Management of hypertension in pregnancy: prevention, diagnosis, treatment and long-term prognosis

A position statement of the Polish Society of Hypertension, Polish Cardiac Society and Polish Society of Gynecologists and Obstetricians

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1. Introduction

This document is the first joint expert opinion of 3 medical societies on hypertension (HT) in pregnancy. It aims at presenting the management of HT in pregnancy, with particular emphasis on pathophysiological differences, clinical manifestation, and sequelae of pregnancy-induced HT and preeclampsia (PE). The document is based on the analysis of existing guidelines, the regulation of the Minister of Health, and a critical analysis of available data. The Regulation of the Minister of Health, which we repeatedly refer to in this expert position statement, albeit expired on 1 January 2019, still applies to this document and its detailed recommendations, due to its undoubted substantive value and the fact that it systematizes the management of normal and complicated pregnancy.[1-9]

Elevated blood pressure (BP) in pregnancy poses a significant clinical challenge, and the observed trend towards delayed childbearing and later age of pregnant women contribute to its higher prevalence. HT in pregnancy affects 6% to 10% of pregnancies in the United States and Europe. Women with chronic HT (1%–5% of the general population) have a higher risk of PE than women without preexisting HT (17%–25% vs 3%–5%, respectively). Furthermore, 7% to 20% of women with chronic HT have poor BP control in pregnancy (excluding those with PE). Significantly elevated BP in pregnancy is a direct threat to maternal and fetal health and life. According to the World Health Organization (WHO), HT and its complications are among the leading causes of mortality in pregnancy in developed countries (approx. 16%).[9-11]

HT promotes low birth weight (LBW), increases the risk of PE superimposed on chronic HT and preterm birth, may cause placental abruption, leads to complications which require prolonged intensive care of a neonate with specialist neonatal treatment, and may cause intrauterine fetal death.[12,13]

PE is the most dangerous maternal complication of HT. PE is associated with a particularly high risk of complications harmful to the mother

and fetus. Each year, PE causes over 500 thousand fetal and neonatal deaths and over 70 thousand maternal deaths worldwide.[1,12,13]

Developing recommendations on the management of HT in pregnancy is challenging for 2 reasons: first, the number of studies, especially with prospective and randomized design, is limited, and second, approved indications and registry data limit the possibility to develop recommendations regarding drug classes. It is only possible to comment on the potential use of selected drugs.[1,2,4,9,11]

Most guidelines and recommendations published to date have been developed separately by societies of cardiology/HT or by societies of obstetrics and gynecology.[1-9] Therefore, a joint position statement was developed in order to avoid discrepant recommendations and to create a single practical document which could provide guidance for physicians responsible for the management of HT from pre-conception to the postpartum period.

TABLE 2.1 Classes of recommendation

Class of recommendation	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

TABLE 2.2 Levels of evidence

Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized clinical trial or large nonrandomized studies
Level C	The consensus of opinion of the experts and/or small studies, retrospective studies, registries

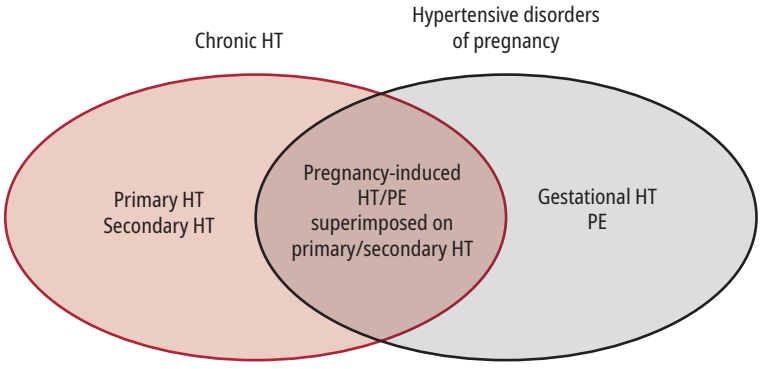

FIGURE 3.1 Classification of hypertension in pregnancy according to Brown et al[1] and Williams et al[4]

Abbreviations: HT, hypertension; PE, preeclampsia

2. Assessing the strength of recommendation

The members of the working group who drafted this position statement have thoroughly reviewed the published results of studies of HT in pregnancy discussing its prevention, diagnostic and therapeutic management as well as long-term prognosis. The level of evidence and the strength of recommendations for each option are balanced and categorized using the previously defined grading systems shown in TABLES 2.1 and 2.2 in harmony with the recommendations of the European Society of Cardiology. In order to simplify the message when presenting individual recommendations, the class of recommendation was omitted, and the following phrases were used instead as equivalent to the classes of recommendations:

- Recommended/indicated (class of recommendation, I)
- Should be considered (class of recommendation, IIa)
- May be considered (class of recommendation, IIb)
- Not recommended (class of recommendation, III).

Furthermore, the recommendations listed in the tables were color-coded: green (class of recommendation I), yellow (class of recommendation IIa and IIb), and red (class of recommendation III).[3] Finally, the quality of research-derived evidence constituting a basis for recommendations was assessed and expressed as levels (TABLE 2.2).

3. Definitions and the classification of hypertension in pregnancy

Based on the differences in pathophysiology, clinical manifestation and management, HT during pregnancy can be divided into 2 distinct conditions (FIGURE 3.1)[1,4]:

- Chronic HT – preexisting or with the onset before 20 gestational weeks, and typically persisting up to 6 weeks postpartum, which can be classified into:
  - Primary (essential) HT
  - Secondary HT
- Hypertensive disorders of pregnancy – with the onset after 20 gestational weeks, which can be classified into:
  - Pregnancy-induced HT with the onset after 20 gestational weeks, which resolves within 6 weeks postpartum
  - PE

It should be noted that the 2 conditions are not mutually exclusive, that is, a woman with chronic HT may develop PE – PE superimposed on chronic (preexisting) HT.

TABLE 3.1 Definitions and classification of hypertension in pregnancy[1,3]

Condition	Definition	Maternal outcomes	Fetal / perinatal outcomes
Chronic HT	HT with the onset prior to conception or before 20 gestational weeks usually persists for over 6 weeks postpartum. It can be classified as primary (essential) HT and secondary HT	Depend on the clinical course, especially in secondary HT. Eg, increased risk of PE, Cesarean delivery, preterm birth	May be associated with LBW, the need for neonatal intensive care, IUGR, and IUFD
Pregnancy-induced HT	New onset of HT after 20 gestational weeks, not concomitant with proteinuria, biochemical and hematological abnormalities. Pregnancy induced HT usually resolves within 6 weeks postpartum	Increased risk of PE	May be associated with LBW, the need for neonatal intensive care, IUGR and IUFD, although less often than preexisting HT
PE	New onset of HT after 20 gestational weeks plus new onset proteinuria and / or maternal kidney injury, maternal liver injury, neurological symptoms, hemolysis or thrombocytopenia and / or IUGR	High risk of complications, including death	High risk of complications, eg, IUGR and IUFD
PE superimposed on chronic HT	PE in women with chronic HT	High risk of complications, including death	High risk of complications, eg, IUGR and IUFD
Other conditions			
White coat HT	Elevated office BP readings and normal out-of-office BP readings	Increased risk of PE	
Masked HT	Normal office BP readings and elevated out-of-office BP readings	No data available	No data available
Transient pregnancy--induced HT	HT diagnosed in the second and third trimester, usually based on office readings, which resolves within a few hours	Increased risk of pregnancy--induced HT and PE	
HT not classified elsewhere	Any HT diagnosed after 20 gestational weeks should be considered pregnancy-induced HT if there is no data regarding preconception BP values		

Abbreviations: BP, blood pressure; HT, hypertension; IUFD, intrauterine fetal death; IUGR, intrauterine growth restriction; LBW, low birth weight; PE, preeclampsia

A number of other possible clinical scenarios in pregnancy have been presented in TABLE 3.1.

It is emphasized that the cutoff point of 20 gestational weeks should only be considered a rough approximation and clinical evaluation should primarily inform the decision-making. Differentiation between different hypertensive disorders of pregnancy is further hindered by the fact that the maximum physiological BP drop occurs at 16 to 18 gestational weeks, which may mask chronic HT, and the BP only returns to the preconception values in the third trimester. Additionally, preconceptive BP values are often unknown.[14] Regardless of the above, physiological pregnancy is associated with a BP drop. This response is also preserved in women with chronic HT. Pregnancy-induced HT superimposed on chronic HT should therefore always be considered with a sudden onset of high BP in pregnancy.

4. Management of hypertension in women at reproductive age

Diagnostic management and treatment of HT in women planning to conceive may affect the course of pregnancy as well as maternal and fetal outcomes.[15] Due to significant unintended pregnancy rates, any woman having menstrual cycles presenting with HT should be considered potentially pregnant. Therefore, this document outlines both the general principles of chronic HT management in women at reproductive age and the specific recommendations of HT management in women planning to conceive.

4.1 Treatment of hypertension in women at reproductive age

The current guidelines for the management of HT do not provide for a separate diagnostic algorithm applicable to women at reproductive age, including those planning to conceive.[2,4]

In women with elevated office BP readings, it is recommended to exclude white coat HT and confirm the HT diagnosis with BP readings obtained elsewhere – using either 24-hour ambulatory BP monitoring or home BP (FIGURE 4.1). If out-of-office BP readings cannot be obtained, it is recommended to confirm the HT diagnosis using repeated office measurements, preferably taken by a nurse.[16,17]

The guidelines for the management of HT point to the urine albumin test as a preferred severity assessment of HT-induced target organ damage. However, this test is not commonly used in Poland.[3,4] On the other hand, the guidelines for the management of HT in pregnancy indicate the validity of urine protein test rather than urine albumin test, whilst not stating a preferred method (especially quantitative assay) (TABLE 4.1).[1,8] Considering the need to develop practical guidelines which ensure standardized management, we recommend that every

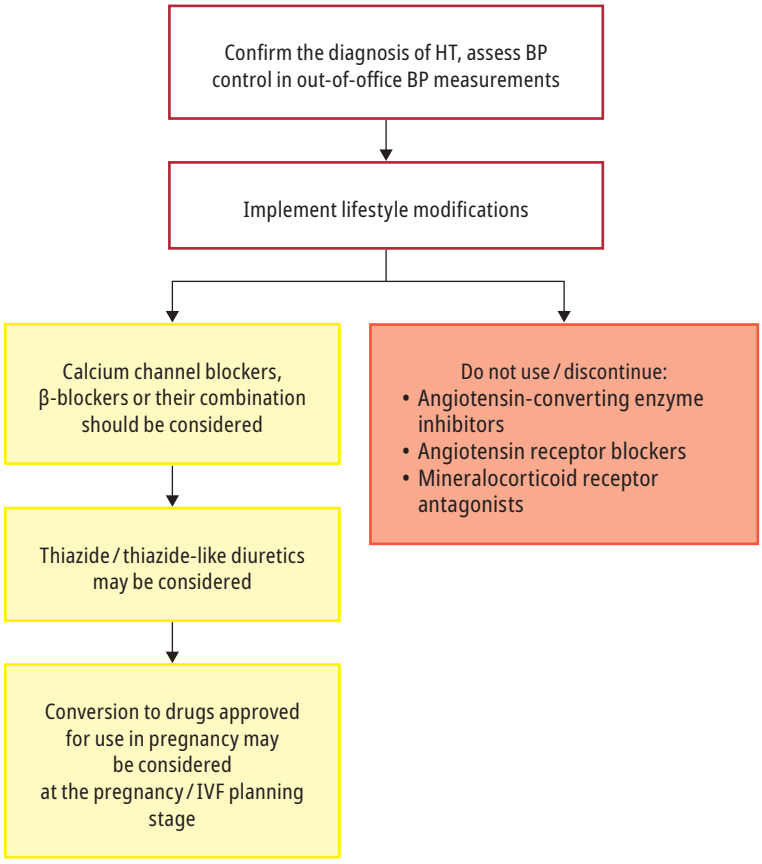

FIGURE 4.1 Management of hypertension in women at reproductive age

Abbreviations: BP, blood pressure; HT, hypertension; IVF, in vitro fertilization

woman at reproductive age presenting with HT be screened for proteinuria at least once using a qualitative assay (urinalysis or strip test). If proteinuria is detected, a quantitative assay should follow. On a similar note, a quantitative urine protein assay should be considered in each woman planning to conceive who presents with HT (FIGURE 4.2). The preferred quantitative method has not been clearly determined. In an outpatient setting, the protein-to-creatinine ratio in the morning urine sample or 24-hour urine collection may be considered (TABLE 4.1).

It is recommended to perform basic tests including, as per guidelines, full blood count, fasting glucose, lipid profile, sodium, potassium, uric acid and creatinine (with estimated glomerular filtration rate [eGFR]), liver function tests (aspartate aminotransferase [AST], alanine transaminase [ALT]), thyroid stimulating hormone, urinalysis with urine sediment examination, and electrocardiography in each woman planning to conceive who presents with HT.[3,4]

Screening for secondary HT should be considered in each woman planning to conceive who presents with HT based on routine assessment findings and detailed medical history[3,4,18] (TABLE 4.2).

Due to their younger age, women planning to conceive may develop HT secondary to chronic kidney disease (CKD) (eg, vesicoureteral reflux, glomerulonephritis), renal artery stenosis from fibromuscular dysplasia, pheochromocytoma, coarctation of the aorta or primary aldosteronism (PA). Secondary HT affects about 0.2% of all pregnancies and is diagnosed in 2% to 5% of all pregnant women with HT treated in highly specialist centers.[18] Diagnostic management of HT in women planning to conceive should be further extended to include kidney ultrasound and renal artery Doppler ultrasound. Echocardiography should be considered to assess for complications and identify secondary causes of HT, such as coarctation of the aorta in women with a detectable heart murmur on auscultation. The descending aorta should be assessed from the suprasternal notch window as an integral part of echocardiography.[3,4]

Women with chronic HT planning to conceive should undergo risk assessment for PE. This issue is discussed in detail in CHAPTER 5.6.1.

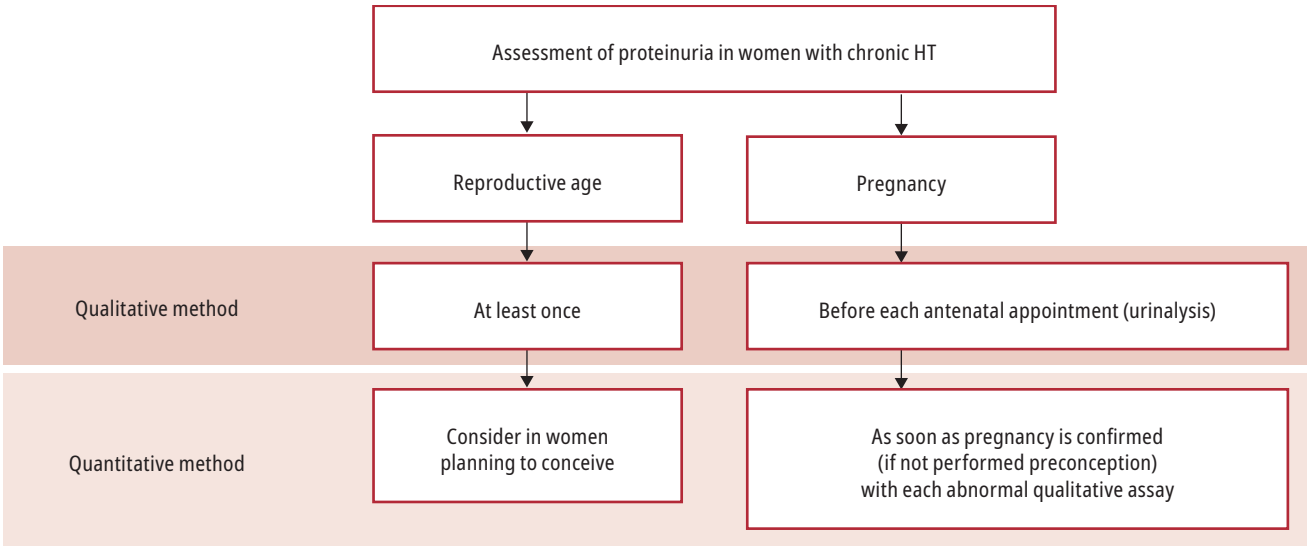

FIGURE 4.2 Assessment of proteinuria in women with chronic hypertension (HT) during the preconception, pregnancy, and postpartum period

TABLE 4.1 Qualitative and quantitative assessment of proteinuria in women at reproductive age and pregnant women as per Brown et al[1] and Regitz-Zagrosek et al[2]

Method	Significant proteinuria cutoff
Qualitative methods	
Urinalysis	Qualitative assessment of proteinuria >15–30 mg/dl[a]
Strip test	Assessing the strip color change by comparing it to a color chart
Automated strip test	(+) indicates the need for further investigations, (++) corresponds to proteinuria of 1 g/l
Quantitative methods	
Urine sample	Protein:creatinine ratio >30 mg/mmol or 0.26 mg/mg (rounded to >30 mg/g)
24-hour urine collection	Proteinuria >300 mg

a Depending on the method

TABLE 4.2 Symptoms and test findings suggestive of secondary hypertension and screening for secondary hypertension (adapted from the 2019 Polish Society of Hypertension recommendations)[3]

Cause of HT	Signs, symptoms, and test findings suggestive of secondary HT				First-choice (screening) test in women planning to conceive and pregnant women
	History	Physical examination	Basic tests	Additional tests	
Renal parenchymal disease	History of UTI or uropathy, hematuria, analgesic overuse, family history of kidney disease	Enlarged kidney on palpation (in patients with polycystic kidney disease)	Presence of red blood cells, white blood cells, and protein in the urine; low GFR	Albuminuria and proteinuria of variable severity	Kidney US
Primary aldosteronism	Muscle weakness, polyuria, polydipsia. Family history of severe HT or early--onset hypokalemia and cerebrovascular accident below the age of 40 Concomitant with OSA	Arrhythmia	Hypokalemia (spontaneous or induced/ exacerbated by diuretics); hypernatremia	Incidental finding of the adrenal lesion severe organ complications of HT Elevated nocturnal BP and worse BP reduction at night	ARR (false negative results in pregnancy)
Fibromuscular dysplasia	Age >30 years Early-onset HT Impaired BP control or exacerbation of HT Refractory or malignant HT FMD affecting at least one other vascular bed History of artery dissection Family history of FMD Unexplained neurological incident	Abdominal vascular murmur	Rapid renal impairment (spontaneous or during treatment with RAAS inhibitors) Hypokalemia	Kidney US: kidney length difference >1.5 cm Small kidney	Doppler US of renal arteries
PPGL	Paroxysmal HT Headaches Excessive sweating Palpitations, pale skin Anxiety Orthostatic hypotension Family history of PPGL	Skin lesions typical of neurofibromatosis (cafe au lait spots, neurofibromas)	Hyperglycemia	Incidental finding of an adrenal (or sometimes extra--adrenal) lesion	Plasma or urinary fractionated metanephrine
Coarctation of the aorta	Intermittent claudication Headaches Loss of consciousness Epistaxis	Murmurs in the left infraclavicular area or in the interscapular region Weak femoral pulse and femoral BP lower than simultaneously taken radial BP Differences in BP readings between the left and right arm	The figure of 3 sign and rib notching is seen in chest radiograms	Echocardiographic abnormalities	Echocardiography

Abbreviations: BP, blood pressure; FMD, fibromuscular dysplasia; GFR, glomerular filtration rate; HT, hypertension; OSA, obstructive sleep apnea; PPGL, pheochromocytoma and paraganglioma; ARR, aldosterone-to-renin ratio; RAAS, renin–angiotensin–aldosterone system; US, ultrasound; UTI, urinary tract infection

Diagnosis of hypertension in women at reproductive age: recommendations	
It is recommended to confirm the diagnosis of HT in women at reproductive age with out-of-office BP reading.	Level B
Qualitative screening for proteinuria is recommended in each woman at reproductive age with HT.	Level C
A quantitative determination of urinary protein should be considered in each woman with HT planning to conceive.	Level C
Basic tests including full blood count, fasting glucose, lipid profile, sodium, potassium, uric acid and creatinine (with eGFR), TSH, liver function tests (AST, ALT), urinalysis with urine sediment examination and ECG are recommended in each woman with HT planning to conceive.	Level C
Screening for secondary HT is recommended in women at reproductive age with HT in whom abnormal history, physical examination or laboratory test findings indicate a secondary cause of HT.	Level C
Kidney ultrasound and renal artery Doppler ultrasound are recommended in women with HT planning to conceive in order to exclude chronic kidney disease and renal artery stenosis from fibromuscular dysplasia.	Level C
Echocardiography should be considered in women with HT planning to conceive, as a part of diagnostic evaluation.	Level C

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BP, blood pressure; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; HT, hypertension; TSH, thyroid-stimulating hormone

Treatment of hypertension in women at reproductive age: recommendations	
It is recommended to monitor BP control in women at reproductive age with out-of-office BP readings.	Level B
Lifestyle modifications, in particular, smoking cessation, alcohol abstinence and weight loss, are recommended in women at reproductive age.	Level B
ACEIs, ARBs, renin inhibitors, and MRAs are not recommended in women at reproductive age.	Level B
β-Blockers and / or calcium channel blockers should be considered for the treatment of HT in women at reproductive age.	Level C
Thiazide / thiazide-like diuretics may be considered for the treatment of HT in women at reproductive age.	Level C
Conversion to hypotensive drugs typically used in pregnancy may already be considered at the preconception stage.	Level C
Conversion to hypotensive drugs typically used in pregnancy may be considered in women planning to use assisted reproductive technology.	Level C

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; MRA, mineralocorticoid receptor antagonists

4.2. Treatment of hypertension in women at reproductive age

Women at reproductive age should be encouraged to implement lifestyle modifications as per current guidelines on the management of HT, with particular emphasis on those aspects which are likely to affect fetal wellbeing, that is, smoking cessation, alcohol abstinence, and weight loss.[4]

Clinical decision-making regarding pharmacotherapy of HT in women at reproductive age should be based on the same principles as in other patients considering individual risk profile, hemodynamic and metabolic profile, with a preference for compound products to be used as a first-line treatment.[3,4] However, reproductive plans and limited use of potentially teratogenic drugs in women at reproductive age always need to be considered, as well. Due to high unintended pregnancy rates, renin inhibitors, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) are not recommended in women at reproductive age and should only be used in patients with special indications (type 1 diabetes mellitus, diabetic kidney disease, heart failure [HF], CKD, PA). If these drug classes are used, patients should be informed about their potential teratogenic effect and the need to immediately discontinue treatment in the event of pregnancy (such information should also be provided to all women at reproductive age).[2-4] Clonidine and calcium channel blockers (CCBs) should be preferred for the management of hypertensive emergency in women at reproductive age. Out of the 5 basic classes of hypotensive drugs, CCBs (preferably dihydropyridine derivatives) and / or β-blockers should be considered in women at reproductive age. Thiazide / thiazide-like diuretics may also be considered. However, these have to be discontinued in pregnancy (FIGURE 4.1). Therefore, β-blockers, which do not have to be changed should the treatment be continued in pregnancy, should be considered in women with HT planning to conceive (CHAPTER 7.2). The basic 2-drug combinations of antihypertensive medications, which are well tolerated, effective, known to reduce cardiovascular risk, and can be used in women at reproductive age, include dihydropyridine CCB and a β-blocker, CCB and a thiazide / thiazide-like diuretic (such fixed-dose combination drugs are available).[3]

Conversion to hypotensive drugs typically used in pregnancy (especially labetalol and extended-release nifedipine, should they be approved in Poland in the future) can be considered in women at reproductive age planning to conceive (FIGURE 4.1). Conversion to hypotensive

drugs recommended in pregnancy can be considered in women planning to use assisted reproductive technology. Once pregnancy has been confirmed in a woman with chronic HT, a conversion to treatment with the well-established favorable safety profile in pregnancy is the best course of action (CHAPTER 5.7)

5. Management of high blood pressure in pregnant women

5.1 Diagnosis of hypertension and blood pressure measurement

5.1.1. Blood pressure measurements in pregnancy

The office BP readings taken using a validated, automatic BP monitor should be preferred.[4] Recommendations on the techniques of office BP measurement in pregnant women are shown in TABLE 5.1.

Although some documents mention 24-hour BP monitoring as the preferred out-of-office measurement technique, we believe that commonly available home BP measurement is a sufficient alternative to out-of-office measurement. The principles of home BP measurement are shown in TABLE 5.1.

The correct cuff size is crucial for both office and out-of-office BP measurements. For the mid-upper arm circumference above 33 cm, a large cuff should be used.[3,19] A list of validated automatic BP monitors, for both office and out-of-office BP measurements, can be found at http://bhsoc.org/bp-monitors/bp-monitors.[20]

Twenty-four–hour BP monitoring should be considered in the following clinical scenarios:

- To rule out white coat HT
- To rule out masked HT in patients with high-normal BP (130–139 / 85–89 mm Hg) and metabolic disorder
- To monitor treatment efficacy alongside home BP measurements (if available)
- If there is a significant discrepancy between the office and home BP readings and / or high BP variability
- In patients with diabetes mellitus or CKD

5.1.2. Diagnosis of HT in pregnancy

The diagnosis of HT in pregnancy is based on the office BP readings. A diagnosis of HT should be made when systolic BP is 140 mm Hg or higher and / or diastolic BP is 90 mm Hg or higher. HT in pregnancy is defined as mild (BP, 140–159/90–109 mm Hg) or severe (BP ≥160/110 mm Hg).[1,4] The diagnosis of mild HT should be confirmed in out-of-office measurements, and if not available, confirmation with office readings obtained on 2 separate occasions should be considered. Hospital referral is recommended in patients with systolic BP 160 mm Hg or higher or diastolic BP 110 mm Hg or higher obtained in multiple consecutive measurements taken within 15 to 30 minutes (FIGURE 5.1).[1,14] Most women before 20 weeks of pregnancy should be counselled by a general practitioner, cardiologist, or hypertensive disorders specialist.

