. A position paper of the ESC Council on
Hypertension and the European Society of Hypertension

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Summary

Hypertensive disorders are the most common medical complications in the peripartum period associated with a substantial increase in morbidity and mortality. Hypertension in the peripartum period may be due to the continuation of pre-existing or gestational hypertension, *de novo* development of pre-eclampsia or it may be also induced by some drugs used for analgesia or suppression of postpartum haemorrhage. Women with severe hypertension and hypertensive emergencies are at high risk of life threatening complications, therefore, despite the lack of evidence-based data, based on expert opinion, antihypertensive treatment is recommended. Labetalol intravenously and metyldopa orally are then the two most frequently used drugs. Short-acting oral nifedipine is suggested to be used only if other drugs or iv access are not available. Induction of labour is associated with improved maternal outcome and should be advised for women with gestational hypertension or mild pre-eclampsia at 37 weeks' gestation. This position paper provides the first interdisciplinary approach to the management of hypertension in the peripartum period based on the best available evidence and expert consensus.

Hypertensive disorders in pregnancy complicate 5–10% of pregnancies and are a major cause of maternal, foetal and neonatal morbidity and mortality (1,2). Women with gestational hypertension or pre-eclampsia require close management during the peripartum period, defined in this document as the last month of gestation and the first few months after delivery. For coding and reporting purposes, the peripartum period is defined as before birth through the 28th day following birth.

The current ESC guidelines on management of cardiovascular disease in pregnancy address the issue of peripartum hypertension within a general context (3). New aspects and advances emerged since their publication, especially in the field of hypertensive emergency/urgency (4). However, in most countries, it is primarily the obstetrician who manages hypertension in the peripartum period, particularly shortly before delivery and during labor. Due to the high rate and unpredictable nature of complications, all pre-eclamptic women should be hospitalized and closely monitored in obstetric care centres with adequate maternal and neonatal intensive care resources. Induction of labour should be attained after 37 weeks of gestation (5). Ten percent of maternal deaths due to hypertensive disorders in pregnancy occur in the postpartum period. Other complications of severe postpartum hypertension include stroke and eclampsia (6). Because of the lack of randomized clinical trials (which is often the case in obstetrics), most of the recommendations are based on expert consensus (7).

The objectives of this position paper are to critically review the current literature on peripartum management of hypertension and to provide recommendations for the clinician.

The position paper should also help hypertension specialists, cardiologists, intensivists, obstetricians and anaesthesiologists to treat hypertension in the peripartum period, including hypertensive emergencies, an issue usually not covered by a majority of guidelines on

hypertension in pregnancy. It could also be relevant to GPs who are responsible for immediate postpartum care in some countries.

Blood pressure changes in the peripartum period

In a normal pregnancy, blood pressure (BP) falls to a nadir at between 20–24 weeks of gestation. Thereafter, the BP gradually increases until term when pre-pregnancy values are achieved.

Blood pressure usually falls immediately after delivery, and then rises progressively with its peak between days 3–6 after delivery (8,9)

Diagnosis and classification of hypertensive disorders in the peripartum period

Blood pressure measurement

The first BP measurement should be taken in both upper arms, with subsequent measurements taken in the arm with the higher BP value, preferably in the sitting position or in the left lateral recumbent position during labour, always using a cuff of appropriate size; the arm should be supported at heart level. Korotkoff V phase should be used to designate diastolic BP. The mercury sphygmomanometer is still considered the gold standard for BP measurement in pregnancy. However, as mercury sphygmomanometers have been banned in European health care institutions, other devices for standard sphygmomanometry or automatic/semiautomatic (usually oscillometric) BP devices, validated according to standardized protocols (specifically for pregnancy and pre-eclampsia) should be used (10) It

is important to note that not all automatic devices are validated for use in pregnancy and pre-eclampsia and those that are not specifically validated for this condition tend to underestimate actual BP levels and are unreliable in severe pre-eclampsia. The best solution may be an auscultatory hybrid device with a liquid-crystal display on a vertical column simulating a mercury sphygmomanometer (11), however, these devices are not yet widely used. Wrist BP monitors are not recommended (12).

In hypertensive emergencies, BP should be also measured in both arms and in lower limbs if there is a clinical suspicion of aortic dissection. (4)

Ambulatory BP monitoring (ABPM) is superior to routine BP measurement for the prediction of pregnancy outcome (13). It can help to rule out white-coat hypertension, a phenomenon quite common in pregnancy (14), and may identify nocturnal hypertension, a finding frequently reported in pre-eclampsia (15).