It is vital to determine the out-of-office BP values required for the diagnosis of HT to be made. The number of studies assessing out-of-office BP values in pregnancy is limited. Informed by the results of studies published to date, some

TABLE 5.1 Techniques of office and home blood pressure measurement in pregnant women (modified from the 2019 Polish Society of Hypertension recommendations)[3]

Office measurement	Home measurement
A validated automatic blood pressure monitor for office BP measurements in pregnancy	A validated automatic BP monitor for home BP measurements in pregnancy
• Cuff size suitable for the patient's arm circumference (ideally, the cuff length should encircle 80% of arm circumference, and cuff width should be equal to 40% of arm circumference) • The patient must avoid caffeine intake and smoking for at least 30 minutes prior to measurement • A few-minute rest is recommended prior to each measurement, with the patient sitting up supported in a quiet room • The patient should sit up supported, with no tight clothing on the arm, her arm supported with the elbow at the level of the fourth intercostal space • The cuff should be at heart level, regardless of the patient's body position • The first measurement should be taken on both arms, the subsequent measurements should be taken on the arm with a higher BP • The BP should be determined based on 2 consecutive readings taken on the same occasion at 1–2-minute interval • The third reading should be taken (and included in calculating the mean BP) if there is an inter-measurement difference above 10 mm Hg	• The measurements should be taken on 7 consecutive days preceding the medical appointment to determine BP control in women with chronic HT during the first trimester and to determine BP values in women with white coat HT or transient HT • The measurements should be taken every day in women with chronic HT during the second and third trimester, and in women with pregnancy-induced HT and PE • The measurements should be taken in the morning and in the evening at regular intervals (eg, 06.00 and 18.00, 07.00 and 19.00). On each occasion, 2 consecutive readings should be taken at several-minute intervals (2 × 2 scheme) • The measurements should be taken directly before taking medications, and the AM measurement before the first meal of the day • The measurements should be taken using the technique for the office BP measurements • The patient should record the BP values in the 7-day Home Blood Pressure Monitoring Chart (APPENDIX 1). It is possible to use BP monitors with built-in memory or a printer • For the purposes of calculating the mean home BP, the readings obtained on the first day are disregarded

Abbreviations: BP, blood pressure; HT, hypertension; MAP, mean arterial pressure; PE, preeclampsia

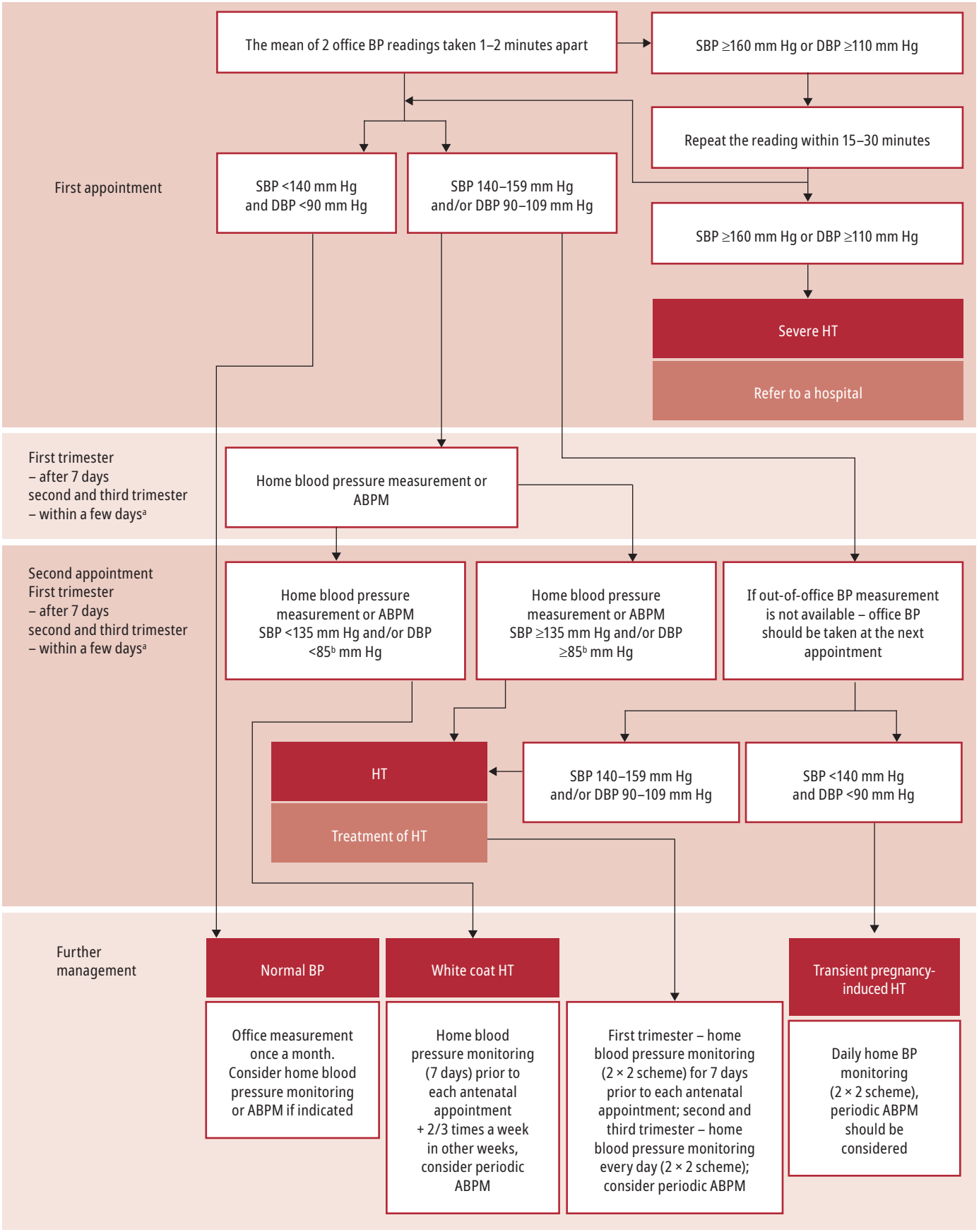

FIGURE 5.1 Diagnosis of hypertension and blood pressure measurements in pregnancy

a Depending on the clinical presentation and next appointment availability

b Mean of home BP monitoring or mean of daily ABPM

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; HT, hypertension; SBP, systolic blood pressure

recommendations consider readings slightly lower than in the general population (mean daytime BP ≥130/80 mm Hg and mean nocturnal BP ≥110/70 mm Hg) as the threshold for HT diagnosis in 24-hour BP recording.[1,16] However, we concluded that in the absence of data unequivocally indicating the prognostic significance and in order to avoid overtreatment in pregnancy, the same threshold BP values which are used in the general population should apply[4]:

- Mean daytime mean BP of 135 mm Hg or higher systolic and/or 85 mm Hg or higher diastolic obtained in 24-hour BP monitoring and home BP measurements
- Mean nocturnal BP 120 mm Hg or higher systolic and/or 70 mm Hg or higher diastolic obtained in 24-hour BP monitoring

5.1.3. Assessing the dynamics of blood pressure changes in pregnancy

There is no optimal algorithm for home BP monitoring in pregnant women. When developing the algorithm presented in this document, we were primarily guided by the need to monitor BP more closely in the second and third trimester alongside the need to take 2 consecutive measurements on each occasion in order to provide reliable readings.[21] In order to assess BP control in pregnant women treated for HT in the first trimester or in order to determine BP in pregnant women with white coat HT, home measurements are recommended with a 7-day algorithm (APPENDIX 1) to be followed in a week preceding each monthly appointment and 2-3 readings per week outside the 7-day periods. Home BP measurements, involving 2 consecutive readings at 1- to 2-minute interval in the morning and 2 consecutive readings at 1- to 2-minute interval in the evening, both before meals and taking medications (the 2×2 scheme), are recommended in women with chronic HT in the second and third trimesters and in women with pregnancy-induced HT or PE.

BP readings obtained in 24-hour BP monitoring better predict the PE and intrauterine growth restriction (IUGR) than office BP readings. However, 24-hour BP monitoring does not offer sufficient sensitivity and specificity to be recommended as a method to assess the risk of these conditions.[22]

5.2. Diagnostic test in pregnant women with hypertension

Women with chronic HT should be provided multidisciplinary care involving a consultant obstetrician/gynecologist and a consultant cardiologist/clinical HT specialist. As HT in pregnancy may be secondary to CKD, each pregnant woman with CKD should also be assessed by the nephrologist. Further management and the frequency of follow-up appointments will be determined by the nephrologist depending on the clinical

Diagnosis of hypertension and blood pressure measurements in pregnancy: recommendations	
Using validated, automatic BP monitors for office BP readings should be considered.	Level C
The BP should be determined based on 2 consecutive readings taken on the same occasion at 1–2-minute interval.	Level C
The threshold BP values required for the diagnosis of HT to be made in a pregnant woman are ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic office confirmed within out-of-office readings taken within 7 days in the first trimester and within a few* days in the second and third trimester.	Level C
Should out-of-office BP measurement be not available, confirmation of diagnosis with office readings taken within 7 days in the first trimester and within a few days in the second and third trimester should be considered.	Level C
In order to confirm the diagnosis of HT, home BP measurements (2 readings in the morning and 2 readings in the evening; APPENDIX 1) or 24-hour BP monitoring are recommended.	Level C
Hospital referral is recommended in patients with systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg obtained in multiple consecutive measurements taken within 15–30 minutes.	Level C
In order to assess BP control in pregnant women treated for HT in the first trimester or in order determine BP in pregnant women with white coat HT, home measurements are recommended with a 7-day algorithm (APPENDIX 1) to be followed in a week preceding each monthly appointment and 2-3 readings per week outside the 7-day periods.	Level C
Home BP measurements, involving 2 consecutive readings at 1–2-minute interval in the morning and 2 consecutive readings at 1–2-minute interval in the evening, both before meals and taking medications (2×2 scheme), are recommended in women with chronic HT in the second and third trimesters and in women with pregnancy-induced HT or PE.	Level C
24-hour BP monitoring should be considered in the following clinical scenarios: • To rule out white coat HT • To rule out masked HT in patients with high-normal BP and metabolic disorder • To monitor treatment efficacy alongside home BP measurements (if available) • If there is a significant discrepancy between the office and home BP readings and/or high BP variability • In women with diabetes/CKD	Level C

a Depending on the clinical presentation and next appointment availability

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; HT, hypertension; PE, preeclampsia

Diagnostic tests in pregnant women with hypertension: recommendations	
Following a confirmation of pregnancy by the consultant gynecologist, it is recommended to perform basic tests including liver enzyme tests (AST, ALT, LDH), liver function tests (INR, bilirubin, and albumin levels), serum creatinine, electrolytes, and quantitative urine protein test at the first appointment with a consultant cardiologist / clinical HT specialist.	Level C
Routine screening for proteinuria is recommended in each pregnant woman prior to each antenatal appointment (FIGURE 4.2 and TABLE 5.2).	Level B

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HT, hypertension; INR, international normalized ratio; LDH, lactate dehydrogenase

presentation of the pregnant woman, the presence of proteinuria and routine laboratory test findings (including eGFR). Following a confirmation of pregnancy by the consultant gynecologist, it is recommended to perform basic tests including liver enzyme tests (AST, ALT, lactate dehydrogenase), liver function tests (international normalized ratio, bilirubin and albumin levels), serum creatinine, sodium, potassium, and quantitative urine protein test at the first appointment with a consultant cardiologist / clinical HT specialist.[1] The results of these tests enable assessing complications of chronic HT and facilitate the diagnosis of PE after 20 gestational weeks.

Pregnant women with HT should be assessed for secondary HT based on medical history, physical examination and laboratory test findings. TABLE 4.2 shows the symptoms and test findings which may be suggestive of secondary HT as well as screening for secondary HT, which may be used in pregnant women.

As part of routine antenatal care, each pregnant woman is regularly screened for proteinuria during scheduled follow-up appointments.

The qualitative screening for proteinuria includes:

- Urinalysis, or alternatively
- Strip test – automated dipstick tests may be used with (+) considered a finding indicative of the need for further investigations and (++) corresponding to proteinuria of 1 g/l.[23]

Some guidelines recommend quantitative screening for proteinuria by a strip test. However, this method is hardly used in Poland. A reliable assessment for proteinuria should be based on 24-hour urine collection or protein / creatinine ratio determination in the urine sample (TABLE 4.1).[6,8,24,25] With any abnormal kidney function tests findings (serum creatinine and electrolytes, urinalysis), kidney ultrasound is recommended.[1]

The algorithm for diagnostic investigations in pregnant women with chronic HT is summarized in TABLE 5.2. In the event of known PE without proteinuria as well as upon any change to clinical presentation, regular monitoring of urinary protein excretion, serum hemoglobin level, platelet count, liver enzyme (AST, ALT) levels, and serum creatinine level is indicated.[1,26]

5.3. Echocardiography in pregnant women with hypertension

Being the most commonly performed diagnostic imaging investigation of cardiovascular diseases, the transthoracic echocardiography (TTE) enables the assessment of cardiac morphology and function.[27] TTE is also a preferred diagnostic imaging method in pregnant women as it is harmless, widely available, relatively inexpensive, and highly repeatable. Due to the growing number of pregnant women with cardiovascular diseases and the delayed childbearing tendency currently seen in Poland, it can be expected that TTE will be used increasingly more often in this group of patients.[2] Pregnancy is associated with physiological adaptation of the cardiovascular system altered hemodynamic conditions, which affects the echocardiographic image of the heart (TABLE 5.3).[28]

Echocardiography is not routinely recommended in normal pregnancy. According to the 2018 Guidelines for the Management of Arterial Hypertension developed by the European Society of Cardiology / European Society of Hypertension (ESC / ESH), patients with left ventricular hypertrophy are considered at least high-risk hypertensive patients. Furthermore, it constitutes an indication for immediate initiation of antihypertensive treatment.[4] Additionally, left ventricular hypertrophy in a pregnant woman with HT may indicate its chronic and severe course. This may be associated with a higher risk of complications in pregnancy and childbirth. Therefore, TTE should be considered in each pregnant woman with HT in order to evaluate heart function and morphology, including the assessment for left ventricular hypertrophy, especially in women who did not have TTE prior to conception. Echocardiographic assessment of the aorta is discussed in CHAPTER 7.3.

TTE should always be performed upon the onset of new cardiovascular symptoms (eg, dyspnea or abnormal heart murmur) in all pregnant women with cardiovascular disease, including HT.[2]

Echocardiography in pregnant women with hypertension: recommendations	
The transthoracic echocardiography should be considered in pregnant women with hypertension in order to evaluate heart function and morphology, including the assessment for left ventricular hypertrophy.	Level C
The transthoracic echocardiography should be performed in pregnant women with the onset of new or unexplained cardiovascular symptoms.	Level C

TABLE 5.2 Diagnostic investigations in pregnant women with chronic hypertension and suggested appointment frequency

	First trimester (up to 12 gestational weeks)	Second trimester (13–26 gestational weeks)	Third trimester (27–42 gestational weeks)
Frequency of antenatal appointments	≥Once a month[b]	≥Once a month[b]	Depending on the maternal and fetal condition
Routine antenatal care	Up to 10 gestational weeks: • Office BP • Out-of-office BP • Full blood count • Fasting blood glucose • Urinalysis • Other[a]	• 15–20 gestational weeks, 21–26 gestational weeks: • Office BP • Out-of-office BP • Full blood count • Urinalysis • Other[a] 24–26 gestational weeks: • OGTT	27–32, 33–37, 38–39 gestational weeks: • Office BP • Out-of-office BP • Full blood count • Urinalysis • Other[a]
Fetal growth and wellbeing assessment	11–13^{+6} gestational weeks: • Ultrasound, possible individual risk assessment for preeclampsia (including but not limited to uterine artery Doppler, see FIGURE 6.2), screening for trisomy, fetal anatomy assessment	18–22 gestational weeks: • Ultrasound, anomaly / anatomy scan, fetal growth assessment, placental position evaluation	28–32 gestational weeks: • Ultrasound, fetal growth assessment, ruling out SGA, intensive surveillance after 34 gestational weeks
Frequency of HT and cardiology appointments	≥Once a month[b]	≥Once a month[b]	≥Once a month[b]
Diagnostic investigations as a part of specialist outpatient cardiac / HT care	First appointment: • Liver enzymes (AST, ALT, LDH), liver function tests (INR, bilirubin, albumin), serum creatinine level, electrolytes, quantitative assessment of proteinuria • Fasting blood glucose, lipid profile and TSH if not done earlier • Office BP • Out-of-office BP Each appointment: • Office BP • 7-day home BP monitoring or ABPM prior to appointment Between the appointments: • Home BP measurements	Each appointment: • Office BP • Consider ABPM prior to appointment Between the appointments: • Home BP measurements (2×2 scheme)	28 and 34 gestational weeks: • Serum creatinine level, electrolytes, liver enzymes Each appointment: • Office BP • Consider ABPM prior to appointmen Between the appointments: • Home BP measurements

a As per the Minister of Health regulation; **b** More frequent appointments should be considered in women with a higher risk of complications (see Chapter 5.6.2.); the frequency of appointments and diagnostic tests should be determined based on clinical presentation, and in particular, changes to clinical presentation

Abbreviations: ABPM, ambulatory blood pressure monitoring; ALT, alanine transaminase; AST, aspartate aminotransferase; BP, blood pressure; HT, hypertension, INR, international normalized ratio; LDH, lactate dehydrogenase; OGTT, oral glucose tolerance test; SGA, small for gestational age

TABLE 5.3 Changes to echocardiographic parameters seen in pregnancy[5]

Mild increase of left ventricle end-systolic and end-diastolic diameter
Mild increase of left ventricular muscle mass
Moderate increase of left and right atrial diameter
Moderate increase of right ventricular dimension
Mild tricuspid, pulmonary, and mitral regurgitation
Mildly reduced left ventricular shortening fraction and left ventricular ejection fraction
Slightly elevated E/e´ ratio indicating a mild increase in the left ventricular filling pressure
Mild pericardial effusion

5.4. Safety of radiographic imaging in pregnancy

Ultrasonography as well as magnetic resonance imaging (MRI) do not use ionizing radiation and are therefore considered safe in pregnancy. However, the duration of color and power Doppler ultrasound scanning should not be prolonged in the first trimester, unless clinically appropriate. The MRI imaging using high-field devices, above 3T, is not recommended. The Food and Drug Administration (FDA) approved acoustic output of ultrasound transducers, express as the spatial-peak temporal-average intensity, is up to 720 mW/cm^2. This acoustic output is believed to increase the tissue temperature by 2°C, which can have an adverse effect on the embryo and fetus during organogenesis.[29,30] In clinical practice, although

the risk of such temperature increase is negligible with the B-scan, it is not impossible with Doppler ultrasound.[29] In order to minimize the risk of the adverse effect of ultrasound on tissue, the American Institute of Ultrasound in Medicine recommends maintaining the target thermal index at more than 0.7 and minimizing the duration of exposure, especially with fetal Doppler ultrasound in the first trimester.[31] Nevertheless, it should be emphasized that Doppler imaging is considered safe as long as the embryo / fetus lies outside the Doppler ultrasound beam, which is of crucial importance for the evaluation of renal arterial flow.

The American College of Radiology does not provide separate recommendations for the first trimester and emphasizes that MRI can be performed at any stage of pregnancy as long as it is considered appropriate based on the individually assessed risk-benefit ratio.[29,32] Despite the lack of sufficient studies on the safety of contrast media used in MRI, gadolinium contrast media are listed as a Class C drug by the FDA, which means that they should not be routinely used for MRI in pregnant women.[33] Modern MRI devices enable not only accurate and reliable assessment of renal artery stenosis but also facilitate diagnosis of many other pathologies (eg, pheochromocytoma) even with non–contrast--enhanced scans.[34,35]

Diagnostic imaging using ionizing radiation is usually considered potentially harmful to the developing fetus. Nevertheless, it should be emphasized that the risk for the fetus depends on the radiation dose and pregnancy stage at the time of the procedure. Fetal exposure to radiation dose below 50 mGy even in the first trimester is not considered harmful to the fetus. It should be noted that a computed tomography (CT) of abdomen or pelvis, if performed appropriately, is associated with radiation exposure below 35 mGy (typically 10–25 mGy).[36] Even lower exposure should be expected if the fetus is not directly exposed to the radiation beam. For example, CT of the pulmonary circulation is associated with fetal exposure of 0.01 to 0.1 mGy, whereas the ionizing radiation dose exceeding 100 mGy is considered harmful to the fetus.[37] Similarly, fetal exposure to radiation during mammography was found to be minimal and is, therefore, considered safe.[38]

That is why the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice makes the following recommendations regarding diagnostic imaging procedures during pregnancy:

- Ultrasonography and MRI are not associated with the risk to the fetus and are the imaging techniques of choice for the pregnant patient. As a principle, though, they should be used prudently and only when use is expected to answer a relevant clinical question.
- Radiation exposure through radiography, CT scan, or nuclear medicine imaging techniques is at a dose much lower than the exposure associated with fetal harm. If these techniques are necessary in addition to ultrasonography or MRI or are more readily available for the diagnosis in question, they should not be withheld from a pregnant patient.
- The use of gadolinium contrast with MRI should be limited. It may be used as a contrast agent only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome.[29]

5.5. Assessing fetal wellbeing

Fetal wellbeing assessment is an essential part of antenatal care in women with HT or PE. As a result of abnormal (ie, high-resistance) uteroplacental circulation, the maternal body needs to generate increasingly higher BP in order to meet the increasing fetal demand for oxygen and nutrients. Abnormal placentation significantly reduces spiral artery diameter. As a result, fetal oxygen intake gradually decreases, causing IUGR and posing a risk to fetal wellbeing. A chain of events triggered by chronic fetal hypoxia is shown in FIGURE 5.2. There are at least several established methods for fetal wellbeing assessment which may be used in pregnant women with HT or PE. The key ones have been listed below.

5.5.1. Fetal movement counting

Subjective fetal movement counting by a pregnant woman is based on evidence that fetal movements are suppressed in response to hypoxemia.[39] Despite a commonly held view that extensive diagnostic management and intensive fetal wellbeing monitoring are appropriate in patients reporting decreased fetal movements, there is no clear guidance so as to the frequency or scope of such monitoring. However, daily fetal movement counting (even 3 times a day after the main meals) has been suggested (FIGURE 5.3).

5.5.2. Cardiotocographic fetal monitoring

Cardiotocography (CTG) is an established method of intensive fetal wellbeing surveillance. A normal CTG indicating proper oxygen delivery to the fetal central nervous system (CNS) is characterized by normocardiac baseline fetal heart rate (110–160 bpm), moderate baseline fetal heart rate variability (amplitude of 10–25 bpm), the presence of at least 2 accelerations and the absence of decelerations within a 30-minute window. However, subjective interpretation is a downside of CTG. In order to ensure objective assessment, modern fetal monitors offer computerized analysis and calculation of short-term variation (the beat-to-beat interval).[40] In an immature fetus, the short-term variation of less than 3 ms is considered abnormal.

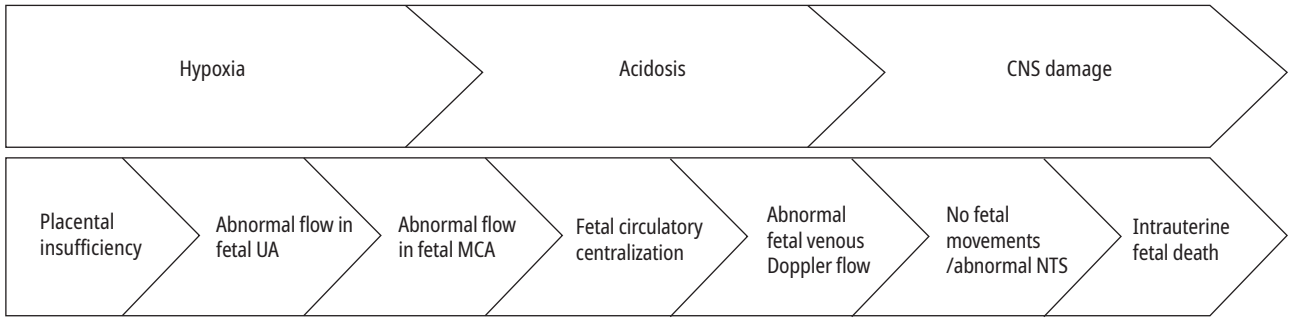

FIGURE 5.2 The effect of placental insufficiency on fetal circulation

Abbreviations: CNS, central nervous system; MCA, middle cerebral artery; NTS, nonstress test; UA, umbilical artery

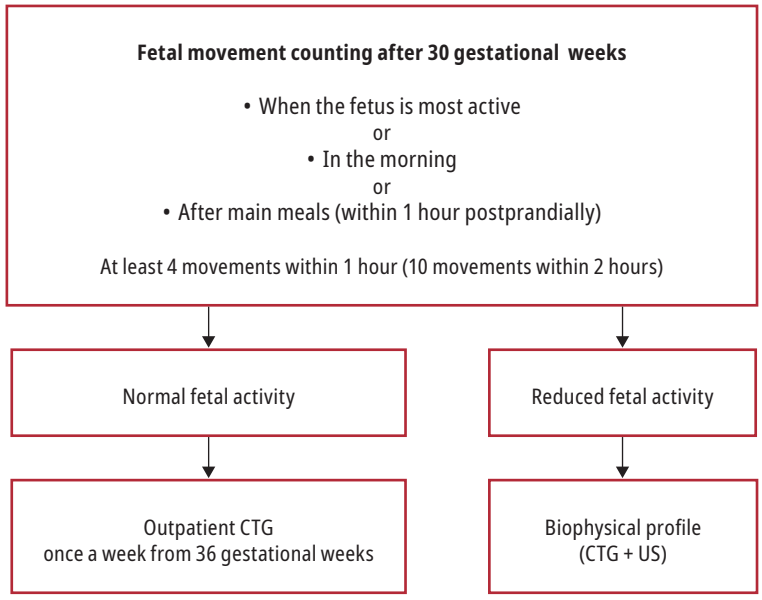

FIGURE 5.3 Fetal movement monitoring in patients with hypertension

Abbreviations: CTG, cardiotocography; US, ultrasound

Assessing fetal wellbeing: recommendations	
Fetal wellbeing surveillance as per the algorithm shown in FIGURE 5.4 is recommended in patients with hypertension and preeclampsia.	Level C
It is recommended to escalate fetal wellbeing surveillance upon sudden changes to a maternal health condition.	Level C

5.5.3. Fetal growth and amniotic fluid volume monitoring

Ultrasonography is a crucial aspect of fetal wellbeing assessment. The aim is to assess fetal anatomy and growth, amniotic fluid volume as well as to confirm normal placental location. Placental insufficiency secondary to PE often leads to IUGR, which is associated with a high risk of iatrogenic preterm birth and prematurity.[41] All fetal biometry parameters should fall in the range of 2 standards deviations from the normal mean for gestational age. The diagnosis of IUGR should prompt the clinician to assess the blood flow in the middle cerebral artery of the fetus and the umbilical arteries (as well as in the ductus venosus in selected cases). The uterine artery blood flow should be assessed to determine whether IUGR is secondary to decreased placental perfusion. Furthermore, algorithms based on uterine artery flow resistance index may be useful in selected clinical scenarios in order to determine the optimal gestational age for delivery.

5.5.4. A fetal biophysical profile

A biophysical profile (BPP) uses a combination of ultrasound and CTG. The BPP assumes that the real-time ultrasound fetal observation combined with assessment of selected parameters may offer better prognostic value than the CTG alone.[42] The assessment of fetal movements, fetal breathing movements, and fetal tone combined with nonstress test and estimation of amniotic fluid volume has been suggested to reduce the false-negative results observed with the nonstress test or fetal movements alone. The BPP correlates well with the cord blood pH and accurately predicts fetal acidosis.[43,44] The BPP is usually recommended once a week.

5.5.5. Fetal blood flow assessment

The maternal and fetal blood flow velocimetry provides information about the uteroplacental circulation and fetal response to potential hypoxia (FIGURE 5.4). Placental vascular remodeling, as seen in PE, causes gradual hemodynamic changes in fetoplacental circulation. Doppler-assessed umbilical artery flow parameters become abnormal when 60% to 70% of the tertiary villous vessels are damaged.[45] As a result of hypoxia, vascular resistance in the fetal middle cerebral artery decreases, but it increases in the fetal aorta in order to preferentially direct blood flow to the fetal brain and heart.[46] In extreme cases, the end-diastolic flow in the umbilical artery is absent (and later reversed), followed by an increased venous resistance (ductus venosus, umbilical vein, inferior vena cava). Changes in Doppler-assessed fetal circulatory parameters correlate with fetal acidosis.[47] Doppler blood flow assessment should be performed in patients with HT or PE, depending on indications.

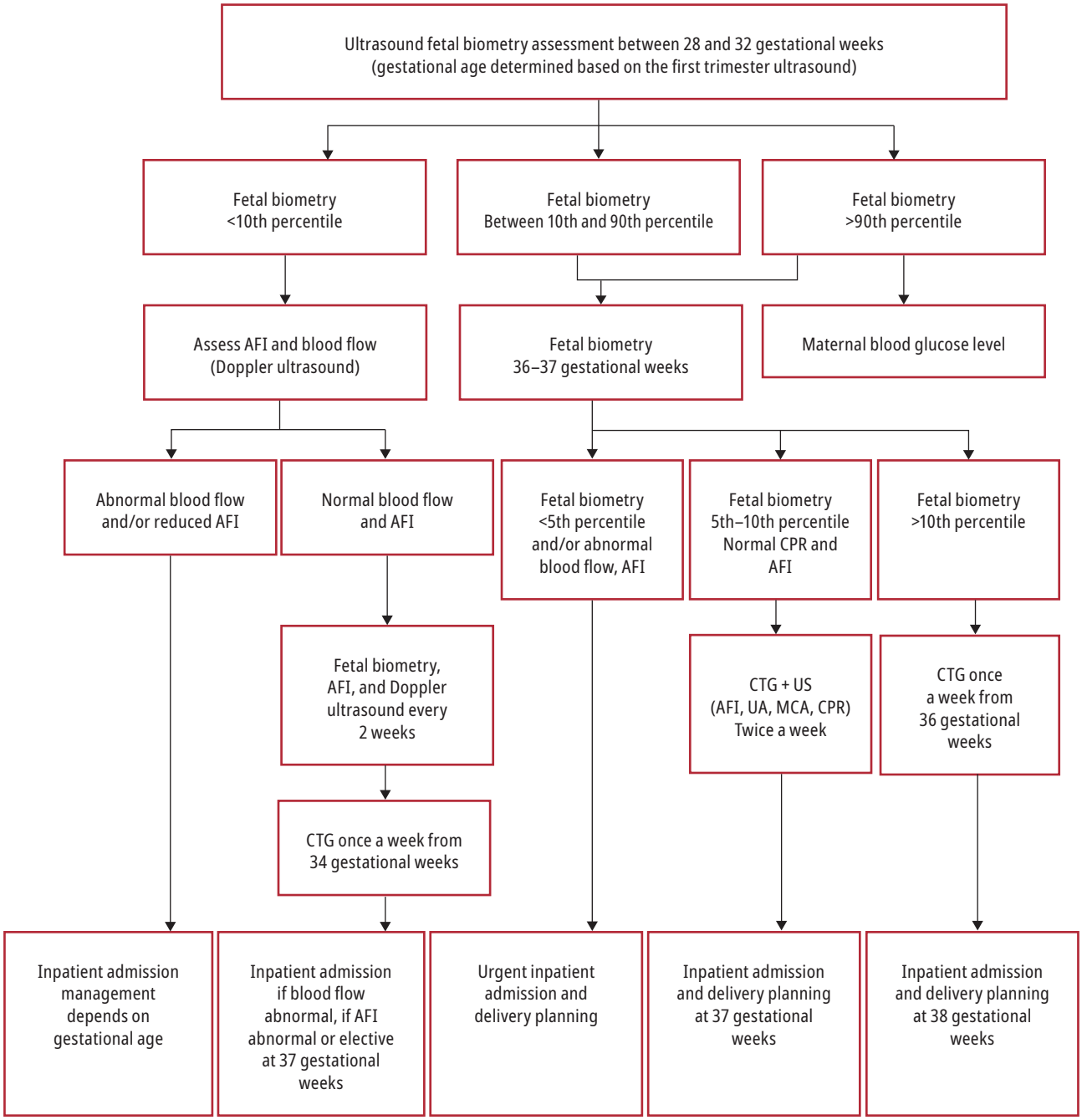

FIGURE 5.4 Assessing fetal wellbeing in women with hypertension

Abbreviations: AFI, amniotic fluid index; CTG, cardiotocography; CPR, cerebroplacental ratio; MCA, middle cerebral artery; UA, umbilical artery; US, ultrasound

5.6. Preconception planning and obstetric care in patients with preexisting hypertension

The aim of obstetric care in women with HT is to reduce the risk of maternal and fetal complications, as well as to achieve the lowest possible neonatal morbidity and mortality. This can be achieved through appropriate assessment and preconception counselling, early antenatal care and frequent antenatal appointments, timely delivery, and appropriate postpartum management.

5.6.1. Preconception care

Preconception planning in women with chronic HT and history of pregnancy-induced HT should be careful and include obstetric consultation as well as other specialist consultations, if indicated. Preconception care should focus on obstetric history and history of chronic diseases (TABLE 5.4), as well as include necessary laboratory tests and diagnostic imaging.

Pregnancy is not recommended in women with inadequate HT control despite optimal use of 3 antihypertensive medications as well as in women with secondary HT without treatment addressing the underlying cause of HT (see CHAPTER 4.2 and TABLE 4.2). A patient with suspected secondary HT should be assessed by a consultant clinical HT specialist or nephrologist (depending on creatinine level and suspected CKD) as a part of preconception care.[6] Medication review should be carried out as a part of preconception

TABLE 5.4 Obstetric assessment of women with chronic hypertension as a part of preconception care

Obstetric history regarding previous pregnancies	PE, eclampsia, or pregnancy-induced HT Premature placental abruption IUGR / IUFD Preterm birth Neonatal morbidity or mortality
History of chronic diseases	Primary / secondary HT HT duration Cardiovascular risk factors: obesity, diabetes, dyslipidemia, kidney disease, smoking status Other cardiovascular diseases HT-induced organ complications (left ventricular hypertrophy, albuminuria / proteinuria, eGFR <60 ml/min/1.73 m^2, retinopathy) Antihypertensive treatment Other chronic diseases: heart and kidney conditions, diabetes, thyroid conditions, history of cerebrovascular events
Recommended diagnostic investigations	As discussed in Chapter 4.1

Abbreviations: eGFR, estimated glomerular filtration rate; HT, hypertension; IUFD, intrauterine fetal death; IUGR, intrauterine growth restriction; PE, preeclampsia

Preconception planning and obstetric care in patients with preexisting hypertension: recommendations	
Pregnancy is not recommended in women with inadequate HT control despite optimal use of three antihypertensive medications as well as in women with secondary HT without treatment addressing the underlying cause of HT.	Level C
Preconception planning is recommended in women with chronic HT.	Level C
Medication review for HT and concomitant conditions should be carried out as a part of preconception care.	Level C
Consultant cardiologist / clinical HT specialist assessment is recommended in patients with suspected secondary HT as a part of preconception care.	Level C
Birth defect prevention, primarily of the central nervous system, with folic acid supplementation, is recommended as a part of preconception care.	Level C

Abbreviations: HT, hypertension

care – see CHAPTER 4.3. Birth defect prevention, primarily of the CNS, with 400 to 800 micrograms of folic acid continued for least 3 months prior to conception should also be recommended.[48] Daily dose of folic acid in patients with preexisting obesity should be about 800 mg.[49]

5.6.2. Antenatal care

The most frequent gestational complications in women with HT include PE superimposed on chronic HT (up to 50% in patients with severe HT) and its complications: IUGR, premature placental abruption, prematurity (including iatrogenic), fetal mortality (perinatal mortality is 3- to 4-fold higher than in the general population). Chronic HT in pregnancy is considered a significant risk factor of PE. However, there has been no evidence to date that good BP control reduces the incidence of PE superimposed on chronic HT. Excessive BP reduction may be detrimental to placental vasculature and fetal development.[9] At the same time, using hypotensive drugs in a woman with chronic HT may potentially adversely affect the fetus. Patients with uncomplicated chronic HT have a higher risk of Cesarean section, perinatal hemorrhage or gestational diabetes than healthy pregnant women.[50-52]

A higher risk of these complications is found in women with chronic HT and:

- Secondary HT
- Age above 35 years
- BP higher than 160/110 mm Hg in the first trimester
- HT duration of 5 or more years
- HT treated with 2 or more medications
- History of obstetric complications (PE, premature placental abruption)
- Chronic diseases: left ventricular dysfunction, retinopathy, lipid disorders, microangiopathy, stroke, diabetes, CKD, connective tissue diseases or the presence of lupus anticoagulant[13]

Pregnant women with these risk factors are more likely to develop rare life-threatening complications, including hypertensive encephalopathy, pulmonary edema, retinopathy, intracerebral hemorrhage, or acute kidney injury (AKI).[53] The risk of obstetric complications increases with age, HT duration, and, in particular, the severity of secondary target organ damage. Proteinuria in early pregnancy is an independent risk factor associated with higher rates of preterm birth, small for gestational age (SGA) neonates and intraventricular hemorrhage.[8] Patients with CKD, diabetic angiopathy, severe collagen vascular disease, cardiomyopathy, or coarctation of the aorta should be informed about the adverse effect of these conditions on pregnancy at the preconception stage. Patients with severe, uncontrolled HT, severe impairment of renal function in early pregnancy, and preexisting left ventricular HF have been identified as a particularly high-risk group.

The proposed obstetric care algorithm including diagnostic investigations is shown in TABLE 5.2. In women with well-controlled BP, after ruling out other maternal and fetal complications, delivery is recommended after 38 gestational weeks. Hospital referral is recommended in patients with systolic BP of 160 mm Hg or higher or diastolic BP of 110 mm Hg or higher.[1,14] Hospital referral should also be considered upon the onset of symptoms suggestive of PE (TABLES 6.2 and 6.3).

The incidence and sequelae of maternal and fetal complications in patients with HT with a higher risk of complications depend on the underlying cause of HT as well as the severity of target organ damage. Antenatal care in these patients should be provided by maternal fetal medicine consultant, with multidisciplinary input from consultant cardiologist / clinical HT specialist and other consultants, if indicated.

5.7. Treatment of hypertension in pregnant women

5.7.1. Nonpharmacological management of hypertension in pregnant women

Lifestyle modifications, including behavioral changes improving fetal and neonatal outcomes, such as smoking cessation and alcohol abstinence are recommended at the preconception stage, in pregnancy, and postpartum.[54] Cigarette smoking is the most common addiction in Polish women at reproductive age and affects approximately 30% of pregnant women.[55] Cigarette smoking in pregnancy adversely affects fetal development, for example, due to the effect of carbon monoxide contained in tobacco smoke, which binds to hemoglobin and reduces fetal oxygen supply.[56]

The teratogenic effect of alcohol on the fetus was first described back in the 1960s. The recommendations of the International Federation of Gynecology and Obstetrics (FIGO) and the Polish expert opinion statement are, therefore, unambiguous and recommend the active promotion of alcohol abstinence in women planning to conceive, and those who are pregnant or breastfeeding.[54,57]

Although no particular diet is recommended in pregnancy, a good diet is based on the general healthy nutrition principles for adults (for example, the Mediterranean diet). A balanced, varied, and healthy diet is very important during pregnancy. According to FIGO, a diet should be rich in vegetables, fruit, pulses, and whole grains. Animal products (milk, dairy, lean meat) as well as oily saltwater fish should be consumed in moderation (fish which may contain higher concentrations of mercury, eg, shark, swordfish, king mackerel should not be consumed), whereas products high in carbohydrates and saturated fatty acids should only be consumed occasionally.[54]

Optimum body weight should be achieved prior to conception. The energy requirement in pregnancy increases slightly (by about 10%) in comparison with the preconception period. According to FIGO, based on American guidelines, the recommended weight gain during pregnancy in women with normal prepregnancy body mass index (BMI, 18.5–25 kg/m^2) is 11.5 to 16.0 kg. The recommended weight gain in overweight and obese women is 7 to 11.5 kg and 5 to 9 kg, respectively.[54,58] A physically active adult with a body weight of about 70 kg needs about 2.5 l of water per day (range from 1.5 to 3 l, including about 700 ml of water contained in food). Pregnant and breastfeeding women should increase their daily water intake by about 300 ml and 600 to 800 ml, respectively. The daily recommended water intake in the second / third trimester and during breastfeeding is 3 l and 3.8 l, respectively. In the first trimester, the daily water requirement is the same as in a nonpregnant woman, that is, 2.7 l.[59]

A significant reduction of table salt intake is not recommended in pregnancy. However, pregnant women should use iodized salt.[54]

Daily intake of caffeinated beverages should be limited to not more than 200 mg of caffeine (1 cup of coffee contains 50–160 mg of caffeine) in pregnant women.[60,61]

It is recommended to advise women with well-controlled BP who regularly exercised prior to conception to continue moderate physical activity.[2,4,6,54] The research shows that moderate physical activity in pregnancy is not only safe but also improves maternal and fetal outcomes (eg, it reduces preterm birth rates and the incidence of pregnancy-induced HT).[61-63]

Importantly, pregnancy should be used as an opportunity to educate patients on lifestyle modifications, including a healthy diet, which should continue even after childbirth.[2]

5.7.2. Initiation of pharmacological treatment of hypertension in pregnancy and target blood pressure values

The guidelines published in recent years provide discrepant thresholds for treatment of HT. We recommend a BP threshold of 140 mm Hg or higher systolic and / or 90 mm Hg or higher diastolic for the treatment of chronic and pregnancy-induced HT in all pregnant women. The 2018 ESC guidelines[2] recommend higher BP threshold for the initiation of antihypertensive drug treatment in pregnant women with uncomplicated chronic HT (BP threshold ≥150/≥95 mm Hg), but there is no published evidence to support different treatment strategies in uncomplicated chronic HT (BP threshold ≥150 / ≥95 mm Hg) and gestational HT, preexisting HT with the superimposition of gestational HT, or HT with subclinical HT-mediated organ damage (BP threshold ≥140 / ≥90 mm Hg). The majority of studies (almost 50 studies) conducted to date, including the CHIPS (Control of Hypertension in Pregnancy) study described below, which evaluated the efficacy and safety of antihypertensive drug treatment in pregnancy, assumed the diastolic BP threshold of 90 mm Hg or higher for the initiation of antihypertensive drug treatment. Fewer studies used systolic BP thresholds for the initiation of antihypertensive treatment with the systolic BP threshold of 140 mm Hg or higher (FIGURE 5.5) assumed by the vast majority (almost 30) of them.[64-66]

Patients with systolic BP of 160 mm Hg or higher or diastolic BP of 110 mm Hg or higher obtained in multiple consecutive measurements taken within 15 to 30 minutes are considered a hypertensive emergency and a hospital referral is recommended. Antihypertensive treatment in such patients should be initiated within 60 minutes (see CHAPTER 5.8).[14]

The ESC guidelines consider a systolic BP of 170 mm Hg or higher or diastolic BP of 110 mm Hg

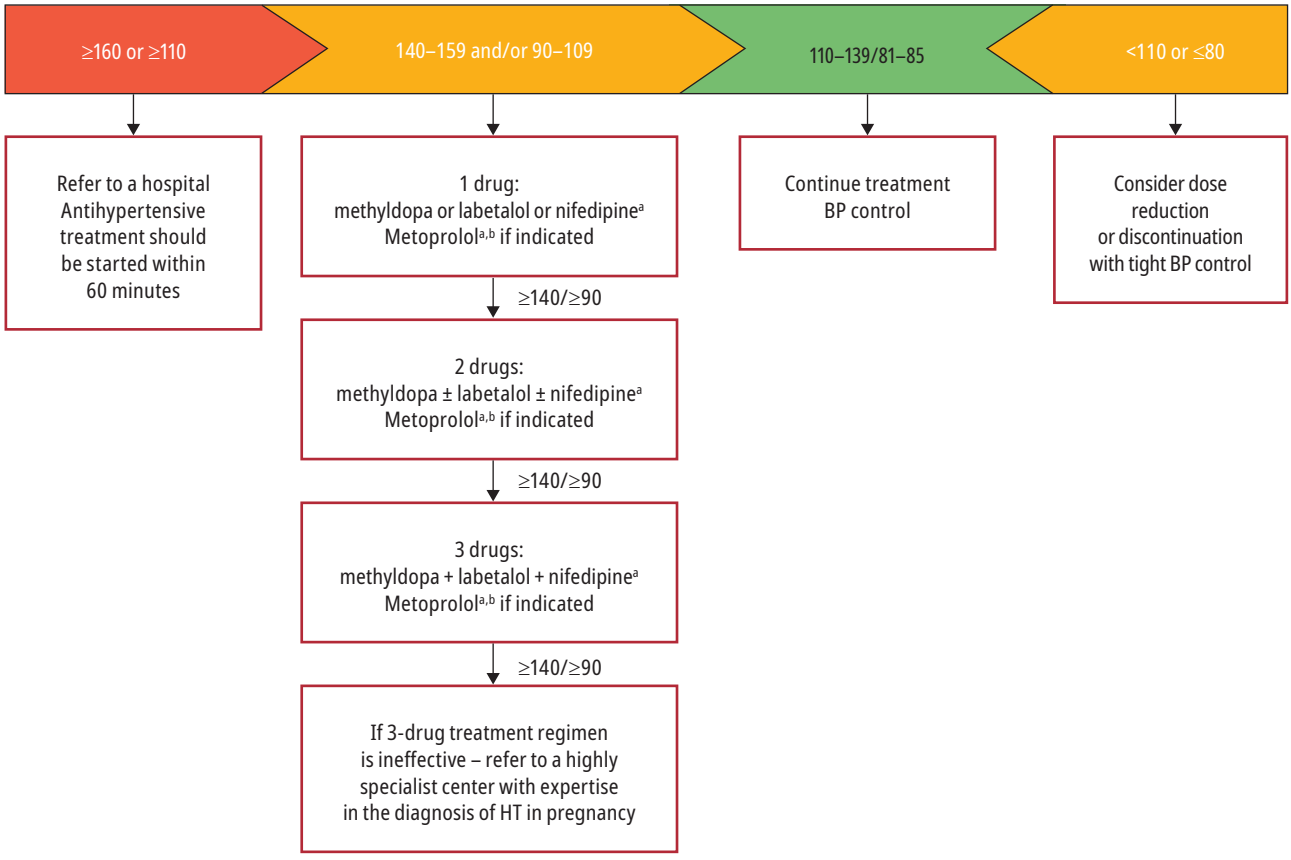

FIGURE 5.5 Principles of antihypertensive treatment in pregnancy

a Extended release formulation

b Do not combine metoprolol and labetalol

Abbreviations: BP, blood pressure; HT, hypertension

or higher an emergency in a pregnant woman. However, following the recommendations of gynecological societies and the Regulation of the Minister of Health, we decided to assume a lower threshold for hypertensive emergency (systolic BP ≥160 mm Hg / diastolic BP ≥110 mm Hg).[1,5,6,14]

Overzealous BP control should be avoided as it may lead to placental hypoperfusion and this will compromise the fetus.

To date, the only randomized study which evaluated the benefits of more or less "tight" BP control in pregnancy was the CHIPS study.[65] A total of 987 women at 14- to 33-week gestation with nonproteinuric preexisting or gestational HT, office diastolic BP of 90 to 105 mm Hg (or 85–105 mm Hg if on antihypertensive drugs), and a live fetus were enrolled.[65]

Patients were randomized to: 1) less tight (target diastolic BP, 100 mm Hg) control, where antihypertensive treatment must be started or increased in dose if diastolic BP was 105 mm Hg or higher and decreased in dose or discontinued if diastolic BP was less than 100 mm Hg or 2) tight control (target diastolic BP, 85 mm Hg) where antihypertensive treatment must be started or increased in dose if diastolic BP was higher than 85 mm Hg and decreased in dose or discontinued if DBP was 80 mm Hg or less.[65]

The composite primary endpoint was pregnancy loss or high-level neonatal care for more than 48 hours in the first 28 days of life. The secondary endpoint was maternal death or serious maternal complications before 6 weeks postpartum. The BP achieved in tight control was 133.1 mm Hg systolic and 85.3 mm Hg diastolic, as compared with less tight control with 138.8 mm Hg systolic and 89.9 mm Hg diastolic. Thus, the mean between-group difference was 5.8 mm Hg systolic and 4.6 mm Hg diastolic (P <0.001 for both comparisons). There was no impact of less tight versus tight control on perinatal death or high-level neonatal care for more than 48 hours (31.4% vs 30.7%, respectively) or serious maternal complications (3.7% vs 2.0%, respectively). However, there was more severe maternal HT in less tight versus tight control group (40.6% and 27.5%, respectively; P <0.001).[65]

Subsequently, in the post hoc analysis of CHIPS study data, an association between severe HT and a higher incidence of maternal and neonatal complications was assessed. It was shown that severe maternal HT was associated with higher preterm birth rate, higher incidence of HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), as well as

with lower birth weight. However, this association was only observed in the less-tight control group.[67]

Subsequent exploratory analysis of the CHIPS data aimed to determine whether less-tight BP control (vs tight control) affects perinatal and maternal outcomes. A tight BP control (vs less-tight control) before 24 gestational weeks was associated with a higher risk of birth weight below the tenth percentile as well as a lower risk of delivery below 37 weeks and of severe maternal HT, particularly so when women were randomized before 28 weeks.[68]

Notably, the CHIPS remains the only randomized study published to date that evaluated the benefits of more or less "tight" BP control in pregnancy. Good BP control (mean BP <140/90 mm Hg) was achieved in both groups. Tight control (diastolic BP, 81–85 mm Hg) was associated with a lower rate of severe maternal HT. Development of severe HT was associated with more adverse perinatal and maternal outcomes. Tight BP control (vs less-tight control) was associated with lower preterm birth rates and lower incidence of severe maternal HT at the expense of lower birth weight. The conclusion following the CHIPS was that tight control is the preferred management strategy in the second and third trimester (women in the first trimester were excluded from the study).[65,67,68]

Based on the CHIPS data, it was concluded that the diastolic BP target in pregnancy should fall in the range of 81 to 85 mm Hg.[65,67,68] However, there are no studies to evaluate the optimum target systolic BP range. The latest International Society for the study of Hypertension in Pregnancy (ISSHP) guidelines recommend the range of 110 to 139 mm Hg as the target systolic BP.[1] We consider it appropriate to assume the same range of target systolic BP values in antihypertensive treatment in pregnant women.

If systolic BP is less than 110 mm Hg or diastolic BP is 80 mm Hg or less, treatment de-escalation should be considered, whereas if systolic BP is higher than 140 mm Hg or diastolic BP is higher than 85 mm Hg, treatment escalation is recommended.

It should be noted that the above target BP is primarily applicable to the second and third trimester. However, we consider it appropriate that the same thresholds apply to women in the first trimester. Only a few studies assessed the effect of antihypertensive treatment in the first trimester. Nzelu et al[69] conducted a prospective study in 586 pregnant women with chronic HT. The patients were subdivided at a median of 10 gestational weeks into group 1, with BP less than 140/90 mm Hg without antihypertensive medication, group 2, with BP less than 140/90 mm Hg with antihypertensive medication and group 3, with systolic BP higher than 140 mm Hg and / or diastolic BP higher than 90 mm Hg despite antihypertensive medication. In group 3, there was a significantly higher incidence of severe HT, preterm PE with onset at less than 37 weeks of gestation, and IUGR than in group 1. In group 2, the incidence of these outcome measures was non-significantly higher than in group 1 and lower than in group 3. On the other hand, the analysis of the German pharmacovigilance database showed that the exposure to methyldopa in the first trimester was associated with a higher incidence of adverse maternal and perinatal outcomes. However, the outcome analysis in that study did not control for the effect of BP values.[70] The results of both studies support the conclusion that the need for antihypertensive treatment in the first trimester (when BP tends to decrease physiologically) may indicate higher severity of HT and the associated increased risk of maternal and perinatal complications. Thus, we believe, that BP reduction to the target values discussed above may be considered in the first trimester. However, as the BP physiologically decreases in the first trimester, also in patients with chronic HT, dose reduction or even discontinuation of antihypertensive treatment may be considered in the first trimester provided that meticulous BP monitoring is continued (with BP of 110–139/81–85 mm Hg).