Home BP measurement (HBPM) is suitable for long-term monitoring, especially in patients on antihypertensive treatment; together with teletransmission of BP data, it may become the future solution saving repeated office visits and hospital admissions (16). Trials are currently assessing its place in pregnancy and in the postpartum period. (17)

Diagnosis of hypertension

Hypertension in pregnancy is diagnosed if systolic BP (SBP) ≥ 140 mmHg and/or diastolic BP (DBP) ≥ 90 mmHg, measured in the office or in hospital; it has to be confirmed,

preferably on 2 separate occasions or at least 15 minutes apart in severe hypertension (i.e. \geq 160/110 mmHg in the obstetric literature) (18).

Classification of hypertensive disorders

Hypertension in the peripartum period may have the following causes:

1. continuation of hypertensive disorders in pregnancy
 - pre-existing hypertension (usually persists > 6 weeks postpartum)
 - gestational hypertension including pre-eclampsia (defined as gestational hypertension associated with significant proteinuria; should resolve within 6 to 12 weeks postpartum)
2. *de novo* pre-eclampsia (headaches, epigastric pain, visual disturbances, seizures)
3. iatrogenic causes
 - drugs: non-steroidal anti-inflammatory drugs (NSAIDs) for analgesia, ergot derivatives for postpartum haemorrhage, or ephedrine, used to correct hypervolemia after regional anaesthesia
4. pain (inadequate analgesia)
5. anxiety

The above definition of pre-eclampsia is in concordance with the 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy (3). However, the International Society for the Study of Hypertension in Pregnancy introduced a new broader definition of pre-eclampsia, being now defined as gestational hypertension accompanied by one or more of the following new-onset conditions at or after 20 weeks of gestation: 1) proteinuria; 2) evidence of other maternal organ dysfunction (including acute kidney injury, liver

involvement, neurological complications, hematological complications); or 3) uteroplacental dysfunction (e.g., fetal growth restrictions, abnormal umbilical artery Doppler wave form analysis for stillbirth) (19).

First-trimester screening and prevention of pre-eclampsia is recommended in all pregnant women (20). All pregnant women with hypertension should be periodically assessed for proteinuria in the second half of pregnancy to screen for pre-eclampsia. Significant proteinuria as a diagnostic criterion for pre-eclampsia is defined as > 0.3 g/24 h or albumin-to-creatinine ratio (ACR) ≥ 30 mg/mmol. If the dipstick test is positive ($\geq 1+$), prompt evaluation of ACR in a single-spot urine sample or 24-h urine collection should follow. An ACR < 30 mg/mmol reliably rules out proteinuria in pregnancy (21). When pre-eclampsia is clinically suspected, a soluble fms-like tyrosine kinase (sFlt)-to-placental growth factor (PlGF) ratio ≤ 38 can be used to exclude the development of pre-eclampsia in the next week (22).

Management of mild to moderate hypertension in the peripartum period

Mild to moderate hypertension (140-159/90-109 mmHg in obstetric literature) in the peripartum period should be treated following the current guidelines (3). As dietary and lifestyle interventions showed only minimal effects on pregnancy outcome, non-pharmacological management of hypertension in pregnancy is only of limited value (23). Regular exercise might be continued with caution and obese women should be advised to avoid a weight gain of more than 6.8 kg. (24) While there is no evidence from randomized clinical trials, the current European hypertension guidelines recommend the initiation of drug treatment in all hypertensive women in pregnancy with BP persistently $\geq 150/95$ mmHg (3,

25). Antihypertensive medication should be initiated at values > 140/90 mmHg in the following clinical conditions:

- gestational hypertension (with or without proteinuria)
- pre-existing hypertension with the superimposition of gestational hypertension
- hypertension with subclinical organ damage or symptoms at any time during pregnancy.

The drugs of choice are methyldopa (centrally acting alpha-2 agonist), beta blockers (most data available for labetalol, a non-selective beta blocker which also acts as an alpha blocker in higher doses; also beta-1 selective drugs such as metoprolol and bisoprolol are widely used and considered safe, with atenolol best avoided) and dihydropyridine calcium channel blockers (most data available for nifedipine; also felodipine and isradipine can be used). ACE inhibitors, angiotensin receptor blockers and renin inhibitors are not recommended in pregnancy (3,26).

Acute-onset, severe hypertension in the peripartum period

The definition of severe hypertension in pregnancy is inconsistent, varying across medical professional societies, with SBP values 160-180 mmHg and DBP \geq 110 mmHg. The 2018 Guidelines on Cardiovascular Disease in Pregnancy (3) recommend considering an SBP \geq 170 or DBP \geq 110 mmHg an emergency with consequent hospitalization.