5.7.3. Antihypertensive drug treatment in pregnancy

Most studies evaluating the efficacy and safety of individual antihypertensive drugs in pregnancy were conducted in the 1980s and 1990s. Only a dozen or so studies, including the CHIPS study, were conducted within the first 2 decades of the 21st century. The most commonly assessed drugs were methyldopa, labetalol, and nifedipine, which were used in over 3000 women. They were compared with placebo, no intervention, and other antihypertensive drugs (including comparisons between the 3 above-mentioned medications). Other antihypertensive drugs were studied less extensively. Metoprolol, verapamil, and clonidine were evaluated in 4, 4, and 3 studies, respectively, in approximately 450 women altogether. Prazosin, isradipine, ketanserin, hydralazine, and β-blockers: atenolol, oxprenolol, and mapindolol were also used in more than 1 study. Acebutolol, amlodipine, bisoprolol, furosemide, nitrendipine, and propranolol were evaluated in single studies in small samples each. Such a large difference between the number of studies and sample sizes between methyldopa, labetalol, and nifedipine compared with other antihypertensive drugs supports their use as preferred treatment of HT in pregnant women (FIGURE 5.5).[14,64-66]

Methyldopa, a centrally active sympatholytic agent (an antagonist to the α2-adrenergic receptor), has long been used in the treatment of HT in pregnancy and has an established safety

record with a 7-year follow-up of child development following in utero exposure.[71] It can be used in pregnancy from the first trimester.[70] However, sedative effect and excessive sleepiness, as well as potential hepatotoxicity (usually transient elevation of liver function markers) limit its use. Other adverse effects of methyldopa include sodium and water retention, dry mouth, impaired sleep, and fatigue. Dosage: 250 mg 2 to 3 times a day orally, up to a daily dose of 2 g (max daily dose of 3 g).[14]

Labetalol is a selective α1-adrenergic and nonselective β-adrenergic receptor antagonist, which is not cardioselective and does not have intrinsic sympathomimetic activity. This drug is considered to provide effective BP control and to be safe in pregnancy. Labetalol was also the recommended antihypertensive of the first choice in the CHIPS study.[65,72,73] Recommendations of different medical societies unequivocally recommend labetalol, alongside methyldopa and extended-release nifedipine, as antihypertensive of the first choice in HT in pregnant women.[2,4,9] Dosage: 100 mg twice a day orally, up to a daily dose of 800 mg (maximum daily dose of 1200 mg divided into 2–4 doses). Importantly, as labetalol may be associated with the risk of maternal and fetal bradycardia, it should not be used in women with impaired left ventricular systolic function, high-grade atrioventricular block, and asthma.[14]

It has been emphasized that all β-blockers (including labetalol) used in pregnancy may be associated with the risk of bradycardia, hypoglycemia, and IUGR (especially following the exposure in the first trimester).[74-77] Recent ESC guidelines does not explicitly address recommending β-blockers other than labetalol in pregnant women, only stating that atenolol should be 'best avoided', and that 'β-adrenergic blocking agents are generally safe in pregnancy' (mainly as antiarrhythmic drugs), while β-1-selective drugs (eg, metoprolol) are preferred.[2] Out of 4 studies evaluating metoprolol in pregnant women with HT, 3 used metoprolol tartrate and 1 metoprolol succinate.[64,66] It should be noted, though, that metoprolol succinate has more approved indications, including functional arrhythmias. Therefore, extended-release metoprolol succinate may be considered in women with HT and sinus tachycardia/heart palpitations, provided that fetal growth is carefully monitored for the potential adverse effect of treatment.

CCBs are a class of antihypertensive drugs with a favorable safety profile in pregnancy, which are currently listed as pregnancy class I drugs in HT.[2,4,67] Out of this drug class, extended release nifedipine has been most commonly used and studied in pregnancy.[78-80] Other dihydropyridine derivatives (L-type CCBs), namely, nicardipine,[81] amlodipine,[82] nitrendipine,[83,84] or isradipine [85] were only evaluated in single studies or used in a small number of pregnant women in database analyses.[86,87] Thus, there is not enough data to draw conclusions regarding their safety in pregnancy. Extended-release nifedipine is, therefore, antihypertensive of the first choice alongside methyldopa and labetalol. Some experts propose a class effect approach to using CCBs in pregnant women, that is, that there are no premises to anticipate the adverse effect of, for example, amlodipine or nitrendipine in pregnancy, as there is no evidence to support such effect of nifedipine. However, the published guidelines have not shared this view to date. The 2018 ESC guidelines state that "calcium antagonists are the drugs of choice" indicating that "most data is available for nifedipine."[2] The combined treatment with CCBs and magnesium sulphate may be associated with a significant BP reduction due to their potential synergism.[88] The recommended daily dose of extended-release nifedipine ranges from 30 mg to 120 mg orally. The most common adverse effects of nifedipine include excessive BP lowering, headaches, dizziness, flushing, and peripheral edema.

Verapamil, a nondihydropyridine CCB, was used in pregnant women, especially those with arrhythmia, in a few studies.[89,90] There is no sufficient data regarding its maternal and fetal side-effects. However, possible tocolytic effect and interaction with magnesium sulphate have been pointed out.[88] Verapamil is referred to in the ESC guidelines as "fairly safe during pregnancy," although mainly indicated for the treatment and prevention of arrhythmias.[4] Dosage: daily dose up to 120 mg orally. Adverse effects of verapamil include first-, second-, and third-degree atrioventricular block, bradycardia, dizziness, headaches, persistent constipation, and flushing.

Metoprolol or verapamil may be considered in women who do not respond or tolerate methyldopa, labetalol, and extended-release nifedipine. Labetalol should not be used in combination with metoprolol or verapamil, whereas metoprolol should not be used in combination with verapamil.

Other antihypertensives, the safety and efficacy of which have been evaluated in a limited number of studies, are clonidine, hydralazine, and prazosin.

Clonidine is a centrally active sympatholytic agent that stimulates α2-adrenergic receptors and, to a lesser extent, imidazoline receptors. The safety of clonidine in pregnancy has been assessed in several studies. Due to similar mechanisms of action, it should not be combined with methyldopa. The most common adverse effects include drowsiness, dry mouth, and reduced cognitive performance.[14]

Hydralazine is a vasodilator used in the treatment of severe HT in pregnant women. Its efficacy and safety have been assessed in several studies, including hypertensive emergencies. The most common adverse effects of hydralazine

Antihypertensive treatment in pregnancy: summary	
Smoking cessation and alcohol abstinence are recommended in pregnant and breastfeeding women.	Level C
Achieving optimum body weight prior to conception is recommended.	Level B
The daily recommended water intake in the second / third trimester and during breastfeeding is 3 l and 3.8 l, respectively. The daily recommended water intake in the first trimester is 2.7 l.	Level C
A balanced, varied, and healthy diet is recommended in pregnancy.	Level C
Moderate physical activity is recommended in pregnant women who regularly exercised prior to conception.	Level C
The recommended BP thresholds for the initiation of antihypertensive treatment are SBP ≥140 mm Hg and / or DBP ≥90 mm Hg.	Level B
The recommended BP targets in pregnancy are 110–139 mm Hg systolic and 81-85 mm Hg diastolic.	Level C
Hospital referral is recommended in patients with SBP ≥160 mm Hg and / or DBP ≥110 mm Hg.	Level C
Methyldopa, labetalol and extended-release nifedipine are antihypertensives of the first choice in pregnant women with HT.	Level B
In women with indications for treatment with cardioselective β-blockers, metoprolol should be considered.	Level C
Diuretics and spironolactone are not recommended as antihypertensive treatment in pregnancy (except in special circumstances).	Level C
Angiotensin-converting enzyme inhibitors, angiotensin II-receptor blockers, renin inhibitors and diltiazem are not recommended as antihypertensive treatment in pregnancy (except in special circumstances).	Level C

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure

Management of hypertensive emergency: recommendations	
Emergency inpatient admission and treatment of hypertensive emergency are indicated in pregnant women with SBP ≥160 mm Hg and/ or DBP ≥110 mm Hg.	Level C
Inpatient admission is recommended in pregnant women with PE or symptoms of PE, regardless of their BP.	Level C
Antihypertensive medications recommended for treatment of hypertensive emergencies include labetalol IV, nifedipine orally and hydralazine IV.	Level C
The 25% reduction in the mean arterial BP, followed by a further BP reduction to <160/110 mm Hg within minutes/hours is recommended in hypertensive emergency.	Level C
Labetalol, in both intravenous and oral formulations, is not approved in Poland. It is only available through direct import. We recommend ensuring appropriate stock, eg, amount sufficient for the treatment of 1–2 patients, for the immediate needs of the ward.	Level C

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; IV, intravenously; PE, preeclampsia; SBP, systolic blood pressure

are a lupus-like syndrome, palpitations, headaches, and flushing. It is not available in Poland.[1-8]

α-Blockers act as antagonists on α-adrenergic receptors located in smooth muscle cells of blood vessels. Individual substances have variable selectivity for α1- and α2-receptors and are quite well tolerated. Prazosin is the only α-blocker evaluated for safety and efficacy in pregnancy.[64,66] Orthostatic hypotension, especially after the first dose, is one of the most common adverse effects.

Due to their teratogenicity, ACEIs are contraindicated during pregnancy.[75,91-93] The same applies to renin inhibitors and angiotensin II receptor blockers / neprilysin inhibitors.[2,75]

Diltiazem should also not be used during pregnancy. Treatment continuation with diuretics started preconception is controversial. We do not recommend diuretics in pregnancy due to possible oligohydramnios and fetal electrolyte imbalance.[75] Spironolactone has been shown to adversely affect fetal development in animal studies (using MRAs in pregnant women is discussed in CHAPTER 7.2).

Labetalol and extended-release nifedipine are only available in Poland through direct import, which requires completing a relevant application, according to the instructions available on the website of the Ministry of Health, Department of Drug Policy and Pharmacy (www2.mz.gov.pl/wwwmz/index).

5.7.4. Combined treatment of hypertension in pregnancy

The results of studies conducted to date show that monotherapy offers good BP control in the majority of pregnant patients with HT. In the CHIPS study, combined treatment was used in about 35% and 30% of women in tight and less-tight control groups, respectively.[94] As shown in FIGURE 5.5, if monotherapy proves ineffective, combined treatment with 2 drugs, followed by 3 drugs (a preferred combination of methyldopa, labetalol, and extended-release nifedipine) should be used. The standard definition of refractory HT does not apply to pregnancy. With uncontrolled BP despite 3 antihypertensive drugs, out-of-office BP measurements should be used to verify the condition. If a failure to control BP despite 3 antihypertensive drugs is confirmed,

TABLE 5.5 Antihypertensive drugs used for emergency blood pressure lowering

Medications	Characteristics, indications, contraindications, adverse effects, limitations of use	Level
Antihypertensive drugs[a] used for emergency BP lowering in pregnant women (first-choice)		
Labetalol[a] IV[2,4,95]	Fast onset of action Should be avoided in women with asthma or heart failure May cause neonatal bradycardia	A
Hydralazine[a] IV[2,4,8,95]	It is associated with more adverse effects than labetalol and other antihypertensive drugs There is some risk of maternal tachycardia and unpredictable hypotension According to the ESC guidelines, hydralazine should not be a drug of choice. However, it is commonly used if other antihypertensive drugs fail to achieve good BP reduction. Safety profile considered acceptable by many gynecologists. Recommended in women with bradycardia (HR <60 bpm) Avoid in women with chronic headaches	A
Nifedipine orally[2,4,8,95]	Used if there is no venous access Fast release from the oral formulation May cause severe adverse effects, if administered in combination with magnesium sulphate Avoid in women with tachycardia	A
Drugs used for the treatment of hypertensive emergencies in pregnant women if first-choice drugs are contraindicated or unavailable, no response to treatment administered so far and in special clinical circumstances associated with HT		
Nitroglycerin IV[2,4,8]	Concomitant pulmonary edema	B
Labetalol[a] orally[95,96]	Contraindications as for the IV formulation; oral formulation may be used before peripheral venous cannulation or if venous access is not available. Dosage, see TABLE 5.6.	B
Urapidil IV[2]	The onset of action is immediate, and so is its cessation when discontinued. It does not cause reflex tachycardia, does not increase intracranial pressure, and does not cause the „rebound" effect. Controlled trials in pregnant women did not demonstrate significant contraindications for using urapidil in pregnancy.	
Sodium nitroprusside[b] IV[2,4,95]	Recurrent HT with high BP values A drug of last resort Risk of cyanide and thiocyanate intoxication	B

a The choice of antihypertensive drug is primarily guided by its contraindications, availability on the ward, viable routes of administration (venous access available / not available), progressing labor, delivery route, potential general anesthesia and maternal general condition

b Not approved in Poland, available through the direct import route only

Abbreviations: BP, blood pressure; ESC, European Society of Cardiology; HR, heart rate; IV, intravenous

the patient should be referred to a specialist center with expertise in the diagnosis and treatment of HT during pregnancy.

5.8. Management of hypertensive emergency

Treatment of hypertensive emergencies is one of the most difficult and widely debated issues in the treatment of pregnant women. Despite the effort of many renowned medical centers, medical societies and organizations worldwide, treatment recommendations are still discrepant with no uniform treatment algorithm.[1,2,4,8,95] In the absence of large, multicenter, randomized trials in pregnant women with HT, it is difficult to develop universal recommendations. The principles presented below are based on the analysis of available studies and guidelines.[1,2,4,8,9,95]

The following principles should inform the treatment of hypertensive emergency:

- Reliable BP measurements (see CHAPTER 5.1) must be ensured
- In patients with systolic BP of 160 mm Hg or higher and / or diastolic BP of 110 mm Hg or higher as well as those with eclampsia or PE (see CHAPTER 6.2.3) even with lower BP values, hospital referral needs to be made[1]
- Regardless of concomitant complications of HT in pregnancy, any patient with BP of 160/110 mm Hg or higher requires treatment as a hypertensive emergency
- In a patient with high BP values and in whom hospitalization is recommended in case of prolonged transport to the hospital, one of the drugs recommended in hypertensive emergencies may be considered (TABLE 5.5). BP values should be closely monitored (reduction in BP values should not delay hospitalization)
- BP reduction should be monitored, preferably with direct arterial BP monitoring. Antihypertensive treatment in a hypertensive emergency should aim at a 25% reduction in the mean arterial BP, followed by a further BP reduction to less than 160/110 mm Hg within minutes / hours.[8] Too rapid BP lowering may cause serious maternal and fetal complications. In hypertensive urgencies, BP lowering should be achieved within hours / days
- In women with severe HT, the intensive antihypertensive treatment aims at achieving BP of less than 160/110 mm Hg.[8] Once the BP values have stabilized, long-term treatment with oral antihypertensives should be started with the aim to achieve target BP (110–140 mm Hg/80–85 mm Hg) within a few consecutive days (see CHAPTER 5.7)
- Diastolic BP reduction to less than 80 mm Hg is an indication for dose reduction or discontinuation of antihypertensive treatment[1]
- Treatment of hypertensive emergency should include close monitoring of maternal and fetal vital signs. Alongside BP measurements, maternal heart rate, respiratory rate, oxygen saturation, temperature, hourly diuresis, fluid balance and neurological condition (even every hour) should be monitored. Early diagnosis of target organ damage, including regular screening for proteinuria, is a vital component of maternal surveillance. In patients with PE, laboratory tests should be performed at least every 12

TABLE 5.6 Antihypertensive drugs used for the treatment of hypertensive emergencies in pregnant women

Medication	Onset of action	Duration of action	Dose
Labetalol IV	5–10 min	3–6 h	20 mg IV for 2 min, followed by 20–80 mg IV every 10–15 min or an infusion 1–2 mg/min Decrease flow velocity once target BP has been achieved. Maximum dose of 300 mg
Labetalol orally			100–400 mg 2–3 times a day, the maximum daily dose of 1200 mg. Some experts recommend the first dose of 200 mg twice a day. If no peripheral venous access, administer 200 mg orally. If no antihypertensive effect, another 200 mg dose can be administered after 30 minutes. If no antihypertensive effect or poor tolerance of oral formulation, an alternative is to administer 50 mg IV for 5 minutes. Repeated doses up to 200 mg every 10 minutes. Intravenous administration can be continued as an infusion
Hydralazine IV	5 min		5 mg IV, repeated doses of 5–10 mg IV every 30 min, a maximum dose of 20 mg
Nitroglycerine IV	2–5 min	30 min	Initial IV infusion of 5 µg/min can be increased every 3–5 min up to the maximum dose of 100 µg/min
Urapidil IV	3–5 min	4–6 h	10–50 mg as an IV infusion or continuous infusion using an infusion pump. Recommended initial max. dose is 2 mg/min, with the mean maintenance dose of 9 mg/h. It seems practical and relatively safe to administer the drug using an infusion pump with gradual, BP-dependent dose adjustment. Maximum drug concentration in a solution is 4 mg/ml. For details regarding the routes of administration and dilution depending on the clinical situation – see the Summary of Product Characteristics

Abbreviations: BP, blood pressure; IV, intravenous

hours, and even every 4 to 8 hours with significant hematological and/or biochemical abnormalities and hemorrhagic complications.[96] In patients with PE, diagnosis and monitoring of target-organ damage are crucial in assessing the indications for delivery. Monitoring fetal vital signs and development is another essential factor to inform clinical decision-making about delivery (see CHAPTER 6.3)

- Antihypertensive drugs used for the treatment of severe HT (TABLES 5.5 and 5.6) share the following common characteristics:
  - High efficacy and rate of BP reduction
  - Low risk of a maternal and perinatal adverse effect
  - Option for parenteral administration
  - Availability at the clinic/hospital 'the medication is waiting for the patient'
- All clinics/hospitals providing care of pregnant women should have a clear antihypertensive treatment algorithm with efficacy assessment and recommended rate of BP reduction, as well as a form to document actions taken and their effect
- Magnesium sulphate should be administered for neuroprotection before 32 gestational weeks. The indications are summarized in TABLE 5.7
- A possibility to immediately end the pregnancy in selected situations (see CHAPTER 6.3) should be available
- Treatment of multiorgan complications, ideally by the multidisciplinary team including consultant gynecologist-obstetrician, consultant cardiologist, clinical HT specialist, consultant anesthesiologist, consultant neonatologist, consultant neurologist, and consultant nephrologist should be possible
- Furosemide (and other loop diuretics) are not recommended in PE due to plasma volume reduction. They should only potentially be used for the treatment of pulmonary edema[8]
- In order to avoid pulmonary edema, the intravenous and oral fluid intake should be limited in patients with PE[8]

TABLE 5.7 Magnesium sulphate administration[9]

Administration of magnesium sulphate to patients with PE in special clinical situations according to the ESH guidelines	Level
Magnesium sulphate IV is recommended in patients with eclampsia or neurological symptoms suggestive of eclampsia, such as severe headache, vision impairment or abnormally increased deep tendon reflexes.	A
To improve fetal prognosis if a delivery before 32 gestational weeks is needed.	C
The current algorithm of magnesium sulphate IV administration involves an initial 4 g injection followed by a continuous infusion of 1 g/h until delivery, for a maximum of 24 hours. Magnesium sulphate should be administered only in the delivery room, operating theatre, postoperative ward or intensive care setting, ie, in a setting where hemodynamic monitoring and observation for possible dangerous symptoms and neurological impairment is possible.	
Although the routine determination of serum magnesium levels is not recommended, it should be performed in patients with suspected magnesium toxicity and in particular in patients with absent deep tendon reflexes.	
Upon onset of magnesium toxicity symptoms, calcium gluconate must be administered intravenously without delay, even if the serum magnesium concentration is not yet known.	

Abbreviations: ESH, European Society of Hypertension; IV, intravenous; PE, preeclampsia

6. Management of pregnancy-induced hypertension and preeclampsia

6.1. Pathogenesis of pregnancy-induced hypertension and preeclampsia

The pathogenesis of gestational HT or PE has not been fully explained to date. It seems that abnormal placentation and increased release of biologically active placental factors causing endothelial dysfunction, systemic inflammatory response, and coagulopathy may be associated with genetic, environmental, and perhaps also dietary factors. However, the most common view is that PE develops secondary to abnormal trophoblast invasion, which under physiological conditions leads to spinal artery remodeling.[97] Physiologically, human extravillous trophoblasts penetrate decidual veins and lymphatics before remodeling spiral arteries during early pregnancy. As a result, the luminal diameter of spiral arteries increases, and they become unresponsive to vasoconstrictive agents, which leads to increased uteroplacental blood flow.[98] The luminal diameter of spiral arteries increases several times as compared with its size before conception. The development of uteroplacental circulation ensures normal intervillous space perfusion. In the early stage of PE, trophoblastic cells only invade the intradecidual portion of the spiral arteries, without the remodeling of myometrial segments of the spiral arteries. Furthermore, patients with PE have fewer spiral arteries and their luminal diameter is halved as compared with normal pregnancy.[99] One of its consequences is reduced uteroplacental blood flow. In a normal pregnancy, the placental vascular bed is a low-resistance circulation. Therefore, abnormal trophoblast invasion, leading to high-resistance placental blood flow, is thought to be the underlying cause of PE. Thus, the processes responsible for the development of PE occur very early in pregnancy. In such situations, the pregnancy seems to develop normally in the first trimester and there is no clear tell-tale sign of upcoming complications. Following the onset of PE, delivery regardless of gestational age is the only known effective treatment in many cases. A number of biologically active placental factors have been identified. In a normal pregnancy, a balance between pro- and antiangiogenic factors is maintained. The vascular endothelial growth factor (VEGF), the placental growth factor (PLGF), and the transforming growth factor β are the key proangiogenic factors, whereas the soluble fms-like tyrosine kinase-1 and soluble transforming growth factor β coreceptor, endoglin, are the key antiangiogenic factors. In PE, both hypoxia and oxidative stress result in a decreased production of vasodilators, VEGF, and PLGF, and a simultaneous upregulated release of their antagonists, fms-like tyrosine kinase-1 and endoglin.[100] The increased BP is a direct consequence of the imbalance between vasodilation and vasoconstriction, and the subsequently triggered inflammatory response. Patients with PE have lower levels of pregnancy-associated plasma protein.[101] Furthermore, agonistic autoantibodies against the angiotensin II type 1 receptor and upregulated expression of angiotensin II type 1 receptor in the placenta have also been described in PE. An increase in many components of the circulating renin–angiotensin system seems to have a significant effect on BP elevation, proteinuria, and inflammatory cytokine stimulation. Based on the time of onset, clinical course and differences in fetal outcomes, early-onset PE and late-onset PE have been distinguished. The early-onset PE developing before 34 gestational weeks affects approximately 10% of cases and is often accompanied by IUGR and chronic fetal hypoxia, which may lead to intrauterine death. The early-onset PE is also associated with high dynamics of BP elevation, proteinuria, and maternal multiorgan complications. As a result, premature delivery is often necessary, because only this intervention can stop further damage and resolve the symptoms.

TABLE 6.1 Risk factors for preeclampsia

Risk factors for PE	
Moderate risk	**High risk**
First pregnancy	HT in previous pregnancies
Maternal age >40 years old	Chronic kidney disease
Pregnancy interval of >10 years	Systemic lupus erythematosus
Pre-conception BMI >35 kg/m^2	Antiphospholipid syndrome
History of PE in a patient's mother	Diabetes mellitus type 1 or type 2
Multiple pregnancy	Chronic HT

Abbreviations: BMI, body mass index; HT, hypertension; PE, preeclampsia

6.2. Risk assessment, prevention, and diagnosis of preeclampsia

6.2.1. Assessing the risk of preeclampsia

The current state of medical knowledge makes it possible to identify women at high risk of PE. There are many factors that may modify the risk of PE. Their classification according to risk levels is shown in TABLE 6.1.[2]

Due to its multifactorial etiology, risk assessment for PE based exclusively on medical history is insufficient. Therefore, the search for biophysical and biochemical markers to enable early identification of pregnant women at risk of PE later in pregnancy have continued for years. Currently, available screening is based on the combination of findings from medical history, biophysical assessments including ultrasonography and mean arterial pressure (MAP = ⅓ [SBP – DBP] + DBP; where SBP indicates systolic blood pressure and DBP diastolic blood pressure), as well as biochemical methods (serum markers) (FIGURE 6.1).

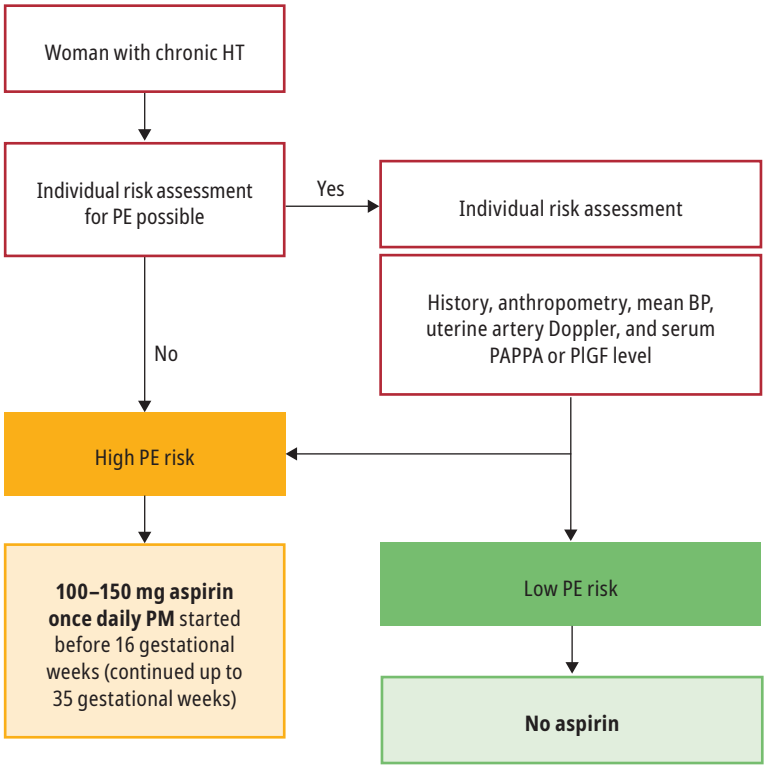

FIGURE 6.1 Assessing the risk of preeclampsia

Abbreviations: BP, blood pressure; HT, hypertension; PAPPA, pregnancy associated placental protein; PE, preeclampsia; PlGF, placental growth factor

According to the recommendation of the Fetal Medicine Foundation, BP should be measured simultaneously in both arms.[102,103]

Abnormal trophoblast invasion in early pregnancy leads to a reduction of uteroplacental blood flow, which increases in severity with gestational age. Increased vascular resistance in uteroplacental circulation can be detected with an ultrasound as early as in the first trimester (between 11+0 and 13+6 gestational weeks). The pulsatility index (PI) is then calculated for the right and left uterine artery. Abnormal placental perfusion, reflected in an elevated PI of uterine arteries, is considered one of the causes of PE. To calculate the PI, it is necessary to determine the maximum systolic velocity (S), maximum diastolic velocity (D), and the mean flow velocity (V_{mean}). The PI is then calculated according to the formula: $PI = (S - D)/V_{mean}$. The higher vascular resistance, the lower maximum diastolic velocity and, in turn, the higher PI. High PI indicating persistently high vascular resistance in uterine arteries should be considered a symptom of abnormal placental circulation, which results in abnormal placental perfusion and subsequent development of PE. The validity of the uterine artery PI was confirmed in extensive meta-analyses, often in groups of over 50 000 patients.[104-106] PE screening based on the uterine artery resistance index was described in detail by Professor Kypros Nicolaides from the King's College Hospital in London.[107-109]

The PI is used for calculating the risk of PE in the algorithm developed by the Fetal Medicine Foundation, which is available online at https://fetalmedicine.org/research/assess/preeclampsia. The values of biochemical parameters, including a PLGF level, are also necessary for the calculation.[110] The calculation yields a number reflecting a specific risk for that individual patient. The Fetal Medicine Foundation calculator also enables estimating the risk of IUGR. Risk of PE higher than 1 to 150 is usually considered an indication for aspirin prophylaxis. Screening based on risk factors, uterine artery flow parameters, MAP as well as pregnancy-associated plasma protein and PLGF levels enables identification of 95% of cases of early PE with a false-positive rate of 10%.[111] The PE management algorithm based on risk stratification is shown in FIGURE 6.1. There is an increasing body of evidence to support the ability to predict PE also later in pregnancy. One of the proposed models for predicting PE in the second trimester (between 19 and 24 gestational weeks) included parity, uterine artery PI, MAP, as well as plasma levels of PLGF and soluble fms-like tyrosine kinase 1 (sFlt-1).[112] It has been demonstrated that sFlt-1 has a very high affinity to PLGF, VEGF-B, and VEGF. In a normal pregnancy, PLGF and sFlt-1 are the prerequisites necessary for normal placental development. It has also been shown that in women with PE, the sFlt-1 level starts increasing from the second trimester, whereas the PLGF level starts decreasing at the end of the first trimester.[113] Importantly, this decrease in PLGF level and the increase in sFlt-1 level precede the onset of PE by even 5 weeks. The sFlt-1/PLGF ratio assessed between 20 and 35 gestational weeks is also a very useful predictor of PE. Within 4 weeks following the assessment, 80% of women with the sFlt-1/PLGF ratio above a derived cutoff developed PE, as compared with only 7% of those with the sFlt-1/PLGF ratio below a derived cutoff.[113,114] The sFlt-1/PLGF ratio of less than 38 virtually rules out the onset of PE within the next 7 days.[115,116]

6.2.2. Prevention of preeclampsia

Early identification of patients at high risk of HT, weeks before the clinical onset, enables effective prevention. Meta-analyses of many randomized studies have shown that aspirin prophylaxis started before the 16 gestational weeks, that is, before the uterine spiral artery remodeling ends, significantly reduces the risk of PE.[117,118] The comprehensive, multicenter ASPRE (Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia) study confirmed that aspirin showed an 80% and a 63% reduction in the risk of developing PE earlier than 34 weeks and earlier than 37 weeks, respectively.[119] Although the mechanism of action of aspirin has not been fully understood to date, its direct

effect on apoptosis and trophoblast proliferation as well as anticoagulant and antiplatelet effect preventing placental infarction have been proposed. Due to the high prevalence (up to 30%) of aspirin resistance found in studies that used aspirin doses below 100 mg, a 100 to 150 mg aspirin dose taken orally at bedtime is recommended.[120] Aspirin is undoubtedly the best prevention in women at high risk for preterm PE, identified using the risk calculation algorithm based on biophysical and biochemical parameters (FIGURE 6.1). However, where individual risk assessment is not possible, aspirin prophylaxis should be considered in all patients with at least 1 high-risk factor or at least 2 moderate risk factors (TABLE 6.1).

Prevention of preeclampsia in pregnant women with hypertension: recommendations	
A single 100–150 mg aspirin dose taken orally at bedtime is recommended in pregnant women with chronic HT. The treatment must be started before 16 gestational weeks and continued up to 36 gestational weeks.	Level A
Where personalized risk assessment for PE is not possible, the decision to start aspirin prophylaxis should be made based on estimated risk. Aspirin prophylaxis as described above is recommended in women whose risk of PE is higher than 1 in 150.	

Abbreviations: HT, hypertension; PE, preeclampsia

TABLE 6.2 Diagnostic criteria of preeclampsia (adapted from International Society for the study of Hypertension in Pregnancy)[1]

Pregnancy-induced HT developing after 20 gestational weeks coexisting with one or more of the following new onset conditions[a]
• Proteinuria (quantitative assay – TABLE 4.1)
• Acute kidney injury (creatinine ≥1 mg/dl or ≥90 µmol/l)
• Liver involvement (elevated transaminases, eg, AST or ALT >40 IU/l) and / or severe right upper quadrant or epigastric pain
• Hematological complications (PLT count <150,000/µl, DIC, hemolysis)
• Neurological complications (eg, eclampsia, altered mental status, amaurosis, stroke, clonus, severe headache, persistent visual scotomata)
• Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth)

a In patients with chronic HT, superimposed preeclampsia can be diagnosed based on the new onset of proteinuria or organ dysfunction (see the criteria above) after 20 gestational weeks. Superimposed preeclampsia cannot be diagnosed based on the rise in BP or IUGR alone. In women with underlying chronic kidney disease manifesting as proteinuria, increased proteinuria alone is not sufficient to diagnose preeclampsia

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BP, blood pressure; DIC, disseminated intravascular coagulation; HT, hypertension; IUGR, intrauterine growth restriction; PLT, platelets

TABLE 6.3 Signs and symptoms of preeclampsia

Headaches
Vision impairment
Nausea and vomiting
Epigastric pain
Oliguria
Elevated liver function tests
Elevated serum creatinine level
Thrombocytopenia
Abnormal cardiotocography and abnormal blood flow in the fetoplacental circulation

6.2.3. Diagnosis of preeclampsia

PE is a syndrome with multisystem involvement, which occurs after 20 weeks of gestation, peripartum or postpartum. It is primarily defined by the occurrence of new-onset HT plus new-onset proteinuria or HT and multisystemic signs in the absence of proteinuria. The diagnostic criteria of PE are shown in TABLE 6.2. In PE, peripheral vascular resistance and systemic arterial BP are increased alongside a reduced plasma volume, unlike in a normal pregnancy. Proteinuria is currently included in the diagnostic criteria for PE, yet its presence is not required for the diagnosis. It is caused by the increased permeability of the glomerular filtration barrier or glomerular injury. During pregnancy, abnormal proteinuria is defined as urine protein excretion greater than 300 mg/24 hours. In women with chronic HT, a stand-alone BP increase is not sufficient for the diagnosis of PE. The criteria for the diagnosis of superimposed PE include de novo onset of proteinuria and / or evidence of significant maternal organ or uteroplacental dysfunction after 20 gestational weeks. Furthermore, superimposed PE is diagnosed in women with persistent proteinuria who have sudden, substantial and sustained increases in protein excretion, or experience a sudden increase of HT not responding to treatment after 20 gestational weeks, or suddenly manifest other signs and symptoms. The signs and symptoms of PE are summarized in TABLE 6.3.

6.3. Management of gestational hypertension and preeclampsia

In a normal pregnancy, a number of significant hemodynamic changes occur in the maternal cardiovascular system to ensure sufficient blood and nutrient supply to the fetus. Accelerated heart rate, increased plasma volume and cardiac output as well as reduced peripheral vascular resistance, resulting in a decreased arterial pressure, are mainly associated with upregulated endothelial activity and vasodilator release. Unfortunately, these adaptations during pregnancy are disturbed in 1 in 10 women, usually during the second half of pregnancy.[121] In rare cases of abnormal trophoblastic proliferation, known as gestational trophoblastic disease, the onset of HT occurs already in the first half of pregnancy.[122] HT is more common and so is the onset before 20 gestational weeks in multiple gestation due to higher maternal physical stress and higher weight of the placenta(e).[121]

PE, which affects about 2% of pregnant women, is the most severe hypertensive disorder in pregnancy.[121] Albeit fairly uncommon, it is one of the leading causes of maternal, fetal, and neonatal mortality and morbidity. PE may progress to eclampsia with stroke and seizures, life-threatening CNS conditions. Pregnancy-induced HT is also associated with other serious complications such as disseminated intravascular coagulation, liver damage, the HELLP syndrome or premature placental abruption.

Based on the time of onset, clinical course and differences in fetal outcomes, early-onset PE and late-onset PE have been distinguished. The early-onset PE developing before 34 gestational weeks affects approximately 10% of cases and is often accompanied by IUGR and chronic fetal hypoxia, which may lead to intrauterine death.[123] The early-onset PE is also associated with high dynamics of BP elevation, proteinuria, and maternal multiorgan complications. As a result, premature delivery is often necessary as the only means to stop further damage and resolve the symptoms. The SGA, preterm infants born to mothers with early-onset PE have a higher risk of neonatal complications, neurological disorder, as well as cardiovascular disease in adult life.[121] The late-onset PE mainly affects women with metabolic syndrome, obesity, and gestational diabetes. The onset of BP elevation usually occurs near the term and the fetal size is normal, although fetal macrosomia is not uncommon. Multiple gestation is a risk factor. Excessive placental weight and suboptimal degradation rate of placental metabolic products seem to be the key contributors in these cases.[123]

Unfortunately, even though both HT and other target organ complications resolve within the 6-week postpartum period in most cases, these women continue to have an increased risk of gestational HT in subsequent pregnancies, as well as an increased risk of cardiovascular disease later in life.

HT usually manifests clinically in the second half of pregnancy, leaving symptomatic treatment as the only treatment option, and delivery as the only curative treatment in severe cases. Therefore, it is vital that women at high risk are identified and prophylaxis is started in the first trimester.

6.3.1. Management of gestational hypertension

With the new-onset BP elevation after 20 gestational weeks the management should include the following:

- Hospital referral in patients with systolic BP of 160 mm Hg or higher and / or diastolic BP of 110 mm Hg or higher
- Monitoring and recording home BP – 2 measurements in the morning and 2 measurements in the evening (TABLE 5.1)
- Maternal biochemical blood and urine tests (TABLE 5.2)
- Fetal ultrasound in order to assess fetal growth

Outpatient monitoring can be considered in women with BP below 160/100 mm Hg, 24-hour urinary protein excretion of not more than 1 g, no other abnormal laboratory test findings and normal fetal growth. Hospital referral should be made in all other cases of PE.

Antihypertensive treatment with α-methyl-dopa or labetalol or extended release nifedipine should be initiated in women with uncomplicated gestational HT to achieve the target systolic BP of 110–140 mm Hg and the target diastolic BP of 80–85 mm Hg. If BP control proves insufficient, a 24-hour BP monitoring and an assessment by the consultant cardiologist / clinical HT specialist should be requested (see CHAPTER 5.7.4).[124,125]

Diuretics should not be used in women with preeclampsia and gestational HT, due to an increased risk of placental abruption. ACEIs and angiotensin II-receptor blockers are contraindicated during pregnancy.[126,127] Atenolol is not recommended during pregnancy due to its reported adverse effect on fetal growth.[128]

In an outpatient setting, antenatal appointments in women with gestational HT should be scheduled at least every 2 to 4 weeks. BP, body weight, urinalysis, and a full blood count should be assessed at each appointment, as well as a biochemistry panel in selected cases (TABLE 5.2, FIGURE 6.2).

Fetal ultrasound for fetal growth assessment should be performed at least once every 4 weeks. The diagnosis of IUGR with abnormal blood flow parameters in uteroplacental and fetoplacental circulation is an indication for inpatient admission and intensive fetal wellbeing surveillance (FIGURE 5.4)

In women with uncomplicated pregnancy-induced HT with no other concomitant maternal abnormality, normal laboratory test findings and normal fetal biometry, fetal wellbeing should be assessed with outpatient CTG once a week from 36 gestational weeks onwards (FIGURE 5.3).

Delivery in women with uncomplicated pregnancy-induced HT should be planned between 37 and 39 gestational weeks. The route and method of delivery should be determined based on obstetric factors and BP values.[129]

6.3.2. Management of preeclampsia

The diagnosis of PE is an indication for hospital referral and for the following actions to be taken (FIGURE 6.3):

- Maternal surveillance including:
  - BP measurement at least 4 times a day
  - Monitoring diuresis and protein excretion in 24-hour urine collection
  - Assessing for other symptoms, such as headaches, vision impairment, abdominal pain, nausea, and vomiting
  - Repeating laboratory blood tests (platelet count, liver function markers, and plasma creatinine level) at least twice a week

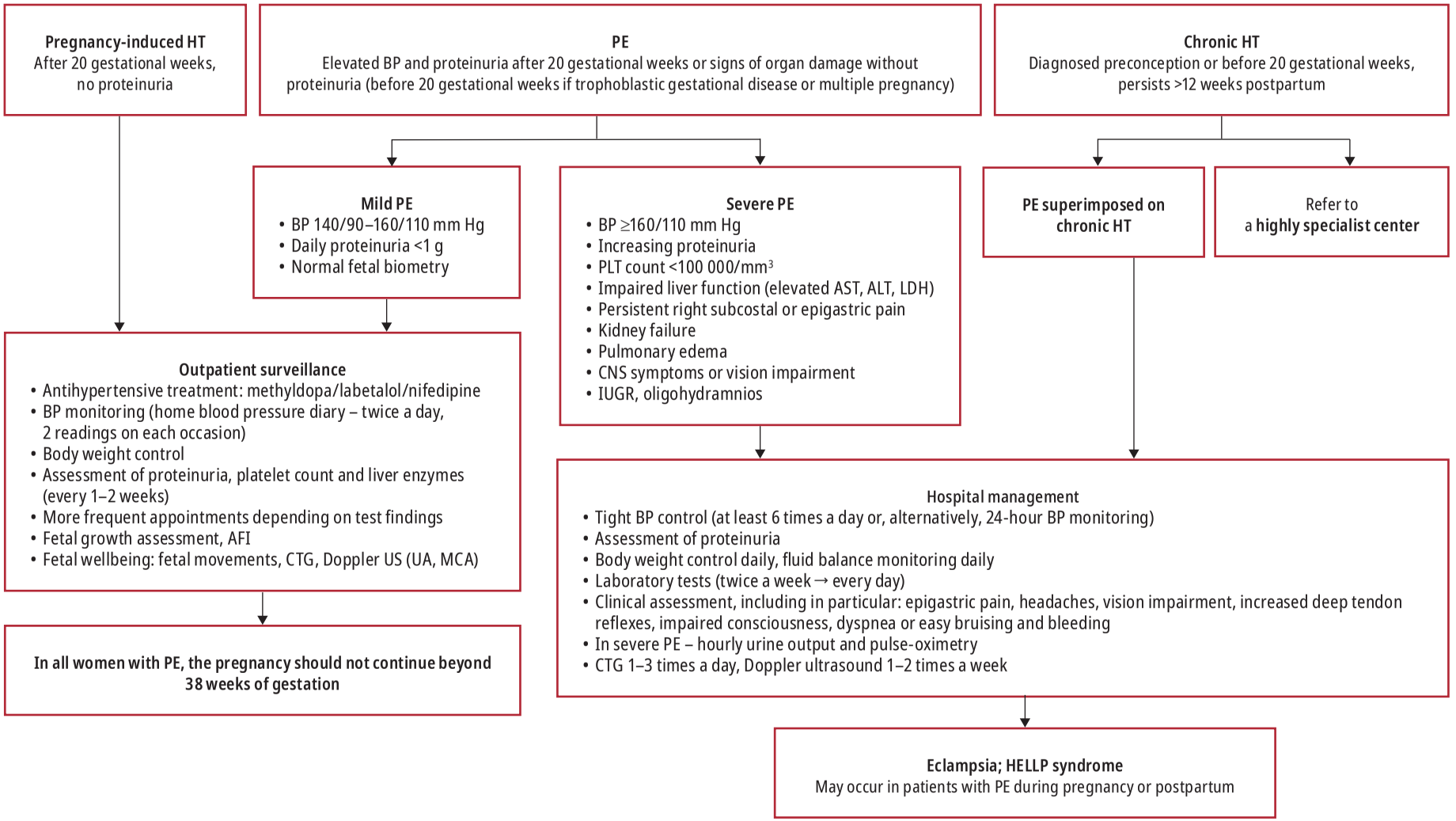

FIGURE 6.2 Perinatal care for women with gestational hypertension and preeclampsia

Abbreviations: AFI, amniotic fluid index; BP, blood pressure; CNS, central nervous system; CTG, cardiotocography; HT, hypertension; IUGR, intrauterine growth restriction; MCA, middle cerebral artery; PE, preeclampisa; PLT, platelet; UA, umbilical artery; US, ultrasound

Management of life-threatening emergencies in pregnant women with hypertension

Severe preeclampsia
Preeclampsia

34–37 gestational weeks
- **Delivery**
- Intrapartum, if clinically possible: magnesium sulphate ($MgSO_4$) (4–6 g IV within the first 30 minutes followed by an infusion at 1–2 g/h)

24–34 gestational weeks
- Conservative management with intensive maternal and fetal surveillance in a highly specialist perinatology center
- Course of steroids (24 mg/48 h – betamethasone)
- Magnesium sulphate ($MgSO_4$) (4–6 g IV within the first 30 minutes followed by an infusion at 1 g/h continued for up to 24 h)
- Emergency caesarean section on any maternal/fetaldeterioration

Before 24 gestational weeks
- The decision to end the pregnancy is made individually in each case; usually as soon as the mother is stable

Delivery
- The delivery method should be determined based on the current maternal and fetal condition, gestational age, and cervical ripening

Postpartum
- Aggressive treatment and monitoring
- Antihypertensive treatment – BP up to 150/100 mm Hg
- Seizure prevention – magnesium sulphate ($MgSO_4$) IV infusion continued for 24–48 h
- Thrombosis prophylaxis

Eclampsia
Tonic-clonic seizure with loss of consciousness not preceded by PE in 40% of cases; classed as eclampsia if at least 2 of the following occur within the next 24 hours: HT, proteinuria, thrombocytopenia, elevated AST

Anticonvulsant therapy
- Diazepam 10 mg IV (max. 30 mg),
- Magnesium sulphate ($MgSO_4$): 4–6 g IV initially, continued at 1–2 g/h

Immediate delivery **regardless of gestational age**

Postpartum
- Aggressive treatment and monitoring:
- Antihypertensive treatment – BP up to 150/100 mm Hg
- Eclamptic seizure prevention – magnesium sulphate ($MgSO_4$) IV infusion continued for 24–48 h
- Ensuring airway patency and good pulmonary ventilation, endotracheal suctioning, oxygen therapy
- Urine output monitoring
- Restoring electrolyte and acid-base balance
- Infection prevention and treatment
- Thrombosis prophylaxis

HELLP syndrome
H – hemolysis: LDH ≥600 IU/l and/or bilirubin >1.2 mg%
EL – elevated liver enzymes: AST ≥70 IU/l
LP – low platelets: PLT <100 000/mm^3
Hypertension is not an essential diagnostic criterion

After 34 gestational weeks
- Immediate delivery
- Intrapartum, if clinically possible: magnesium sulphate ($MgSO_4$) (4–6 g IV within the first 30 minutes followed by an infusion at 1–2 g/h)

27–34 gestational weeks
- Delivery within 48 hrs
- Course of steroids (24 mg/48h – betamethasone)
- Magnesium sulphate ($MgSO_4$) (4–6 g IV within the first 30 minutes followed by an infusion at 1 g/h continued for up to 48 hours)

Before 27 gestational weeks
- Watchful waiting attempt

Emergency delivery regardless of gestational age in the hospital where the patient has been admitted, upon the onset of:
- DIC
- Kidney failure
- Severe liver injury
- Premature placental abruption
- Biochemical marker deterioration
- Fetal deterioration

FIGURE 6.3 Management of life-threatening emergencies in pregnant women with hypertension

Abbreviations: BP, blood pressure; DIC, disseminated intravascular coagulation; IV, intravenous

Management of preeclampsia: recommendations	
Delivery in women with uncomplicated HT should be planned between 37 and 39 gestational weeks	Level A
A diagnosis of PE is an indication for inpatient admission as well as intensive maternal and fetal surveillance	Level C
In patients with PE diagnosed before 34 gestational weeks, if there is a risk of preterm delivery, a course of antenatal corticosteroid therapy for fetal maturation is recommended	Level A
Magnesium sulphate in an intravenous infusion to prevent seizures and for fetal neuroprotection is recommended in pregnant women with PE, if a delivery before 32 gestational weeks is needed	Level A
Emergency delivery at 37 gestational weeks or earlier is indicated in women with PE if there is no response to antihypertensive treatment, if there are signs of multi-organ damage or if there is a fetal life-threatening emergency	Level C

Abbreviations: HT, hypertension; PE, preeclampsia

Management of fibromuscular dysplasia in women at reproductive age and in pregnancy: recommendations	
Ultrasound of the kidneys and Doppler ultrasound of renal arteries are recommended in all women at reproductive age with HT.	Level C
If FMD is found in renal arteries of women at reproductive age, the remaining vascular beds should be imaged to detect FMD and aneurysms.	Level C
Treatment of clinically significant renal artery stenosis secondary to FMD is recommended prior to conception.	Level C
Doppler ultrasound of renal arteries is recommended in women after revascularization procedure due to renal artery stenosis secondary to FMD prior to conception in order to rule out restenosis.	Level C
Endovascular or surgical treatment of stenosis[a] and aneurysms, if indicated, is recommended prior to conception.	Level C

a In arteries other than renal

Abbreviations: FMD, fibromuscular dysplasia; HT, hypertension

- In women with severe HT, the intensive antihypertensive treatment aims at achieving BP of less than 160/110 mm Hg.[8] Once the BP values have stabilized, long-term treatment with oral antihypertensives should be started with the aim to achieve target BP (110–140 mm Hg/80–85 mm Hg) within a few consecutive days (CHAPTER 5.7)
- If protein excretion in 24-hour urine collection is above 3.5 g, anticoagulant prophylaxis using low-molecular-weight heparins should be started
- If a delivery before 32 gestational weeks is needed, magnesium sulphate should be administered in an intravenous infusion to prevent eclampsia and for fetal neuroprotection[130,131]
- If a delivery before 34 gestational weeks is needed, a short (48-hour) course of an antenatal glucocorticoid (betamethasone or dexamethasone in a total dose of 24 mg) therapy for fetal maturation should be administered[132]
- Fetal well-being surveillance including:
  - Fetal movement counting every day
  - CTG at least once a day
  - Fetal ultrasound for fetal growth assessment every 2 weeks
  - Additionally, if IUGR is confirmed, Doppler ultrasound should be performed in order to assess fetoplacental blood flow and BPP of the fetus. Depending on the findings, it should be repeated at least once a week

Timing of delivery in patients with PE should be determined on a number of factors including current maternal and fetal condition, gestational age, fetal position and cervical ripening.

Emergency delivery is indicated in women with PE:

- After 37 gestational weeks[133]
- Before 37 gestational weeks, if:
  - The systolic BP is above 160 mm Hg and diastolic BP is above 110 mm Hg, despite intensive antihypertensive treatment
  - There is a significant liver or kidney function impairment, hemolysis, thrombocytopenia, and disseminated intravascular coagulation
  - There is a new onset of eclampsia or other neurological symptoms including vision impairment and / or headaches
  - There are symptoms suggestive of premature placental abruption;
  - There is a fetal life-threatening emergency
  - There is intrauterine fetal death

Intensive maternal surveillance and antihypertensive treatment should be continued postpartum for at least 48 hours, due to the risk of postpartum eclampsia.