On the other hand, by a recent American College of Obstetricians and Gynaecologists (ACOG) Committee Opinion (18), an acute-onset of severe hypertension (\geq 160/110 mmHg), accurately measured by standard techniques and persisting for \geq 15 minutes, is considered a hypertensive emergency in pregnancy. This stricter definition of hypertensive emergency in

pregnancy takes into consideration the data from the confidential enquiries into maternal deaths in the UK (27).

Women developing severe hypertension or severe postpartum hypertension are at high risk of life-threatening complications. Data on antihypertensive drugs for postpartum use are extremely limited and again based on expert opinion rather than on evidence.

Hypertensive emergencies

Hypertensive emergency is generally defined as severe hypertension (in pregnancy, SBP \geq 160 mmHg or DBP \geq 110 mmHg) with acute hypertension-mediated organ damage (HMOD) which is often life threatening (aortic dissection, acute myocardial infarction, pulmonary oedema, respiratory failure and stroke). The majority of hypertensive emergencies occur with a DBP > 120 mmHg (4,25).

Hypertensive emergency in pregnancy is specifically defined as pre-eclampsia/eclampsia **and** SBP \geq 160 mmHg and DBP \geq 110 mmHg **or** markedly elevated BP (DBP > 120 mmHg) **and** progressive acute end-organ damage (aortic dissection, acute myocardial infarction, pulmonary oedema and respiratory failure).

The recent ESC Council on Hypertension position document on the management of hypertensive emergencies (4) suggested not using the term hypertensive urgency because there is no evidence that patients without acute HMOD are different from those with asymptomatic uncontrolled hypertension. Therefore, the term hypertensive crisis, coined to discriminate between hypertensive urgencies and emergencies, has become obsolete.

Risk factors for hypertensive emergencies in pregnancy

are listed in **Table 1**.

History, clinical presentation and diagnostic workup

History: The physician should focus on emergency symptoms (headache, visual disturbances, chest pain, dyspnoea, neurological symptoms, abdominal pain, nausea, anorexia) and possible causes such as non-adherence/non-compliance with antihypertensive drugs, use of drugs (with special attention to those affecting BP; e.g., NSAIDs, steroids, sympathomimetics, cocaine, uterocontractive drugs, etc.), current antihypertensive medication or treatment withdrawal and secondary causes of hypertension. Hypertension-specific questions should include the duration of hypertension and previous BP control.

Physical examination: Physical examination should assess signs of complications: impending eclampsia, brisk reflexes, papilledema; the presence of hepatic tenderness suggesting hepatic swelling and risk of rupture; pulmonary oedema suggestive of heart failure and risk of peripartum cardiomyopathy (increased in the presence of pre-eclampsia).

Diagnostic tests: The basic diagnostic workup in a case of suspected hypertensive emergency is provided in **Table 2**. Further diagnostic tests depend on the clinical presentation and may include echocardiography, abdominal and vascular ultrasound, specific laboratory tests (troponin in patients experiencing acute chest pain; N-terminal pro B-type natriuretic peptide (NT-proBNP) in those developing heart failure; urine drug screen in suspected drug abuse).

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2 An sFlt-1:PlGF ratio of 38 or lower can be used to predict the short-term absence of pre-
3
4 eclampsia in women in whom the syndrome is clinically suspected (22,28).
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9 Plasma-free metanephrines or urinary fractionated metanephrines are the tests of first choice
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11 to rule out pheochromocytoma, a rare and usually curable cause of hypertension (the tests
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13 have a nearly maximal negative predictive value). False-positive tests (10–15%) are mostly
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15 due to inappropriate sampling, effect of medication as a confounder (e.g., labetalol and
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17 methyldopa) or elevated sympathetic activity. In suspected cases, only magnetic resonance
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19 imaging reducing radiation exposure is suitable for reliable tumour localization (sensitivity >
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21 90%).
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29 Assessment of foetal wellbeing is an integral part of patient evaluation, which includes
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31 electronic foetal heart monitoring, ultrasound for foetal growth and amniotic fluid assessment.
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33 Uterine artery Doppler velocimetry may be useful; a mean pulsatility index > 95th percentile
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35 in the second trimester and/or bilateral notching may contribute to the suspicion of clinical
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37 diagnosis of pre-eclampsia (29).
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43 *Management of hypertensive emergencies*

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49 A retrospective cohort study conducted in 15 hospitals in California, USA, in women with
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51 acute severe intrapartum hypertension, found a significantly higher risk of severe maternal
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53 morbidity compared with those not developing severe hypertension (30).
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Maternal abnormal parameters requiring immediate bedside evaluation in order to provide timely diagnostic and therapeutic interventions with the intention to improve the quality of care (31) are listed in Table 3.

The immediate goal is to decrease mean BP by 15–25% with the target to achieve SBP 140–150 mmHg and DBP 90–100 mmHg.

Table 4 shows the most commonly used drugs for BP exceeding 160/100 mmHg in pregnancy. Labetalol is considered safe and effective for i.v. treatment of severe pre-eclampsia. Intravenous hydralazine is still widely used, particularly in North America, despite being associated with a number of adverse effects mostly related to maternal hypotension, including a greater risk of Caesarean section, more frequent placental abruption, more maternal oliguria and foetal tachycardia, suggesting the need for close monitoring of maternal BP and foetal wellbeing during its use (32).

Short-acting oral nifedipine is still popular with some obstetricians, although it has been shown to induce uncontrolled hypotension, particularly when combined with magnesium sulfate resulting in fetal compromise, thus its use should be avoided except in low-resource settings when other drugs are unavailable or until i.v. access can be obtained and alternative drugs administered. If immediate-release oral nifedipine is not available and i.v. access has not yet been established, either 200 mg of labetalol or 1.0-1.5 gr of methyldopa can be administered orally.

A recent pooled analysis of seven trials comparing oral nifedipine with i.v. labetalol in severe hypertension during pregnancy found nifedipine as efficacious and safe as i.v. labetalol (33)

although this meta-analysis included 4 studies from developing countries and based its conclusions on only 363 women-infant pairs.

Alternatively, i.v. urapidil or nicardipine can be used. Sodium nitroprusside should be only used as the drug of last choice for extreme emergencies and for the shortest possible period of time (if BP cannot be controlled by other means) because prolonged treatment is associated with an increased risk of foetal cyanide poisoning and increased intracranial pressure in the pregnant woman (with potential worsening of cerebral oedema).

When pre-eclampsia is associated with pulmonary oedema, the drug of choice is nitroglycerine (glycerol trinitrate) in i.v. infusion (5 µg/min), gradually increased every 3–5 minutes to a maximum dose of 100 µg/min.

The American College of Obstetricians and Gynecologists Committee Opinion concluded that labetalol i.v., hydralazine i.v. (i.m.) and immediate-release oral nifedipine are the three most frequently used drugs in hypertensive emergencies during pregnancy and that they can be used without cardiac monitoring (18).

Management of heart failure

Thirty percent of patients with pre-existing heart disease with pre-eclampsia also develop heart failure during pregnancy (34), it typically occurs at the end of the second trimester or immediately postpartum. Pulmonary oedema may occur as a complication of pre-eclampsia without cardiac impairment (35). N-terminal pro-B type natriuretic peptide levels predict

cardiovascular events during pregnancy, but these are also elevated in women with pre-eclampsia without any cardiac abnormality (36,37). A low NT-proBNP has a strong negative predictive value, but its high levels do not have a strong positive value (38).

A pregnant woman presenting with heart failure should be evaluated by a multidisciplinary team, which decides on the management based on the maternal and foetal condition: if the foetus is viable, the choice is between immediate delivery or continuing the pregnancy with heart failure therapy (39). In the case of severe heart failure and/or foetal distress, deliver is the only option. In mild heart failure and no foetal distress, the pregnancy should continue with heart failure management. Drug treatment of acute heart failure in pregnancy follows the guidelines for non-pregnant patients with few exceptions (38). Diuretics are considered safe during pregnancy but intravascular volume depletion should be avoided and prophylactic anticoagulation considered. ACE inhibitors and angiotensin receptor blockers are contraindicated during pregnancy and can be only used in exceptional circumstances. Other afterload reducing agents such as nitrates or hydralazine may be considered for treatment of heart failure. Noninvasive positive-pressure ventilation can be considered, based on a number of case reports and lack of reported side-effects.

Use of magnesium sulphate

Intravenous magnesium sulphate is recommended for the prevention of eclampsia and for the treatment of seizures, it should not be given concomitantly with calcium-channel blockers because of the risk of hypotension due to potential synergism (40). Most of the guidelines agree that primary prevention of eclampsia is recommended for patients presenting with severe pre-eclampsia with the onset of persistent neurological signs (severe headache, visual

disturbances, hyperactive deep-tendon reflexes) during pregnancy but, also, in the postpartum period (41,12). The standard dosing of magnesium sulphate is 4 g i.v. as a loading dose followed by continuous infusion of 1 g per hour until delivery for a maximum of 24 hours; magnesium sulphate should only be administered under close maternal monitoring.

Delivery

Induction of labour is associated with improved maternal outcome and should be advised for women with gestational hypertension or mild pre-eclampsia at 37 weeks' gestation (5).