7. Preconception and antenatal management of secondary hypertension and selected comorbidities

7.1. Fibromuscular dysplasia

Fibromuscular dysplasia (FMD) typically affects renal arteries leading to HT. The second most common location is carotid and vertebral arteries. FMD can affect virtually any vascular bed. FMD affecting several vascular areas is not uncommon. FMD is also associated with a relatively high incidence of intracranial and abdominal aortic branches aneurysms.[134-136] The arterial walls of FMD-affected vessels are prone to dissection. Renal artery dissection may have detrimental clinical consequences, leading to the sudden onset of severe, refractory or malignant HT, AKI, and renal infarction. Dissection of other arteries, including coronary, carotid, and vertebral arteries, is also possible in patients with FMD.[137-141] The risk of PE in women with FMD is probably higher than in women without FMD; however, this data comes from 1 study in a small sample.[142]

7.1.1. Definition of fibromuscular dysplasia

FMD is an idiopathic, segmental, non-inflammatory, and nonatherosclerotic vascular disease leading to stenosis of small- and medium-sized arteries.[136,143]

7.1.2. Indications for the diagnosis of fibromuscular dysplasia

Patients with HT, especially women at reproductive age, should be assessed for renal artery stenosis secondary to FMD if any of the following indications are present:[3]

- Rapidly progressing HT or a poor BP control in patients with previously well-controlled HT
- Stage 3 HT (≥180/110 mm Hg), accelerated HT, or malignant HT
- Refractory HT
- A small kidney in patients without known uropathy
- Abdominal murmur without obvious features of atherosclerosis
- FMD affecting at least 1 other vascular bed
- Previous spontaneous artery dissection
- Family history of FMD
- Unexplained neurological incident

According to the latest American–European consensus, screening for renal artery stenosis secondary to FMD should be considered in all women with HT planning to conceive.[136] It is our view that Doppler ultrasound of renal arteries should be performed in every woman of reproductive age with HT. If FMD is found in renal arteries, the remaining vascular beds should be imaged to detect FMD and aneurysms.[3,136,144]

7.1.3. Diagnosis of renal artery stenosis secondary to fibromuscular dysplasia

A screening test which can be performed in pregnant women is Doppler ultrasound of renal arteries. All findings positive for FMD and negative for FMD but in patients with significant clinical suspicion should be confirmed with another imaging investigation.[3,136] Other diagnostic imaging of renal arteries with magnetic resonance angiography, computed tomography angiography, and digital subtraction angiography is limited in pregnancy, which is discussed in detail in CHAPTER 5.8.

7.1.4. Treatment of renal artery stenosis secondary to fibromuscular dysplasia

If revascularization procedure is indicated in women with HT and renal artery stenosis secondary to FMD, it should be performed prior to conception.[3,136] Patients with HT after revascularization or those without indications for revascularization should be monitored clinically, with biochemical tests and diagnostic imaging. In order to rule out restenosis, Doppler ultrasound of renal arteries should be performed in women after angioplasty due to renal artery stenosis secondary to FMD who plan to conceive.[143]

Antihypertensive treatment in women with FMD should follow principles presented in CHAPTER 5.7. A 75- to 100-mg dose of aspirin is considered reasonable in women with FMD to prevent thrombotic and thromboembolic events.[136] The dose of aspirin should be increased in pregnant women with FMD and high risk of PE according to the principles outlined in CHAPTER 6.2.

7.1.5. Vascular complications in women with fibromuscular dysplasia

Each woman with FMD in 1 vascular bed should be assessed for the presence of FMD in other arteries. Endovascular or surgical treatment of stenosis and aneurysms, if indicated, is recommended prior to conception. Surgical treatment of renal or splenic artery aneurysms should be considered for aneurysms over 2 cm in diameter. Due to the risk of aneurysm rupture during pregnancy, the latest American–European consensus indicates that surgical treatment of aneurysms smaller than 2 cm should be considered in women planning to conceive.[136]

A spontaneous coronary artery dissection (SCAD) occurs during or shortly after pregnancy in about 10% of cases, which has been discussed in CHAPTER 7.8.

7.2. Primary aldosteronism

7.2.1. Definition and prevalence

Primary aldosteronism (PA) is defined as endocrine HT caused by autonomous production of aldosterone. Based on this definition, PA is diagnosed by demonstrating that aldosterone levels in an individual are not affected by the factors that physiologically mediate its secretion.[145,146] The detailed guidance on the diagnosis and treatment of PA has been provided in the 2019 Recommendations of the Polish Society of Hypertension.[3]

Pregnancy is associated with physiological changes to the activity of the renin–angiotensin system[147-149]:

- Increased synthesis of angiotensin
- Increased secretion of renin and angiotensin-converting enzyme
- These changes lead to the increase in angiotensin II levels, which stimulates aldosterone secretion, resulting in elevated plasma aldosterone level, which can be up to 10-fold higher towards the end of pregnancy than at conception

Despite aldosterone level elevation, its action is antagonized by a simultaneous significant increase in the levels of progesterone, a competitive inhibitor of aldosterone at the mineralocorticoid receptor.[147-149]

Although PA is the most common cause of secondary HT, the number of case reports published to date discussing challenges of the management of PA in pregnancy is relatively low. This may be due to the competitive effect of progesterone, which acts as a natural MRA, favorably affecting PA in pregnancy.[147-149]

7.2.2. Clinical presentation

Clinical presentation of PA results from excessive autonomic aldosterone production and its

effect on kidneys and the cardiovascular system. The key symptoms are presented in TABLE 5. There are only limited data regarding the clinical presentation of PA in pregnant women. Classical symptoms, such as hypokalemia and dysregulated BP predominate the clinical presentation.[147-149]

Due to limited research data, it is impossible to develop recommendations regarding indications for the diagnostic assessment of PA in pregnant women, beyond those presented in the current guidelines.[145] PA should be particularly suspected in pregnant women with HT diagnosed before 20 gestational weeks, especially if concomitant with hypokalemia or incidental finding of an adrenal tumor.

7.2.3. Screening for primary aldosteronism

The key screening for PA involves the determination of the aldosterone-to-renin ratio (ARR). When assessing and interpreting ARR, it is necessary to restore normal potassium levels in patients with hypokalemia. Antihypertensive therapy should be modified and drugs which do not interfere with the renin–angiotensin–aldosterone system (RAAS) should only be used.[145] For the sake of a quick diagnosis, the ARR may be determined in pregnant women during antihypertensive treatment whilst considering the effect of treatment on renin and aldosterone levels. ARR is low in pregnant women due to a physiological upregulation of the RAAS; renin levels are normal or elevated and aldosterone levels are elevated. Therefore, low renin concentration is the key prerequisite for the diagnosis of PA in pregnant women. This indicates a stronger effect of aldosterone than the one of progesterone. However, it should be emphasized that the ARR may be normal in pregnant women with PA. Therefore, repeated testing for PA after pregnancy and breastfeeding should be considered in women with suspected PA and normal ARR.[147-149]

Management of suspected primary aldosteronism in women at reproductive age and in pregnancy: recommendations	
The determination of the ARR is recommended as a part of screening for PA in pregnant women.	Level C
Confirming the diagnosis of PA in pregnant women is not recommended.	Level C
MRI may be considered to assess adrenal structure in pregnant women with PA, but only in cases where surgical treatment is considered due to uncontrolled BP and potassium levels.	Level C
Replacing spironolactone with medications approved for use in pregnancy should be considered in women with PA planning to conceive.	Level C
Spironolactone is not recommended in women at reproductive age with PA who are pregnant or plan to conceive.	Level C
Surgery should be performed in women at reproductive age with unilateral PA either before or after pregnancy.	Level C
Surgery can only be considered in the second trimester, in women with unilateral adrenocortical adenoma and PA diagnosis confirmed with biochemical tests, in whom sufficient control of BP and potassium levels cannot be achieved with pharmacological treatment.	Level C

Abbreviations: ARR, renin-to-aldosterone ratio; BP, blood pressure; MRI, magnetic resonance imaging; PA, primary aldosteronism

7.2.4. Confirming the diagnosis of primary aldosteronism

In Poland, the saline suppression test and the captopril challenge test are the most commonly used to confirm the diagnosis of PA. In women at reproductive age, the assessment for PA, if indicated, should be done prior to conception. Confirming the diagnosis of PA in pregnancy is not recommended, due to a potentially harmful effect of hypervolemia during the saline suppression test and contraindications to the use of captopril.[147-149]

7.2.5. Primary aldosteronism subtyping

Once the diagnosis of PA has been made based on clinical presentation and biochemical assays, the nature and location of adrenal lesions should be determined. The differential diagnosis should include bilateral adrenal hyperplasia and adrenocortical adenoma, the 2 main causes of PA. According to the guidelines, CT and adrenal vein sampling should be performed as a part of PA subtyping.[145,150] As neither of these can be performed in pregnancy, MRI may be considered to assess adrenal structure, but only in cases where surgical treatment is considered due to uncontrolled BP and potassium levels. In other cases, PA subtype should be determined after the delivery.[147-149]

7.2.6. Treatment of primary aldosteronism

Surgical treatment is used in adrenocortical adenoma, whereas antimineralocorticoids are recommended in patients with bilateral adrenal hyperplasia. The initial daily dose of spironolactone should be 12.5 to 25 mg administered in a single dose; the lowest effective dose should be determined by gradual daily dose adjustments up to 100 mg or more. Due to a possible teratogenic effect of spironolactone shown in animal studies (rats and rabbits, but not mice) and a possible feminizing effect (by its direct action on androgen and progesterone receptors), spironolactone should not be used in pregnant women. It should be noted, however, that spironolactone has been commonly used for over 50 years and the number of its reported adverse effects in pregnancy is relatively low. There is one case report of ambiguous genitalia in the male fetus of a woman treated with spironolactone during early pregnancy, and a number of case reports where spironolactone treatment in pregnancy was not associated with detrimental fetal outcomes. A potentially adverse effect of spironolactone-induced natriuresis on intrauterine growth has been postulated.[2,147-149]

Eplerenone is a newer, selective MRA, which has a lower antiandrogenic effect and a lower

agonist effect on the progesterone receptor. Due to the shorter duration of action, eplerenone should be administered more often than once a day (starting from 25 mg twice a day) and in the dose twice as high as the one of spironolactone. However, eplerenone is not approved in the European Union for the treatment of PA. There is no evidence to support the adverse effect of eplerenone on the fetus. Furthermore, as mentioned above, eplerenone has no antiandrogenic effect. In the old FDA terminology, eplerenone had a pregnancy category B. Eplerenone may be considered in pregnant women with PA who have uncontrolled BP despite using other antihypertensives and/or uncontrolled potassium levels.[2,147] Some experts do not share this view, pointing out that there is an insufficient body of evidence to support the recommendation of eplerenone, which also has limited approved indications. They recommend spironolactone after the second trimester in patients with uncontrolled BP.[149]

However, the question of how to treat women with PA planning to conceive still remains unanswered. Replacing spironolactone with medications approved for use in pregnancy should be considered first, and when these prove ineffective, some experts suggest considering eplerenone.[147-149]

Surgery should be performed in women at reproductive age with unilateral PA either before or after pregnancy. Surgery can only be considered in the second trimester, in women with unilateral adrenocortical adenoma and PA diagnosis confirmed with biochemical tests, in whom sufficient control of BP and potassium levels cannot be achieved with pharmacological treatment.[147-149]

It should be noted that a sudden drop in progesterone levels may worsen the BP and potassium level control postpartum. Both spironolactone and eplerenone have been found in the breast milk of exposed mothers. Since the concentration of eplerenone in breast milk is believed to be negligible and too low to affect the infant, it should be considered in breastfeeding women who need treatment with MRAs, provided that the above limitations have been taken into account.[147-149]

7.3. Catecholamine-secreting tumors

7.3.1. Definition

Catecholamine-secreting adrenal tumors are referred to as pheochromocytoma, whereas other chromaffin cell-derived tumors, which may also be hormonally active, located outside the adrenal glands, are referred to as paraganglioma. They are jointly referred to as the PPGL (pheochromocytoma and paraganglioma).[151]

The prevalence of PPGL in pregnancy is estimated at 1 in 54 000 pregnancies. Despite advances in medical knowledge and availability of contemporary diagnostic methods, a large number of PPGLs are still only detected during pregnancy. An undiagnosed PPGL poses a significant risk to both the mother and fetus. Early diagnosis in pregnancy and appropriate treatment reduce the maternal and fetal mortality to less than 5% and less than 15%, respectively.[151-154]

Only a small portion of maternal catecholamines are transferred to fetal circulation. Furthermore, fetuses have high catecholamine clearance, which ensures their low levels in fetal circulation. Transient catecholamine peaks in women with PPGL may adversely affect the uteroplacental circulation causing vasoconstriction, which may lead to placental abruption and fetal hypoxia.[151-154] Antenatal care of women with PPGL should be provided by a multidisciplinary team with expertise and experience in the diagnosis and treatment of PPGL.

7.3.2. Clinical presentation

The proportion of noradrenaline to adrenaline secreted by PPGL determines its variable clinical presentation. The characteristic feature is paroxysmal symptoms, which may vary in severity and recur at variable intervals, as shown in TABLE 4.2. PPGL is most commonly symptomatic in pregnant women, and most patients (90%) experience symptoms before the delivery. PPGL should be suspected in pregnant women with refractory HT.[152]

Physical exercise, abdominal compression, ample meals, some medications (ephedrine, phenylephrine, corticotropin, phenothiazine, amphetamine, metoclopramide, tricyclic antidepressants, some anesthetics), psychological stress, and alcohol are known triggers. Catecholamine secretion from the tumor may also be induced by glucocorticoid administration. In pregnant women, symptom severity tends to increase with gestational age, as a result of tumor compression by the expanding uterus, fetal movements, uterine contractions, and abdominal palpation. Pheochromocytoma may also be asymptomatic (including normotension).[151-156]

The maternal and fetal risk is the highest during the perinatal period in patients with PPGL. Both maternal and fetal morbidity and mortality were shown to be the highest in the perinatal period, especially in patients with undiagnosed PPGL. It is associated with labor, anesthesia, abdominal palpation, and perinatal medications, including metoclopramide. It should be noted that severe symptoms associated with sudden-onset, excessive catecholamine release from the tumor may occur within hours after the trigger.[151-154]

7.3.3. Diagnosis of pheochromocytoma and paraganglioma

Plasma or urinary fractionated metanephrines (normetanephrine and metanephrine measured

Management of suspected pheochromocytoma and paraganglioma in women at reproductive age and in pregnancy: recommendations	
Plasma or urinary fractionated metanephrines are recommended as screening for PPGL.	Level C
Diagnostic investigations in order to determine the PPGL location are recommended in pregnant women with excessive catecholamine excretion confirmed in biochemical assays (elevated plasma or urinary fractionated metanephrines).	Level C
Metanephrines, measured either in blood or in urine, are recommended in women at reproductive age with the history of PPGL both preconception and as soon as the pregnancy is confirmed.	Level C
Biochemical, anatomical and functional tests are recommended in female carriers of PPGL predisposing gene mutation at the reproductive age prior to conception in order to rule out PPGL.	Level C
Phenoxybenzamine or doxazosin are recommended as a part of preoperative management.	Level C
Too aggressive BP lowering is not recommended in pregnant women with catecholamine-secreting PPGL. Methyldopa and labetalol are not recommended, either.	Level C
A surgical resection of abdominal catecholamine secreting PPGL should be considered in the second trimester.	Level C

Abbreviations: BP, blood pressure, PPGL, pheochromocytoma and paraganglioma

separately) are the most useful and the most sensitive biochemical tests for PPGL, also in pregnant women. The determination of free metanephrines levels in plasma offers the highest diagnostic sensitivity (sensitivity, 97%–99%; specificity, 82%).[157] The urinary adrenaline and noradrenaline excretion have a lower sensitivity and specificity, whereas vanillylmandelic acid and dopamine levels in urine, as well as blood catecholamine levels, are considered the least useful.[151,152]

Plasma or urinary fractionated metanephrines are recommended in women at reproductive age with the history of PPGL resection both preconception and as soon as the pregnancy is confirmed.

Biochemical, anatomical, and functional tests are recommended in female carriers of PPGL predisposing gene mutation at reproductive age prior to conception to rule out PPGL.

7.3.4. Treatment of pheochromocytoma and paraganglioma

Methyldopa and labetalol should not be used in pregnant women with PPGL, as they can aggravate the symptoms of PPGL and impair BP control. Furthermore, methyldopa may interfere with catecholamine metabolite assays.[151-154]

The treatment of choice in catecholamine-secreting PPGL is surgical resection. A surgical resection of abdominal catecholamine-secreting PPGL in a pregnant woman may only be considered in the second trimester, before 24 gestational weeks.[151-154] In women with PPGL diagnosed after 24 gestational weeks, pharmacological treatment continued until the delivery may be considered. The elective resection can then be performed either as a combined procedure with the Cesarean section or after the delivery. The Cesarean section seems to be the preferred delivery method in women with catecholamine-secreting PPGL, despite controversies due to limited evidence to support this recommendation. The timing and method of delivery should be determined individually for each patient by a multidisciplinary team.[151-154]

Preoperative management, which should aim at lowering the BP and the heart rate as well as achieving the control of paroxysmal HT and other circulating catecholamine-induced symptoms, is a vital stage. For this purpose, α-blockers – phenoxybenzamine (in doses increased gradually from 10 mg 2 times a day to the maximum daily dose of 1 mg per kg of body weight orally in 2–3 divided doses) or doxazosin (in doses increased gradually from 2 mg to the maximum daily dose of 32 mg orally in 1–2 divided doses) – are used for 2 to 3 weeks prior to surgery. As phenoxybenzamine passes through the placenta, neonatal surveillance for hypotension and respiratory failure is recommended during the first few days after birth. About 1% of phenoxybenzamine passes to human breast milk. The FDA considers phenoxybenzamine as the pregnancy category C drug. Due to its more favorable pharmacokinetic profile, shorter duration of action, and competitive binding to α-adrenergic receptors, doxazosin seems to be a more preferred drug. It is also considered the pregnancy category C drug.[151-154] Furthermore, the use of phenoxybenzamine is restricted in Poland, as it is only available through the direct import route.

If an α-blocker seems ineffective, a CCB (extended release nifedipine) can be added as the second antihypertensive drug. In patients with significant tachycardia, cardioselective β-blockers may be considered, but only after α-blockers have been used. Catecholamines secreted by PPGL act on both α- and β-adrenergic receptors. Using β-blockers without prior administration of α-blockers is contraindicated as it poses a risk to upregulate α-receptors, which may further increase the BP. Hypotension should be avoided in antihypertensive treatment of women with hormonally active PPGL. As both phenoxybenzamine and doxazosin pass through the placenta, too aggressive BP lowering should be avoided (BP >120/80 mm Hg) and fetal wellbeing surveillance should be continued throughout the treatment. As a part of preoperative management, it is important to address hypovolemia by ensuring an adequate supply of sodium and fluids to avoid orthostatic hypotension.[151-154]

Pregnant women with PPGL are at particularly high risk of hypertensive crisis due to the perinatal catecholamine surge. Paroxysmal HT secondary to catecholamine-secreting PPGL can be controlled with phentolamine administered intravenously, usually at the dose of 2 to 5 mg, and repeated if necessary.

Management of coarctation of the aorta in pregnancy: recommendations	
Antihypertensive treatment as in all pregnant women with HT should be considered in pregnant women with CoA and HT whilst avoiding placental hypoperfusion.	Level C
Cardiac follow-up in normotensive pregnant patients after CoA correction should be scheduled once every trimester. However, in women with significant CoA, cardiac follow-up should be scheduled at least once a month.	Level C

Abbreviations: CoA, coarctation of the aorta; HT, hypertension

7.4. Coarctation of the aorta

Coarctation of the aorta (CoA) accounts for 5% to 10% of all congenital heart defects. Despite the surgical correction, about 32.5% (25%–68%) of patients with the history of CoA develop HT, with the rate depending on the treatment method and timing.[158]

Even after a successful surgery, patients with CoA have a moderate/high risk of cardiovascular disease in pregnancy, as per the modified WHO classification of maternal cardiovascular risk (mWHO II/III).[2] Patients with CoA generally tolerate pregnancy well. Particular attention should be paid to patients with uncorrected CoA and those with persistent HT, residual CoA or aortic dilation. Bicuspid aortic valve in patients with CoA increases cardiovascular risk due to the risk of aortic dissection. A higher incidence of PE and higher miscarriage rate were reported in pregnant women with CoA.[2,159,160]

The ESC guidelines classify the corrected CoA as associated with a moderate mortality risk or a moderately high morbidity risk (mWHO II/III), and severe CoA in pregnancy (uncorrected or corrected) as associated with an extremely high risk of mortality or serious cardiovascular complications (mWHO IV).[2] There are no published data regarding the optimum medical treatment of pregnant women with CoA and HT. Antihypertensive treatment as in the general population should be considered in pregnant women with HT whilst avoiding placental hypoperfusion.[2] Therefore, antenatal care of pregnant women with CoA and HT should be provided by multidisciplinary teams in a highly specialist center.

In women with significant aortic dilation and a very high risk of aortic dissection, echocardiography should be performed once a month. Patients with low risk of aortic dissection and mild aortic dilation require echocardiographic assessment every 12 weeks.	Level C
Treatment with β-blockers throughout the entire pregnancy should be considered in patients with ascending aortic dilation.	Level C
In patients with the diameter of the aorta between 40–45 mm, vaginal delivery with spinal anesthesia and a shortened second stage should be considered. Delivery by Cesarean section may be considered in women with the diameter of the aorta between 40–45 mm and should be considered in women with the diameter of the aorta >45 mm.	Level C
Pregnancy is not recommended in patients with bicuspid aortic valve and the diameter of the ascending aorta >50 mm.	Level C

7.5. Ascending aortic dilation

The management of Turner syndrome, Marfan syndrome, and Ehlers–Danlos syndrome type 4 has been discussed in detail in the 2018 ESC guidelines.[2] Ascending aortic dilatation occurs most commonly in women with HT as a consequence of bicuspid aortic valve (BAV) or as a consequence of chronic HT.

7.5.1. Bicuspid aortic valve

The most common site of ascending aortic dilatation in patients with BAV is above the sinotubular junction. The risk of aortic dissection is low and depends on the diameter of the ascending aorta, aortic valve morphology, and potential concomitant CoA.[161] Pregnancy is not recommended in patients with BAV and the diameter of the ascending aorta larger than 50 mm prior to the ascending aortic replacement.[2] CoA should be ruled out in women with BAV and HT.

7.5.2. Management of ascending aortic dilation

Regular BP monitoring is a key element of antenatal care. Monitoring the aortic diameter with echocardiography is necessary both throughout the pregnancy and up to 6 months postpartum. In women with significant aortic dilation and a very high risk of aortic dissection, echocardiography should be performed once a month.[2] Patients with low risk of aortic dissection and mild aortic dilation require echocardiographic assessment every 12 weeks. If another imaging technique is necessary, plain (non–contrast-enhanced) MRI is recommended.

According to the ESC guidelines, treatment with β-blockers throughout the entire pregnancy should be considered in patients with ascending aortic dilation secondary to congenital aortic anomalies (including BAV).[2]

Treatment with β-blockers started during pregnancy should also be continued postpartum. The delivery method should be determined based on the degree of ascending aortic dilation. In patients with the diameter of the aorta between 40 to 45 mm, vaginal delivery with spinal anesthesia and a shortened second stage should be considered. Delivery by Caesarean section may be considered in women with the diameter of the aorta between 40 to 45 mm and should be considered in women with the diameter of the aorta larger than 45 mm.[2]

7.6. Sleep disorder

Objective studies of human circadian rhythms clearly indicate that pregnancy is associated with impaired sleep quality, especially in the third trimester. Sleep in late gestation is significantly fragmented (cortical arousal and awakening), which results in a disarray of successive sleep stages, as well as shortened slow-wave and rapid eye movement sleep.[162]

Non-invasive treatments (positional therapy, mandibular advancement devices, CPAP) are recommended in pregnant women with diagnosed OSA.	Level B
For the sake of fetal wellbeing, weight loss is not recommended in the treatment of OSA in obese pregnant women. Myorelaxant agents, including hypnotic and analgesic drugs, are prohibited in pregnancy.	Level C

Abbreviations: CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea

7.6.1. Epidemiology of sleep-disordered breathing in pregnancy

The incidence of sleep-disordered breathing (SDB) in women at reproductive age is the lowest in the general population of adult women and men.[163] The incidence of obstructive sleep apnea (OSA) in pregnancy depends on gestational age. OSA is estimated to affect several percent of pregnant women during the first trimester, as compared with almost 30% during the third trimester.[164] Diagnostic criteria of SDB assumed for adult populations also apply to pregnant women. Based on them, mild apnea, defined as apnea–hypopnea index (ie, the mean number of apnea and hypopnea events per hour of sleep) of less than 15 is diagnosed the most commonly.[164]

7.6.2. Pathogenesis of obstructive sleep apnea in pregnancy

It seems that hormone-dependent fluid retention is the key mechanism responsible for the increased risk of sleep apnea in pregnant women. The direct consequence of hypervolemia is soft tissue edema affecting the upper respiratory tract, which narrows the airway lumen.[165-167]

7.6.3. Maternal and fetal complications of obstructive sleep apnea

Patients with apnea have an increased risk of gestational diabetes, pregnancy-induced HT, and PE. As a result, preterm delivery is more likely in women with SDB. On the other hand, there is no clear evidence to suggest that untreated maternal sleep apnea causes IUGR. However, it has been demonstrated that SDB in pregnant women is an independent risk factor for neonatal HF and cardiorespiratory failure, which require postnatal resuscitation and/or neonatal intensive care.[168,169]

7.6.4. Diagnostic management, diagnostic criteria, and classification of obstructive sleep apnea in pregnancy

Diagnosis and assessment of the severity of OSA should be based on objective evaluation with cardiorespiratory polygraphy or polysomnography.[170,171]

7.6.5. Treatment of obstructive sleep apnea in pregnancy

The current guidelines do not recommend specific treatment of SDB in pregnant women. A few studies have shown partial efficacy of behavioral treatments in sleep apnea including complete alcohol abstinence, a complete hypnotic and narcotic analgesic abstinence, and sleeping in a lateral decubitus position (which is also beneficial as it lessens the effect of the inferior vena cava compression). However, weight loss is not recommended in obese pregnant women. Such interventions as mandibular advancement devices and the continuous positive airway pressure devices offer better efficacy.