Optimal timing of delivery depends on foetal wellbeing, gestational age and type of hypertensive disorder. While pre-eclampsia without severe features is potentially manageable by expectation, the presence of eclampsia usually requires delivery soon after maternal stabilization.

Vaginal delivery should be considered for women with any hypertensive disorders in pregnancy unless a Caesarean delivery is required for obstetric indications (41).

All women with severe pre-eclampsia should be delivered promptly, either vaginally or by Caesarean section, regardless of gestational age.

Legislation in most countries allows termination of pregnancy if the mother's life is at imminent threat.

Antihypertensive treatment should be continued during labour and delivery to keep SBP < 160 mmHg and DBP < 110 mmHg.

Prevention of pre-eclampsia

Women at high or moderate risk of pre-eclampsia should take low-dose (100–150 mg) acetylsalicylic acid (aspirin) daily from week 12 to weeks 36–37 (42). High dose calcium supplementation ($\geq 1\text{g/day}$) may reduce the risk of pre-eclampsia and pre-term birth, particularly for women with low calcium diet (43).

Corticosteroids for acceleration of foetal pulmonary maturity

Antenatal corticosteroid therapy should be considered for all women presenting with pre-eclampsia at ≤ 34 weeks of gestation and in women with gestational hypertension presenting at ≤ 34 weeks only if delivery is considered within the next 7 days.

A rescue dose of corticosteroids may be considered for women at ≤ 34 weeks remaining at high risk of pre-term delivery 14 days or more after an initial course of antenatal corticosteroids; repeated doses are recognized to reduce infant birthweight and head circumference (44).

Antenatal corticosteroids may be considered for women delivering by elective Caesarean section at ≤ 38 weeks' gestation to reduce respiratory morbidity (41).

Pheochromocytoma in pregnancy

Pheochromocytoma in a pregnant woman is rare (0.002% of all pregnancies), but extremely dangerous (45, 46). If undiagnosed, maternal and foetal mortality is around 50%. Early detection and proper treatment during pregnancy decrease maternal (< 5%) and foetal (~15%) mortality. The crucial factor is early recognition of a pheochromocytoma in a pregnant woman with hypertension (see Diagnostic workup, Table 2). When pheochromocytoma is diagnosed within the first 24 weeks of gestation, laparoscopic adrenalectomy after 10–14 days of medical pre-treatment with alpha-adrenergic blockade (lowering maternal and foetal mortality) is recommended. Calcium channel blockers are an alternative option but are frequently used as complementary treatment to alpha-adrenergic blockade. If the tumour is not diagnosed until the third trimester, the patient should be managed using the same protocol as for surgical preparation until the foetus is viable. Caesarean section with tumour removal in the same session or at a later stage is strongly preferred as vaginal delivery is associated with higher mortality. Epidural, general or combined anaesthetic techniques can be used.

Identification of postpartum hypertension

Blood pressure should be checked within 6 hours of delivery in all normotensive women without complications because of the risk of late onset pre-eclampsia. Blood pressure fluctuations postpartum are a usual finding. Transient hypertension may appear postpartum in normotensive uncomplicated pregnancies; this may be due to pain (inadequate analgesia), drugs (NSAIDs for analgesia, ergot derivatives for postpartum haemorrhage, or ephedrine), excess fluid administration (hypervolemia after regional anaesthesia), salt and water accumulated during pregnancy moving into the intravascular compartment or restoration of non-pregnant vascular tone. A BP rise postpartum is physiological and, should mild

1 hypertension develop (mostly on days 3 to 6), it usually resolves spontaneously without the
2 need for drug treatment (47). As pre-eclampsia may also have late presentation, checking BP
3
4 postpartum on regular basis (i.e. at least once daily) for the first 5 days after delivery is
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6 important. It is recommended to check BP every other day after discharge from hospital for
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8 up to one week (26).
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13 *De novo* development of pre-eclampsia in the postpartum period should be suspected in
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15 women with hypertension associated with headaches, epigastric pain (possibly with nausea
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17 and vomiting), visual disturbances (e.g., blurred vision, flashing lights, double vision, floating
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19 spots, etc.), dyspnoea (potentially caused by pulmonary oedema), sudden swelling of the face,
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21 hands or feet, or with seizures up to 4 weeks postpartum.
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28 **Management of postpartum hypertension**

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34 All women with hypertension in pregnancy should have their BP and urine checked at 6
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36 weeks postpartum and persistent hypertension confirmed by 24-hour ambulatory monitoring
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38 (48,49). It is also suggested that all women with persisting hypertension under the age of 40
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40 are assessed for a secondary cause of hypertension. Women with persisting hypertension or
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42 proteinuria 6 weeks after delivery should be referred to a specialist.
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48 Antihypertensive medication should be selected with respect to breastfeeding. Many
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50 guidelines still consider methyldopa the drug of choice for management of postpartum
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52 hypertension; however, it should be used with caution in women at risk of developing
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54 depression (50).
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1 All antihypertensive agents taken by nursing mothers are transferred into breast milk;
2 however, most of the agents are present at very low concentrations except for propranolol,
3
4 atenolol, acebutolol, and nifedipine, achieving levels similar to those in maternal plasma.
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6 Betablockers are generally considered safe, even though some of them (propranolol, atenolol
7
8 and acebutolol) may induce signs of neonatal beta-blockade. Recommended beta-blocking
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10 drugs are labetalol and some beta-1 selective blockers of which metoprolol has both
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12 favourable pharmacokinetics and the most available data on safety. Calcium channel blockers
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14 are also generally considered safe with the dihydropyridine type calcium channel most
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16 frequently used, with felodipine and nifedipine having acceptable safety and efficacy profile.
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18 Nonetheless, the manufacturer does not recommend using nifedipine in nursing mothers;
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20 despite this, nifedipine is widely used without neonatal side effects reported. Nifedipine may
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22 be the drug of choice in black women of African or Caribbean origin.
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31 **Table 5** provides a list of antihypertensive drugs usually compatible with breastfeeding,
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33 however, this list may be updated periodically and it is advised that all prescribers should
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35 review current prescribing information. Most guidelines suggest labetalol, nifedipine and
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37 enalapril as first-line antihypertensive drugs for breastfeeding mothers (51). While generally
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39 contraindicated in pregnancy, ACE inhibitors can be used in lactating mothers unless the
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41 neonate is premature or has renal failure. Enalapril is specifically listed in **Table 5** as the most
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43 widely used ACE inhibitor in this indication (due to its safety and favourable
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45 pharmacokinetics) and may be particularly suitable for treatment of peripartum
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47 cardiomyopathy. Diuretics (furosemide, hydrochlorothiazide and spironolactone) may reduce
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49 milk production and are generally not preferred in breastfeeding women.
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Antihypertensive medication is usually continued until BP has normalized, which may be days to several weeks postpartum. Home BP monitoring is suggested.

Hypertension within gestational hypertension and pre-eclampsia will normalize within 3 months postpartum in most cases (52).

Self-monitoring with self-titration of antihypertensive medication has shown promise but further trials are needed to confirm this on a wider scale (17)

Transfer to the intensive care unit (ICU)

The decision to transfer a patient to the ICU (either antenatal or postpartum) should be made collectively by a team of specialists based on the stability of the patient, physical examination, vital signs, laboratory values, imaging and expected care required. There might be local differences; however, in the presence of any of the following factors, transfer to the ICU should be strongly considered (31):

- Need for respiratory support and possible intubation;
- Heart rate > 150 bpm or < 40 bpm;
- Tachypnoea > 35 min;
- Acid-base imbalance or severe electrolyte abnormalities;
- Need for pressor support or other forms of cardiovascular support;
- Need for more invasive monitoring;
- Abnormal EKG findings, e.g., requiring further intervention such as cardioversion or defibrillation;

- Need for i.v. antihypertensive medication once first-line drugs have failed.

Long-term cardiovascular consequences of gestational hypertension

Several population-based retrospective cohort studies have shown that women with gestational hypertension or pre-eclampsia in particular are at increased risk of developing hypertension, stroke, ischemic heart disease and thromboembolic disease in later adult life (53). In a 50-year follow-up study, an association between pre-eclampsia and cardiovascular mortality was confirmed (54). Data from the National Patient Register and the National Birth Register in Denmark have shown a small but significant increased risk of cardiomyopathy in women with a history of hypertensive disorders in pregnancy (compared with normotensive women) more than 5 months after delivery (55). A more recent analysis of the nationwide Danish register data found the risks of peripartum cardiomyopathy significantly higher in women with hypertensive disorders in pregnancy and with pre-eclampsia in particular (56). Thus, cardiovascular risk assessment and lifestyle modifications are recommended in all women with a pregnancy related hypertensive disorder to avoid complications in subsequent pregnancies and to reduce maternal cardiovascular risk in the future (57,58). As these women have an increased risk of early onset of hypertension, regular visits for checking their BP and metabolic factors are strongly recommended, preferably on an annual basis.