7.7. Kidney disease

7.7.1. Chronic kidney disease

CKD significantly increases the risk of HT in pregnant women.[172] HT affects about 20% to 50% of pregnant women with CKD and the prevalence of HT increases with the severity of CKD.[173] Data regarding distinctive pathophysiology of HT in pregnant women with kidney disease are derived from studies in experimental animals and studies in small groups of pregnant women with CKD. They point to the kidney maladaptation to pregnancy-induced physiological changes, which include about 50% increase in glomerular filtration, as the main cause of HT in pregnant women with CKD. As a result, sodium retention and hypervolemia occur, which leads to HT.[174]

It can be assumed that, as it is true for the CKD in nonpregnant women, the pathogenesis of HT also involves hyperactivity of the sympathetic nervous system and the RAAS.[175] With the increasing severity of CKD, the risk of HT and associated maternal and fetal complications increases. At the same time, maternal and perinatal outcomes are likely to be worse. PE, eclampsia, prematurity, and LBW are more common in these women. Furthermore, neonatal intensive care is more likely to be required and the perinatal mortality rate is higher.[176] Bateman et al[177] found a higher risk of miscarriage, PE, IUGR, and prematurity in women with CKD concomitant with HT than in women with normal BP during pregnancy.

The eGFR cannot be calculated in pregnant women with commonly used formulas, such as the Modification of Diet in Renal Disease formula or the Chronic Kidney Disease Epidemiology Collaboration formula.[6] Therefore, the severity of CKD in pregnant women is primarily based on the preconception eGFR values, whereas the clinical observation during pregnancy is based on the creatinine serum level measurements.[178]

Upon a positive pregnancy test in a woman with CKD, it is necessary to assess the risk factors of maternal and fetal complications. It is necessary to determine the stage of kidney disease preconception, urinary protein (preferably albumin) excretion in a 24-hour urine collection, as well as serum levels of urea, creatinine, uric acid, and glucose. Kidney function tests (serum levels of urea and creatinine), as well as urinary protein/albumin excretion assays, should be repeated at least once a month.[176] Tight BP monitoring (home BP – 2 measurements in the morning and 2 measurements in

It is recommended to reduce the dose of methyldopa (by extending the interval between the doses) in pregnant women with an impaired renal function depending on the eGFR.	Level C
Diuretics (especially loop diuretics) may be considered in patients with very severe edema, mainly secondary to nephrotic syndrome.	Level C
Starting aspirin treatment at a daily dose of 100–150 mg before 16 gestational weeks is recommended in pregnant women with CKD.	Level C
Folic acid supplementation at a daily dose of 5 mg is recommended in pregnant women with CKD.	Level C
Limited protein intake is not recommended in pregnant women with CKD.	Level C
Maintaining hemoglobin levels within the range of 10–11 g/l is recommended in pregnant women with CKD.	Level C
It is recommended to start renal replacement therapy (preferably hemodialysis) with maternal serum urea level of about 100 mg/dl (15 mmol/l).	Level C

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

the evening) is necessary for pregnant women with CKD. A 24-hour ambulatory BP monitoring should also be considered.[176] Target BP in pregnant women with CKD is similar to the target BP in pregnant women without CKD, that is, the target diastolic BP in pregnant women with HT and CKD should be 81 to 85 mm Hg.[65,67,68] The choice of antihypertensive drugs in pregnant women with CKD should be informed by the same principles as in pregnant women without kidney disease. However, antihypertensive drugs with known nephroprotective effect recommended in nonpregnant women, such as ACEI, ARBs, and MRAs, are prohibited in pregnant women with CKD. Since methyldopa is largely excreted by the kidneys, the Summary of Product Characteristics states that the dose should be reduced in patients with impaired renal function. It is recommended that with the eGFR between 60 and 89 ml/min/1.73 m^2, the interval between the doses be extended to 8 hours, with the eGFR between 30 and 59 ml/min/1.73 m^2 the interval between the doses be extended to 8 to 12 hours, and with the eGFR of less than 30 ml/min/1.73 m^2 the interval between the doses be extended to 12 to 25 hours. Dialysis removes methyldopa; therefore, a booster dose of 250 mg is recommended to prevent BP elevation after the procedure. As an exception, diuretics may be indicated in pregnant women with CKD (especially in advanced stages of the disease). Loop diuretics may be considered in very severe edema, mainly secondary to nephrotic syndrome.[30] However, as the first line intervention in peripheral edema, the patients should be advised to rest with their legs up and to use elastic stockings.[172] Diuretics are contraindicated in PE due to hypovolemia.[175] Pregnant women with CKD should be started on aspirin at a daily dose of 100 to 150 mg before 16 gestational weeks. This reduces the risk of PE, prematurity, and IUGR.[179] Limited protein intake is not recommended in pregnant women with CKD, especially those on dialysis, whose daily protein intake should range between 1.5 and 1.8 g per kg of body weight.[175,180] However, there are no recommendations as to the salt intake in pregnant women with HT and CKD. Anemia is a symptom of CKD, and may additionally increase in severity in pregnancy, due to a physiological increase in plasma volume, which is disproportionate in relation to other blood elements. It may also be associated with iron, vitamin B_{12}, and folic acid deficiency.[181] Erythropoiesis-stimulating agents may be considered in pregnant women with CKD after normalizing iron levels, initially with oral iron supplements.[182] Intravenous formulations are also safe in pregnant women, although one should bear in mind that they may cause an allergic reaction and stimulate uterine contractions. Hemoglobin levels in pregnant women should be maintained within the range of 10 to 11 g/l. However, erythropoiesis-stimulating agents should be used with great caution in pregnant women, as they may contribute to the BP increase, especially when the treatment was too aggressive and the hemoglobin level increased too rapidly or above the recommended value, that is, 12 g/l.[183]

Renal replacement therapy is an important treatment aspect in pregnant women with CKD, including those with concomitant HT. Further kidney function deterioration is seen in some patients with CKD during pregnancy. Indications for hemodialysis in a pregnant woman are determined based on clinical assessment (eg, hypervolemia resistant to medical management with the resulting HT) and the laboratory test findings (serum urea, potassium, and bicarbonate levels). Elevated serum urea level is the most common indication for hemodialysis.[181] It is now believed that the hemodialysis should be started in pregnant women with serum urea level of about 100 mg/dl (15 mmol/l). The minimum duration of hemodialysis in patients with no residual diuresis, both those started on hemodialysis during pregnancy and those who have already been on hemodialysis at conception should be 36 h/wk. It is necessary to maintain serum urea levels of 60 to 90 mg/dl (10–15 mmol/l) prior to the next dialysis. Such intensive renal replacement therapy requires very tight electrolyte control (at least once a week) with potassium, magnesium, calcium, and phosphorus supplementation. Using 1.5 mmol/l calcium dialysate is recommended. It is also advisable to supplement calcium and vitamin D.[15] Folic acid supplementation at a daily dose of 5 mg, multivitamin supplements as well as avoiding smoking and alcohol consumption are recommended from the beginning of pregnancy.[175] It is suggested not to start renal replacement therapy in pregnant women with peritoneal dialysis and to adopt a personalized approach in patients previously treated with peritoneal analysis. The conversion to hemodialysis seems to be particularly indicated in patients with low residual diuresis, fluid retention tendency, and multiple

pregnancies.[184] In the light of reports of successful pregnancy outcomes in patients on peritoneal dialysis, peritoneal dialysis continuation can be considered in patients with significant residual diuresis.[174]

7.8. Arrhythmia

7.8.1. Epidemiology

Palpitations and arrhythmia are common clinical problems in pregnant women, which do not require treatment in most cases.[185] The incidence of arrhythmia in pregnancy is closely linked to comorbidities. Supraventricular tachycardia occurs in 0.02% to 1.3% of pregnant women without structural heart disease. However, in women with congenital heart defects, ventricular and supraventricular arrhythmia, which require treatment may occur in 5% to 15% of patients.[186-188] Premature ventricular contractions, usually originating from the ventricular outflow tract, occur in more than 50% of patients referred for 24-hour electrocardiography (ECG) due to heart palpitations. In most cases, they do not require antiarrhythmic treatment and usually resolve after delivery.[189]

Alongside extrasystoles, atrial fibrillation (AF) and supraventricular tachycardia (SVT) are the most common arrhythmias in pregnant women.[2] The increased prevalence of AF is associated with maternal older age, HT, diabetes, obesity, and congenital heart defects.[185,186]

7.8.2. Pathogenesis of arrhythmia in pregnancy

Pregnancy is associated with increased blood volume and cardiac output, which reach 150% of their baseline values around 32 gestational weeks. The increase in cardiac output in the first half of pregnancy is largely due to an increase in stroke volume and in the second half of pregnancy due to an increased heart rate.

Maternal cardiac rotation by 15 to 20 degrees to the left causes changes to the ST segment and T wave. However, usually, there is no problem to confirm the sinus rhythm using the standard diagnostic criteria.[2] The heart rate of a pregnant woman increases by 10 to 15 beats per minute as compared with the nonpregnant state, which is a physiological phenomenon, but it may hinder the diagnosis of HF or pulmonary embolism.

Increased stress to the maternal heart can lead to arrhythmia, especially in patients with organic heart disease. The new onset of arrhythmia in pregnancy occurs in approximately one-third of affected pregnant women. Exacerbation of preexisting arrhythmia in pregnancy occurs in another 30% to 40% of affected pregnant women.[2] Arrhythmia in pregnancy significantly increases the risk of gestational and perinatal complications and may lead to the development of fetal congenital anomalies.[190]

7.8.3. Diagnosis of arrhythmia before conception and in pregnancy

The ESC guidelines recommend ECG and echocardiography as the minimum assessment possibly complemented with a stress test to assess the risk in women with a history of cardiac or aortic disease planning to conceive.[186] The same guidelines recommend the ECG Holter monitoring in pregnant women with palpitations, history of supraventricular, and ventricular tachycardias as well as AF or atrial flutter.

Women with arrhythmia present both before conception and in pregnancy should be actively assessed for congenital cardiomyopathy and channelopathies. Organic heart disease must be ruled out in each case of new-onset ventricular tachycardia in pregnancy.[191] Postpartum cardiomyopathy should be ruled out in patients with ventricular tachycardia with the onset within the last 6 gestational weeks or postpartum.[171]

The ESC experts have also proposed the scope of perinatal care and surveillance in patients with arrhythmias, based on their stratification to one of the 3 risk groups.[186]

7.8.4. Treatment

Sinus tachycardia

Sinus tachycardia is a frequent problem in pregnancy. The current European guidelines on the management of arrhythmias in pregnancy do not provide a clear treatment algorithm. The above guidelines do not recommend routine use of β-blockers in pregnant women with asymptomatic or even symptomatic sinus tachycardia. Considering the benefits and risks of β-blockers seems reasonable in pregnant women with symptomatic sinus tachycardia. It should be noted that ivabradine is contraindicated in pregnancy.

The ESC guidelines recommend ECG and echocardiography as the minimum assessment possibly complemented with a stress test to assess the risk in women with a history of cardiac or aortic disease planning to conceive.	Level C
The ECG Holter monitoring is recommended in pregnant women with a history of ventricular tachycardia, atrial fibrillation and / or flutter or heart palpitations.	Level C
Consulting clinical data from Table 7 of the 2018 ESC guidelines, and should the information be missing, checking the online database www.safefetus.com is recommended prior to starting pharmacological treatment of a pregnant woman.	Level C
β-Blockers are recommended during pregnancy and postpartum in women with LQTS or CPVT.	Level C
Ablation guided by electroanatomical mapping in an experienced center should be considered in women with poorly tolerated or refractory supraventricular tachycardia.	Level C
Routine use of β-blockers in pregnant women with sinus tachycardia is not recommended, and ivabradine is contraindicated in pregnancy.	Level C
Non-vitamin K oral anticoagulation drugs (apixaban, dabigatran, rivaroxaban) are contraindicated during pregnancy.	Level C

Abbreviations: CPVT, catecholaminergic polymorphic ventricular tachycardia; ECG, electrocardiography; ESC, European Society of Cardiology; LQTS, long QT syndrome

A

Management of supraventricular tachycardia or AF in pregnant women based on the ESC 2018 guidelines

Recommendations for the management of supraventricular tachycardia in pregnant women (intravenous medications)

- In order to quickly stop an episode of SVT, the maneuver stimulating the vagus nerve is recommended, followed by intravenous administration of adenosine
- An intravenous administration of a selective β1-blocker should be considered to immediately stop an episode of SVT
- Ibutilide or flecainide[a] may be considered in order to stop AFL or AF in hemodynamically stable patients without organic heart disease
- In each case of paroxysmal supraventricular tachycardia in hemodynamically unstable patients or those with accessory pathway-mediated AF, immediate cardioversion to sinus rhythm is recommended

B

Prevention of SVT and AF in pregnant women based on the ESC 2018 guidelines

Long-term management of supraventricular arrhythmia in pregnant women

- Selective β1-blockers or verapamil[b] are recommended in SVT prevention in patients without ventricular pre-excitation in ECG
- Selective β-blockers are recommended to control ventricular rhythm in patients with AT and AF
- Flecainide[c] or propafenone[c] are recommended to prevent SVT in patients with WPW syndrome
- Flecainide[c], propafenone[c] or sotalol[d] should be considered in patients with SVT, AT and AF, if AV nodal blocking drugs prove ineffective
- With no response to β-blockers, digoxin[b] or verapamil[b] should be considered to control ventricular rhythm in patients with AT and AF
- Ablation guided by electroanatomical mapping in an experienced center should be considered in women with poorly tolerated or refractory SVT

C

Management of ventricular tachycardia in pregnant women based on the ESC 2018 guidelines

Emergency management of ventricular arrhythmia in pregnant women (intravenous drugs)

- Immediate cardioversion to sinus rhythm is indicated in each patient with VT, whether hemodynamically stable or unstable
- In order to terminate sustained, monomorphic VT in a hemodynamically stable patient, a β-blocker, sotalol[e], flecainide[d], procainamide or overdrive stimulation should be considered

FIGURE 7.1 A–C – Management of arrhythmia in pregnancy

D

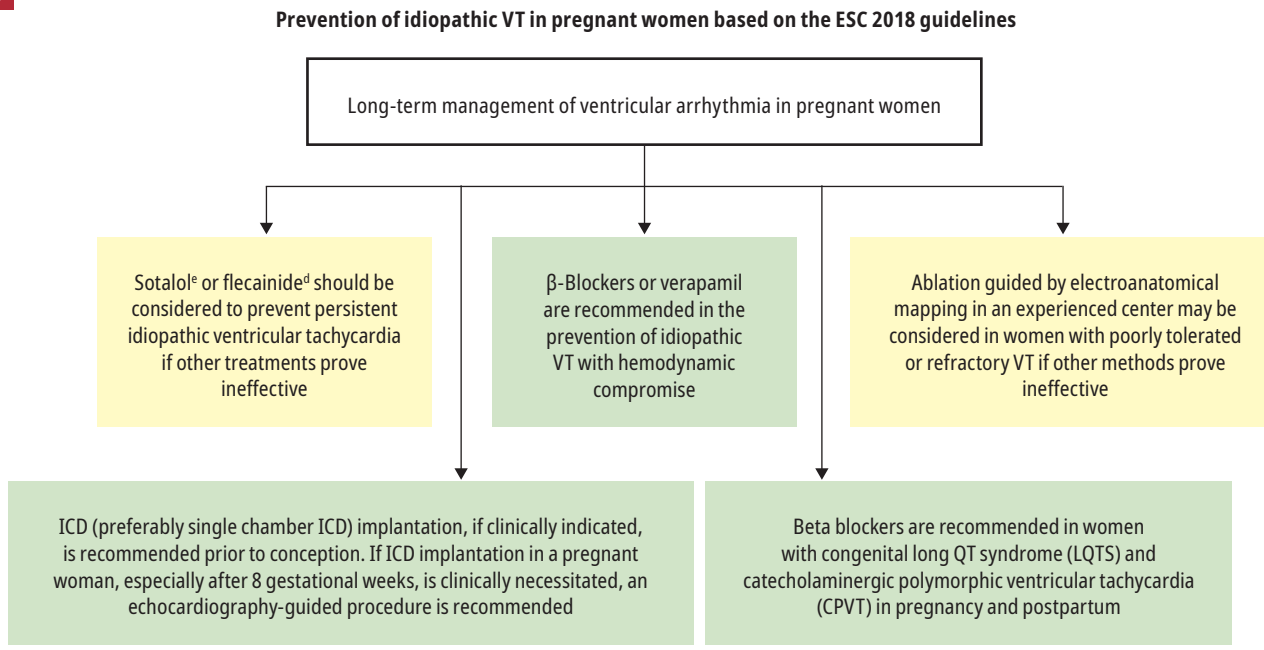

FIGURE 7.1 **D** – Management of arrhythmia in pregnancy

a Cardioversion in patients with atrial fibrilation or AFL should generally be preceded by antithrombotic treatment;

b AV nodal blocking drugs should not be used in patients with ventricular pre-excitation or atrial fibrillation with ventricular pre-excitation;

c In patients with definitive AT, flecainide and propafenone should be used in combination with AV nodal blocking drugs. Rule out: organic heart disease, reduced EF and left bundle branch block

d Class III (according to the Vaughan-Williams classification) antiarrhythmic drugs should not be used in patients with long QT syndrome

e Rule out: organic heart disease, reduced EF and left bundle branch block

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; ECG, electrocardiography; ESC, European Society of Cardiology; ICD, implantable cardioverter-defibrillator; SVT, supraventricular tachycardia; VT, ventricular tachycardia; WPW, Wolff–Parkinson–White syndrome

Emergency and long-term treatment

Whereas an emergency restoration of normal heart rhythm with cardioversion, intravenous administration of adenosine or a β-blocker is fairly safe for the fetus, long-term treatment with antiarrhythmic drugs to prevent arrhythmic episodes may pose a significant clinical problem.[192]

The newest ESC guidelines clearly recommend consulting Table 7 of the 2018 ESC guidelines ("Drug and safety data"), and should the information be missing, checking the online database www.safefetus.com prior to starting pharmacological treatment of a pregnant woman.

It should be noted that non–vitamin K oral anticoagulants are contraindicated during pregnancy.[193]

Women with congenital long QT syndrome and catecholaminergic polymorphic ventricular tachycardia have a high risk of perinatal and postpartum arrhythmia, which can be reduced with β-blockers.[194]

Ablation guided by electroanatomical mapping in an experienced center should be considered in women with poorly tolerated or refractory SVT. Ablation should be at least considered in young women with paroxysmal arrhythmia (SVT, VT, AF) prior to conception.

The detailed management of arrhythmias in pregnant women has been explained in the 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy[2] and in FIGURE 7.1A–7.1D.

7.9. Acute coronary syndromes

7.9.1. Etiology and epidemiology

The risk of myocardial infarction in pregnancy is 3- to 4-fold higher than in age-matched nonpregnant women.[2] Risk factors include maternal age, HT, diabetes, obesity, smoking, hyperlipidemia, eclampsia, multiple gestation, thrombophilia, cocaine misuse, and perinatal hemorrhage or infection.[2] SCAD is the most common cause of the prenatal and perinatal acute coronary syndrome. Less common findings are atherosclerosis, coronary artery thrombosis, normal coronary arteries or coronary vasospasm.[195] Relatively high rates of pregnancy-associated SCAD (P-SCAD) were reported in the past. The more recently reported prevalence of P-SCAD is about 10% of all SCADs. In a large Canadian register of 4.4 million pregnant women, the prevalence rate of P-SCAD was estimated at 1.8 cases per 100 000 pregnancies.[196]

7.9.2. Pathogenesis

Two potential mechanisms of P-SCAD development are currently postulated: noniatrogenic and nontraumatic intimal tear or spontaneous vasa vasorum rupture. In both mechanisms, intramural hemorrhage creates a false lumen and a separation of the coronary arterial wall, which narrows the true lumen and disturbs the blood flow.[197,198] Based on the reported P-SCAD cases, potential mechanisms contributing to coronary artery dissection during pregnancy have been identified. These include increased cardiac output (secondary to increased blood volume and heart rate) and elevated progesterone and estrogen levels leading to loss of normal corrugation of elastic fibers, impaired collagen synthesis and structural weakening of the vascular wall, especially the tunica media.[199] In a relatively high percentage of women with SCAD, FMD affects other vascular beds as well. Therefore, extensive diagnostic investigation of FMD is necessary (see CHAPTER 7.1).

7.9.3. Patient characteristics and clinical presentation

P-SCAD typically occurs during the early postpartum and less frequently in the third trimester.[200] The clinical presentation of SCAD includes the symptoms of an acute coronary syndrome, mainly chest pain, less often dyspnea, nausea, or abdominal pain. An electrocardiogram is in keeping with ST-segment elevation myocardial infarction (STEMI; 57%–85% of cases) or non–ST-segment elevation myocardial infarction (NSTEMI; 15%–43% of cases).[2,200,201] P-SCAD may cause cardiogenic shock or cardiac arrest. Compared with nonpregnant patients with SCAD, the left main stem coronary artery dissection, dissection of the proximal coronary artery segments, and multivessel involvement are more common coronary angiography findings in pregnant women. Conventional risk factors for myocardial infarction are only seen in about one-third of patients.[201]

7.9.4. Diagnosis

The diagnosis of SCAD is made based on clinical presentation and coronary angiography findings. Five types of SCAD have been identified based on angiographic findings: type 1 with visible false lumen; type 2A with visible long segmental stenosis and a normal artery segment distally to the stenosis; type 2B with visible extensive stenosis, which reaches the distal tip; type 3 with stenosis mimicking atherosclerosis; and type 4 with distal coronary artery closure. In some cases, intravascular ultrasound or optical coherent tomography of coronary arteries are additionally needed to confirm the diagnosis of SCAD.[197,198]

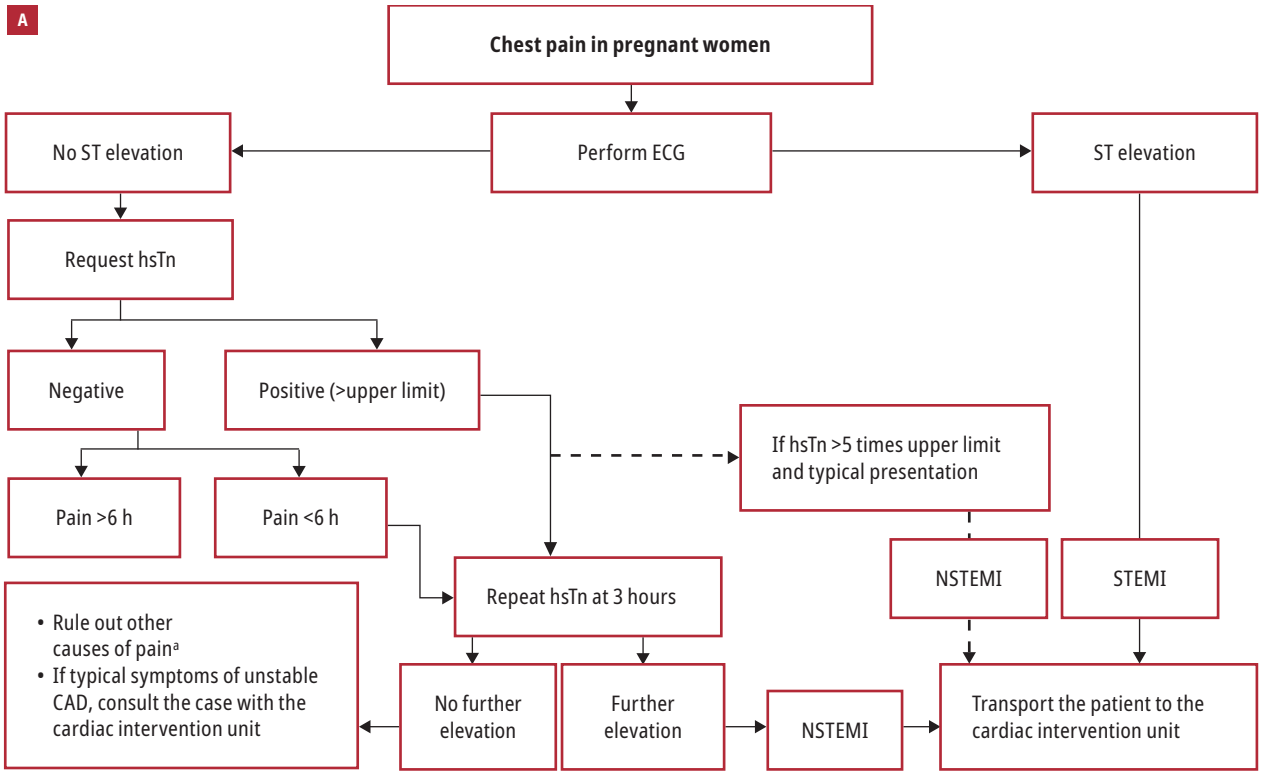

FIGURE 7.2 **A** – Management of chest pain in pregnant women

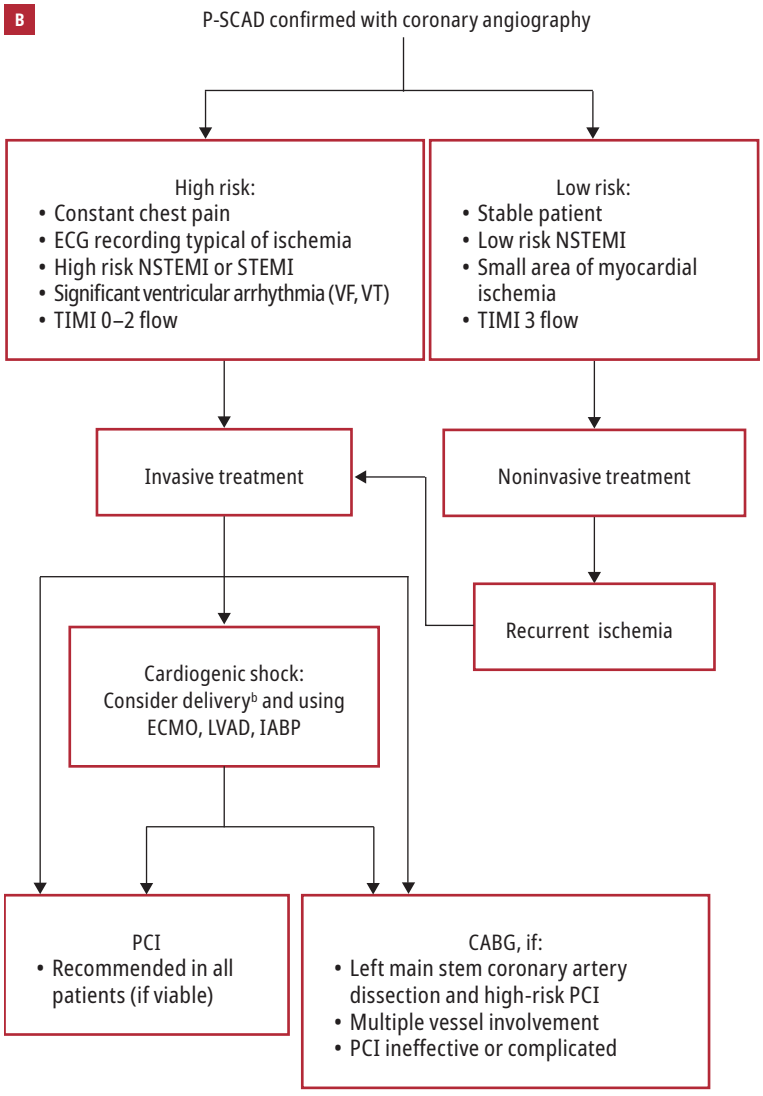

FIGURE 7.2 **B** – Treatment algorithm for the pregnancy-associated spontaneous coronary artery dissection;

a For example, pulmonary embolism, aortic dissection, gastroesophageal reflux disease, muskuloskeletal disorder, pericarditis or myocarditis

b Multidisciplinary team management including consultant cardiologist, consultant gynecologist, consultant neonatologist, consultant anesthesiologist and consultant cardiac surgeon