Gaps in evidence

There are no specific studies designed for the treatment of hypertension in the entire peripartum period. Most of the studies were performed in women with mild to moderate

1 hypertension in pregnancy showing efficacy and safety but no clear benefit from the treatment
2 for mothers nor the babies (no difference in outcome of pre-eclampsia, neonatal death, pre-
3 term birth, small-for-gestational-age babies). The only positive finding from antihypertensive
4 treatment is halving the risk of developing severe hypertension. The current guidelines are
5 based on expert consensus recommending thresholds to initiate treatment with
6 antihypertensive drugs. Prospective studies, even observational, are desperately needed.
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17 Postpartum hypertension is probably more frequent than previously thought; it can have
18 devastating consequences including maternal stroke and death. There are only a few
19 randomized clinical trials, mostly of short duration with no hard endpoints. No trial with a
20 prospective design has been initiated for the prevention of postpartum hypertension.
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26 Therefore prophylactic treatment of hypertension to prevent pre-eclampsia is not
27 recommended. It is not clear whether drugs used for severe hypertension antepartum have the
28 same efficacy postpartum. It is also not known which agent in treatment of acute severe
29 hypertension postpartum is preferred.
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39 **Key messages**

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- 44 • Hypertensive disorders in the peripartum period contribute substantially to maternal and
45 foetal morbidity and mortality;
 - 46 • Systolic blood pressure > 160 mmHg is associated with an adverse maternal outcome
47 (e.g., stroke, pulmonary oedema);
 - 48 • Early diagnosis and adequate treatment are essential;
 - 49 • Blood pressure \geq 160/110 mmHg lasting > 15 minutes warrants immediate drug
50 treatment;
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- Labetalol i.v. and oral nifedipine are currently suggested as first-line treatment for hypertensive emergencies during pregnancy;
- Methyldopa should not be used primarily for urgent BP reduction;
- Magnesium sulphate is recommended for the prevention of eclampsia and treatment of seizures but should not be given concomitantly with calcium-channel blockers (risk of hypotension due to potential synergism);
- Early maternal warning signs, e.g., SBP > 160 mmHg, tachycardia and oliguria, should be followed by proper diagnostic workup and, possibly, treatment.
- Labetalol, nifedipine, enalapril and metoprolol are considered safe for breastfeeding mothers.

Conflict of interest: none declared

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Table 3. Maternal early warning criteria

- Systolic blood pressure < 90 or > 160 mmHg
- Diastolic blood pressure > 100 mmHg
- Heart rate < 50 or > 130 beats per minute
- Oxygen saturation on room air, at sea level, < 95%
- Oliguria (< 35 ml/h for 2 hours or more)
- Maternal agitation, confusion, or unresponsiveness (changed mental status)
- Non-remitting headache in patient with hypertensive disease of pregnancy
- Shortness of breath

Adapted from ref. 31

Table 2. Diagnostic workup in suspected hypertensive emergency in pregnancy**Primary work-up**

Fundoscopy

EKG

Haemoglobin, platelet count, fibrinogen

Serum creatinine, eGFR, electrolytes, LDH, haptoglobin

Urine: ACR

Urine microscopy: red cells, leukocytes, casts

Specific tests

Troponin (acute chest pain)

NT-proBNP (heart failure)

Plasma or urinary fractionated metanephrines (to rule out pheochromocytoma)

sFlt-1/PlGF (pre-eclampsia)

Echocardiography (aortic dissection, heart failure or ischemia)

Brain CT or MRI

Renal ultrasound (renal parenchymal disease) and duplex renal artery Doppler (renovascular disease)

Urine drug screen (suspected methamphetamine or cocaine use)

Assessment of foetal wellbeing

Electronic foetal heart monitoring

Ultrasound examination for foetal growth

Amniotic fluid assessment

Uterine artery Doppler velocimetry (mean pulsatility index $>95^{\text{th}}$ percentile in the second trimester and/or bilateral notching)

Abbreviations: EKG, electrocardiography; eGFR, estimated glomerular filtration rate; LDH, lactate acid dehydrogenase; ACR, albumin/creatinine ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; sFlt-1/PlGF, soluble fms-like tyrosine kinase 1 to placental growth factor; CT, computed tomography; MRI, magnetic resonance imaging

Adapted from ref. 25 and 29

Table 1. Risk factors for hypertensive emergencies in the peripartum period

- pre-eclampsia
- cardiac disease
- chronic renal disease
- concomitant use of recreational drugs (e.g. cocaine, methamphetamine) and other BP raising medication (e.g. erythropoietin, anabolic steroids and some herbal remedies)
- non-compliance with antihypertensives
- use of uterocontractive drugs (e.g. ergonovine maleate, methyl ergonovine maleate) for prevention and treatment of postpartum haemorrhage caused by uterine atony
- non-Hispanic black population
- low socioeconomic status

Table 4. Most commonly used drugs for treatment of hypertensive emergencies in pregnancy

Drug	Mechanism	Route	Onset of action	Duration of action	Starting dose	Titration dose	Maximum dose	Perinatal concerns	Contra-indications	Adverse effects
Labetalol	Alpha-1 and non-selective beta-blocker	iv (intermittent)	5–10 min	2–6 h	10–20 mg iv (over 2 min)	20–80 mg iv every 20–30 min	300 mg	Foetal distress secondary to abrupt maternal hypotension; neonatal bradycardia and hypoglycaemia	II or III degree AV block; systolic heart failure; asthma; bradycardia	Bronchoconstriction (CAUTION in women with asthma); foetal bradycardia; postural hypotension; sleep disturbances; rebound hypertension; masking hypoglycaemia
		iv (infusion)			1–2 mg/min	Increase by 1 mg/min every 10 min				
Hydralazine	Direct vasodilator	iv (intermittent)	10 min	12 h	5 mg/ iv or im	5–10 mg iv every 20–40 min	30 mg	Foetal distress secondary to abrupt maternal hypotension; caesarian section; abruptio; APGAR score < 7 more common; rarely neonatal thrombocytopenia and neonatal lupus		Headache; palpitations; tachycardia; nausea/vomiting; flushing; hypotension; lupus-like syndrome; CAUTION: side effects may mimic worsening pre-eclampsia
Nifedipine short acting formulation	Dihydropyridine calcium-channel blocker	Oral	5–10 min	2–4 h	10–20 mg	Repeat in 30 min if needed	30 mg	Foetal distress secondary to abrupt maternal hypotension; increased liver clearance may		Uncontrolled hypotension (high when combined with magnesium sulphate); stroke; M (particularly when given

								require higher doses		sublingually); headache; flushing; reflex tachycardia
Nitroglycerine	Direct vasodilator	iv (infusion)	1-5 min	3-5 min	5 µg/min	Increase by 5 µg/min every 5 min	200 µg/min			Headache; reflex tachycardia
Esmolol	Beta-1-blocker	iv (infusion)	< 1 min	15–30 min	Bolus 500 µg/kg; maintenance 50 µg/kg/min	Increase by 50 µg/kg/min every 4 min	300 µg/kg/min	Foetal bradycardia; resistant foetal beta-blockade	II or III degree AV block; systolic heart failure; asthma; bradycardia	First-degree heart block; maternal bradycardia; CHF; bronchospasm
Nicardipine	Dihydropyridine calcium-channel blocker	iv (infusion)	1-5 min	4-6 h	5 mg/h	Increase by 2.5 mg/h every 5-15 min	15 mg/h		liver failure	Tachycardia; flushing; headache
Urapidil	Alpha-1 blocker and weak central 5-hydroxytryptamine agonist	iv (infusion)	3-5 min	4-6 h	Bolus 12.5-25 mg; maintenance 5-40 mg/h		40 mg/h			
Sodium nitroprusside	Non-selective direct NO inhibitor	iv (infusion)	< 1 min	2–3 min	0.25 µg/kg/min	Increase by 0.25-0.5 µg/kg/min every 2-3 min	5 µg/kg/min	Foetal cyanide and thiocyanide toxicity if used > 4 h		Nausea; vomiting

AV, atrioventricular; CHF, chronic heart failure; iv, intravenous; im, intramuscular; NO, nitric oxide.

Table 5. Maternal antihypertensive medication usually compatible with breastfeeding**ACE inhibitors**

Benazepril
Captopril
Enalapril
Quinapril

Calcium-channel blockers

Diltiazem
Nifedipine
Verapamil

Beta-blockers

Labetalol
Metoprolol
Nadolol
Oxprenolol
Propranolol
Timolol

Diuretics

Furosemide
Hydrochlorothiazide
Spironolactone

Other

Clonidine
Hydralazine
Methyldopa
Minoxidil

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Hypertensive disorders are the most common medical complications in the peripartum period associated with a substantial increase in morbidity and mortality. Hypertension in the peripartum period may be due to the continuation of pre-existing or gestational hypertension, de novo development of pre-eclampsia or it may be also induced by some drugs used for analgesia or suppression of postpartum haemorrhage. Women with severe hypertension and hypertensive emergencies are at high risk of life threatening complications, therefore, despite the lack of evidence-based data, based on expert opinion, antihypertensive treatment is recommended. Labetalol intravenously and metyldopa orally are then the two most frequently used drugs. Short-acting oral nifedipine is suggested to be used only if other drugs or iv access are not available. Induction of labour is associated with improved maternal outcome and should be advised for women with gestational hypertension or mild pre-eclampsia at 37 weeks' gestation. This position paper provides the first interdisciplinary approach to the management of hypertension in the peripartum period based on the best available evidence and expert consensus.