Abbreviations: CAD, coronary artery disease; ECG, electrocardiography; hsTn, high-sensitivity troponin; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; P-SCAD, pregnancy associated with spontaneous coronary artery dissection

7.9.5. Treatment

The diagnostic management of chest pain in pregnant women is similar to that in nonpregnant women and is shown in FIGURE 7.2A. The management of myocardial infarction in pregnant women is not different from that in other patients with myocardial infarction. According to the 2018 ESC Guidelines, primary percutaneous coronary intervention (PCI) is recommended as the preferred reperfusion therapy in pregnant women with STEMI (class of recommendation I, level of evidence C) or high-risk NSTEMI (class of recommendation IIa, level of evidence C). In stable, low-risk NSTEMI, a noninvasive approach should be considered (class of recommendation IIa, level of evidence C).[2] However, given the predominant nonatherosclerotic etiology of acute coronary syndromes (P-SCAD), the optimum management strategy for patients with P-SCAD needs

ECG and a serum troponin test are recommended in a pregnant woman with chest pain.	Level C
Primary percutaneous coronary intervention (PCI) is recommended as the preferred reperfusion therapy in pregnant women with ST-elevation myocardial infarction (STEMI).	Level C
Invasive treatment should be considered in pregnant women with high-risk non-ST-elevation myocardial infarction (NSTEMI).	Level C
Invasive treatment may be considered in pregnant women with low-risk non-ST-elevation myocardial infarction (NSTEMI).	Level C
The non-invasive treatment is recommended the most appropriate approach in clinically stable patients with SCAD ACS with a patent true lumen or a short-segment obstruction.	Level C
Invasive treatment (preferably percutaneous coronary intervention) should be considered in clinically unstable patients with SCAD ACS and long-term myocardial ischemia.	Level C
Surgery (coronary artery bypass grafting) should be considered in patients with SCAD ACS, with the left main stem coronary artery dissection (as long as not proceeding with immediate PCI is a viable option taken their clinical presentation), multiple vessel involvement, as well as those after ineffective PCI or upon onset of PCI complications which necessitate emergency surgical intervention.	Level C
Abdominal shielding with X-ray protective clothing and optimization of ionizing radiation parameters (radiation field, FPS) are recommended during coronary angiography and percutaneous coronary intervention.	Level C
Dual antiplatelet therapy is recommended in patients after stenting.	Level C
Breastfeeding is not recommended in mothers who take antiplatelet agents other than aspirin.	Level C

Abbreviations: ECG, electrocardiography; FPS, frame per second; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SCAD ACS, spontaneous coronary artery dissection in acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction

The evaluation of LVEF during transthoracic echocardiography and serum BNP or NT-proBNP assay are recommended as a part of diagnostic assessment for PPCM.	Level C
MRI should be considered as a part of a differential diagnosis of PPCM to rule out coronary artery disease and myocarditis.	Level C
Before delivery, β-blockers and vasodilators are recommended in the treatment of PPCM.	Level C
After delivery, treatment of PPCM is recommended in accordance with the current guidelines for HF.	Level A
Bromocriptine may be considered as a causal treatment of PPCM.	Level B
Antithrombotic therapy should be considered in patients with ejection fraction <35% and / or those treated with bromocriptine.	Level C

Abbreviations: BNP, B-natriuretic peptide; HF, heart failure; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-natriuretic peptide; PPCM, peripartum cardiomyopathy

to be discussed separately. It is currently believed that noninvasive treatment is the most appropriate approach in clinically stable patients with a patent true lumen or a short-segment obstruction. In clinically unstable patients with long-term myocardial ischemia, invasive treatment should be considered. PCI with stenting is the method of choice which effectively restores normal coronary blood flow in about half of cases.[200,203] The coronary artery bypass grafting is an alternative treatment option, which should be considered in patients with the left main stem coronary artery dissection (as long as not proceeding with immediate PCI is a viable option taken their clinical presentation) and multiple vessel involvement, as well as those after ineffective or complicated PCI. In patients with cardiogenic shock, the left ventricular assist device, the extracorporeal membrane oxygenation or intra-aortic balloon pump should be considered alongside reperfusion therapy. In exceptional cases, a heart transplant may be necessary.[201] Should surgical treatment or assist devices be necessary, delivery timing should be determined by a multidisciplinary team consisting of consultant gynecologist-obstetrician, consultant anesthesiologist, consultant perinatologist, and consultant cardiac surgeon.

Patients after P-SCAD should be started on dual antiplatelet therapy after stenting, and in those with postpartum left ventricular dysfunction, standard pharmacological treatment (β-blockers, ACEIs, MRAs) should be used. Breastfeeding is not recommended in mothers on dual antiplatelet therapy (class of recommendation III, level of evidence C). The management of P-SCAD is presented in FIGURE 7.2B.

7.9.6. Prognosis

In the studies published to date, the hospital mortality rate was 0% to 4%, and the mean left ventricular ejection fraction was about 50%. Although long-term prognosis is favorable, there is a 10% to 20% risk of subsequent SCAD.[200,201] Therefore, regular cardiac follow-up is needed in those patients.

7.10. Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is idiopathic cardiomyopathy presenting with HF secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery. The diagnosis can only be confirmed in the absence of a preexisting cardiovascular disease as a key prerequisite. PPCM is diagnosed with a left ventricular ejection fraction (EF) reduced to below 45%. The left ventricle may not be dilated. The risk factors for PPCM include HT, diabetes, smoking, and such gestational risk factors as maternal age, parity, use of β-blockers for tocolysis or malnutrition.[204]

The pathophysiology of PPCM has not been fully explained. Recently, the signal transducer and activator of transcription 3 have been postulated to play a role in PPCM. Another putative underlying mechanism involves oxidative stress, which appears to trigger induction of cathepsin D in cardiomyocytes, which subsequently causes increased cleavage of prolactin into an antiangiogenic and proapoptotic 16-kDa isoform. The 16-kDa prolactin has been shown to inhibit endothelial cell proliferation and migration, induce endothelial apoptosis and disrupt already formed capillary structures.[205]

The diagnosis of PPCM is based on ruling out other causes of symptomatic HF. Most frequent initial presentation is NYHA class III or IV symptoms. The majority of patients present with symptoms in the first 4 months after delivery (78%), and only 9% present in the last month of pregnancy. Early diagnosis is the key determinant of prognosis. The ECG, serum B-natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) and echocardiography are recommended in women with dyspnea, who present with congested lung fields, peripheral edema, and jugular venous distention.[204] Magnetic resonance imaging (MRI) should be considered. Although there are no PPCM-specific MRI findings, it enables ruling out acute myocarditis and myocardial ischemic injury.[206] A biopsy is not recommended as routine management (FIGURE 7.3).[207]

Hemodynamically stable patients should be treated according to the recommendations for treatment of chronic and acute HF developed by the Heart Failure Association of the European Society of Cardiology Working Group on PPCM.[2,206,208] Treatment choices will depend on the clinical presentation and the timing of onset (before or after delivery). Before delivery, β-blockers (preferred β1-selective), vasodilators (preferably dihydralazine which is not available in Poland), nitrates and possibly (sparingly) diuretics are recommended. Vaginal delivery is preferred in stable patients.

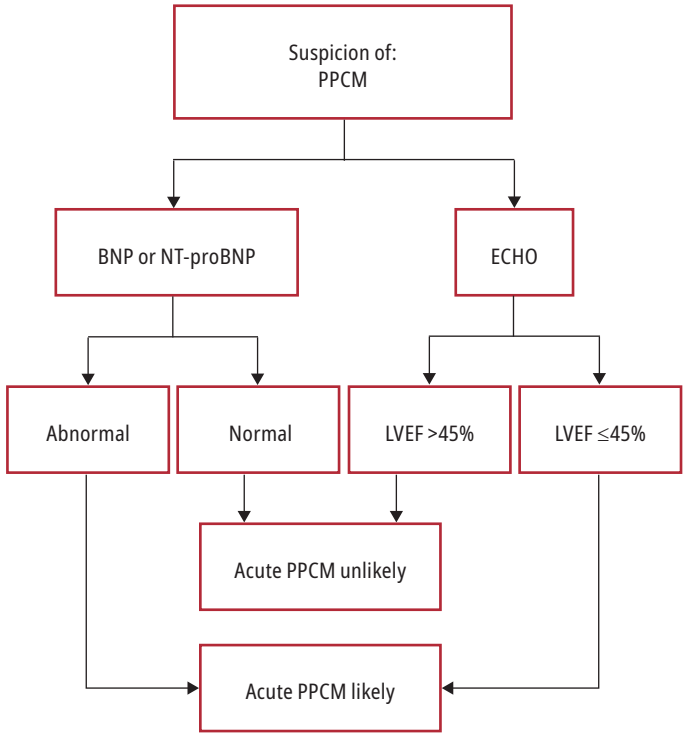

FIGURE 7.3 Diagnostic algorithm for peripartum cardiomyopathy (PPCM)

Abbreviations: BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PPCM, peripartum cardiomyopathy

After delivery, ACEI/ARB and β-blockers in maximum tolerated doses are recommended. Furthermore, MRAs (eplerenone) are recommended in women with EF of less than 40%. With a persistently low EF despite standard treatment for HF, a conversion from ACEI/ARB to sacubitril/valsartan is recommended. Ivabradine should be considered in patients presenting with persistent tachycardia despite β-blocker treatment.

Causal treatment may be considered after delivery. Bromocriptine dose of 2.5 mg twice a day for 14 days followed by 2.5 mg once a day for 42 days is recommended. Additionally, anticoagulant treatment with heparin is recommended in patients with EF of 35% or less or those treated with bromocriptine.[2,206] In hemodynamically unstable patients (systolic BP <90 mm Hg, O_2 saturation <90%, lactates >2 mmol/l), treatment with levosimendan (0.1 mg/kg/min for 24 hours) or mechanical circulatory support devices such as intra-aortic balloon pump or transcutaneous temporary ventricular support device (eg, Impella) with or without extracorporeal membrane oxygenation[206] is recommended. Cesarean section is the preferred delivery method in unstable patients with PPCM.[209] In patients with persistently low EF below 35% despite optimal medical therapy, wearable cardioverter-defibrillator, implantable cardioverter-defibrillator, and possibly listing for heart transplantation should be considered.

8. Management of postnatal hypertension

Blood pressure generally decreases immediately after delivery both in women normotensive and hypertensive during pregnancy and may later increase to a peak at 3 to 6 days postpartum. A transient BP elevation may also occur in women after normal pregnancy and is associated with pain, medications, excessive fluid supply, water and sodium shift to the intravascular space or changes in the vascular tone which returns to its pre-gestational values. Having in mind the physiology of postnatal BP changes, antihypertensive treatment should be continued with a tight BP control during the first week postpartum to avoid unnecessary or too aggressive antihypertensive treatment.[210] FIGURE 8.1 shows the postpartum management algorithm in women with HT during pregnancy. Breastfeeding should not be discouraged in women with HT, including those on medical treatment. Although most antihypertensive drugs pass to human breast milk, their concentrations are usually much lower than in serum.

Methyldopa passes to human breast milk in small amounts. However, what limits its use in breastfeeding women is that it may trigger or exacerbate postpartum depression, sedation, and orthostatic hypotonia, which is why some guidelines recommend a conversion from methyldopa to another antihypertensive drug after delivery.[210] β-Blockers pass to human breast milk in small amounts, although there are significant differences between the individual agents in this drug class. Metoprolol and labetalol are approved for use in breastfeeding women.[9,211,212] Newer β-blockers (nebivolol) and newer drugs with the mechanism of action identical to the one of labetalol (carvedilol) cannot be currently recommended in breastfeeding women due to lack of data.

Extended-release nifedipine is allowed in breastfeeding women with HT,[9,17] as it is passed to human breast milk in small amounts and no adverse effects have been reported in children breastfed by nifedipine-treated mothers.[19,213] There is no data on the safety of amlodipine in breastfeeding women. Some guidelines allow it[210], however, and amlodipine seems a reasonable choice if extended-release nifedipine is unavailable. The data on the safety of verapamil in breastfeeding women is contradictory.

ACEIs are contraindicated in pregnancy, but as they pass to human breast milk in negligible amounts, some of them are approved for the treatment of breastfeeding women by the American Academy of Pediatrics[214] as well as recommended by British[215] and French experts,[9] subject to their contraindications in women who breastfeed preterm infants and infants with suspected kidney disease. Available data supports the recommendation of enalapril, captopril, and quinapril in breastfeeding women.

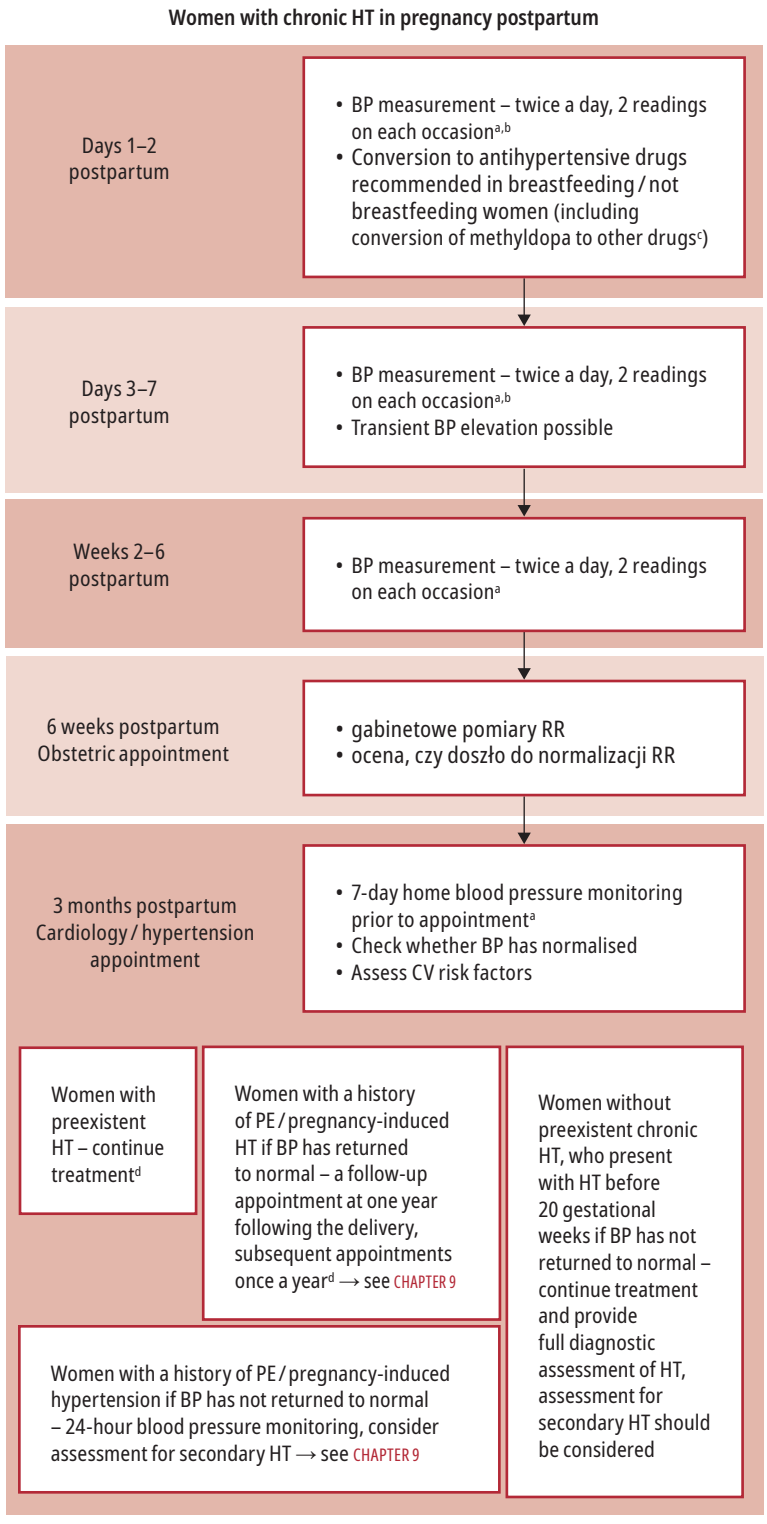

FIGURE 8.1 Postpartum management of women with hypertension during pregnancy

a Or more frequently, depending on clinical presentation

b Four times a day if admitted as an inpatient

c Do not discontinue methyldopa suddenly

d Appointment frequency should be determined based on clinical presentation

Abbreviations: BP, blood pressure; CV, cardiovascular; HT, hypertension; PE, preeclampsia

Some guidelines only recommend enalapril. There are special indications for using ACEI in breastfeeding women with HF and PPCM. There is no data regarding other ACEI or sartans. Diuretics should not be used in breastfeeding women as they suppress lactation. The detailed information on the safety of medications in breastfeeding women (including their concentration in breast milk and infantile blood, as well as possible and reported adverse effects) can be found in the LactMed database (https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm), published by the United States National Library of Medicine National Institute of Health and updated on an ongoing basis.

9. Management of women with a history of gestational hypertension, preeclampsia, and other gestational complications

9.1. Long-term cardiovascular risk in women with history of gestational hypertension and preeclampsia

In recent years, there has been a growing interest in the relationship between gestational HT and PE (jointly referred to as 'pregnancy-induced hypertensive disorders') and cardiovascular complications and HT later in life. It has been noted that pregnancy-related hypertensive disorders and cardiovascular diseases share common risk factors, such as age, obesity, glucose metabolism disorders, kidney disease, as well as inflammatory and genetic factors.[216] Furthermore, women with gestational HT or PE had higher BMI, higher BP values, and preexisting abnormal lipid profile preconception as compared with women without gestational HT or PE.[217]

9.1.1. The risk of hypertension in women with a history of gestational hypertension and preeclampsia

It was shown that women with a history of pregnancy-induced hypertensive disorder had a higher risk of HT than women with no history of pregnancy-induced HT or PE. An analysis of the Nurses' Health Study II showed that women with a history of pregnancy-induced HT or PE have a higher risk of HT in 25- to 32-year follow-up. The risk was the highest in the first 5 years after delivery.[218]

It should be emphasized that the association between PE and pregnancy-induced HT and subsequent HT can be seen as early as in the first months following delivery. The BP fails to normalize postpartum in some women. The study in women with a history of PE demonstrated HT in 24% of women, white coat HT in 18% of women, and masked HT in 9.5% of women assessed with 24-hour BP monitoring at 6 to 12 weeks following delivery.[219] It also demonstrated that older age, earlier onset, and longer duration of gestational HT were associated with persistent BP elevation postpartum in women with a history of gestational HT.[220]

A postpartum conversion from methyldopa to another antihypertensive drug should be considered.	Level C
Metoprolol and labetalol should be considered in breastfeeding women.	Level C
Extended-release nifedipine should be considered in breastfeeding women. If extended-release nifedipine is unavailable, amlodipine may be considered.	Level C
Angiotensin-converting enzyme inhibitor (preferably enalapril, followed by captopril or quinapril) may be considered in breastfeeding women previously treated with ACEI and other drugs contraindicated in pregnancy or if the current treatment proves ineffective to achieve cardiovascular risk reduction.	Level C
Other angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and diuretics are not recommended in breastfeeding women.	Level C
It is not recommended to discourage breastfeeding in women with HT, including those on medical treatment.	Level C
It is recommended to assess BP and determine indications for adjusting antihypertensive treatment during inpatient admission on days 1–7 postpartum, obstetric follow up at 6 weeks postpartum and cardiological-hypertensive follow up at 3 months postpartum.	Level C

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; HT, hypertension

It is recommended to assess the severity of cardiovascular risk factors as well as the effect of their management (non-pharmacological and pharmacological) and a potential need to upscale it in women with a history of pregnancy-induced HT or PE at 3 months and one year following delivery and then once every year.	Level B
Assessment for secondary HT should be considered in women with a history of gestational HT or PE, whose BP has not normalized postpartum.	Level C
Both office and out-of-office BP measurements are recommended in women with a history of pregnancy-induced HT or PE.	Level C

Abbreviations: BP, blood pressure, HT, hypertension; PE, preeclampsia

9.1.2. Gestational hypertension and preeclampsia and the severity of cardiovascular risk factors

It was shown that the history of the pregnancy--induced hypertensive disorder is associated with significantly higher severity of modifiable cardiovascular risk factors. The HUNT (Nord Trøndelag Health Study) showed that women with a history of pregnancy-induced HT or PE in their first pregnancy had a higher preconception BMI, waist circumference, BP, heart rate as well as glucose and triglyceride levels as compared with women without the history of pregnancy-induced HT or PE in their first pregnancy. After the first pregnancy, there was a parallel development in cardiovascular risk factor levels, but women with a normotensive first pregnancy had a time lag of 10 years compared with the PE group.[221]

The PREVEND (Prevention of Renal and Vascular End-Stage Disease) study showed that women with a history of pregnancy-induced HT or PE more often had HT (a significant difference from the age of 35–40 years), diabetes mellitus (a significant difference from the age of 50 years), and lipid disorders (a significant difference from the age of 40 years) as compared with women without pregnancy-induced HT.[222] This indicates the need to monitor BP, and lipid and carbohydrate metabolism disorder in women with a history of pregnancy-induced HT from middle age onwards.

9.1.3. Gestational hypertension and preeclampsia and the risk of cardiovascular events

It was also shown that women with a history of pregnancy-induced HT or PE have a higher risk of cardiovascular diseases and cardiovascular events than women without a history of pregnancy-induced HT.

The coronary artery calcium scoring with multislice CT indicated that the frequency of coronary artery calcium score of 95th percentile or higher determined for the general population aged 45 to 55 years was 17% higher in women with a history of PE than in the general population. Atherosclerotic plaques were found in 47% of women and significant coronary artery stenosis was found in 4% of women. These results may indicate the accelerated progression of coronary artery atherosclerosis in women with a history of PE.[223] Women with a history of PE, HELLP syndrome, and placental abruption were significantly younger (54 vs 64 years old) upon the onset of stroke as compared with stroke survivors without the history of PE.[224]

Furthermore, a large Norwegian study demonstrated an increased risk of cardiovascular death in women with a history of preeclampsia in the first pregnancy.[225] The observational study from Northern California (median follow up of 37 years) also showed that the history of PE was associated with a higher risk of cardiovascular death as compared with women without a history of PE. This risk was particularly high in women with the onset of PE before 34 gestational weeks.[226] The association between PE and cardiovascular risk was also confirmed in 2 large meta-analyses. The risk of PE remained significant even after adjustment for conventional cardiovascular risk factors.[227,228]

9.1.4. Other gestational complications and cardiovascular risk

Research shows a higher risk of HT and cardiovascular diseases in women with a history of gestational and perinatal complications, such as prematurity, LBW, stillbirth. These complications should be ascertained as a part of taking history to determine cardiovascular risk factors in women.[229]

9.1.5. Long-term management of women with a history of gestational hypertension or preeclampsia

The studies discussed above indicate a significant association between pregnancy-induced HT and/or PE, and cardiovascular risk in later life.[230] Regular monitoring of cardiovascular risk factors, including regular BP measurements,

TABLE 9.1 Management of women with a history of gestational hypertension / preeclampsia

Time point	Specialty	BP measurement	Actions	Assessments
6 weeks after delivery	Obstetrics	Office BP measurement Home BP measurement (FIGURE 8.1)	Educate on high cardiovascular risk Refer to cardiologist / HT specialist	Depending on the clinical presentation
3 months after delivery	Cardiology/HT	Office BP measurement Home BP measurement (FIGURE 8.1) Consider ABPM	CV risk determination; CV risk assessment; patient education on the need and possibility to address modifiable cardiovascular risk factors (nonpharmacological and pharmacological strategies)	Waist circumference and BMI Fasting blood glucose; lipid profile; serum creatinine level; qualitative assessment of proteinuria (quantitative in women with a history of PE) Assessment for secondary HT should be considered in women with pregnancy-induced HT or PE with poor BP control
One year after delivery	Cardiology/HT	Office BP measurement Home BP measurement (7-day home BP monitoring according to the 2×2 scheme) Consider ABPM	Evaluation and intensification of nonpharmacological and pharmacological cardiovascular risk reduction strategies	Waist circumference and BMI; OGTT; lipid profile; serum creatinine and uric acid levels
Once a year	Cardiology/HT	Office BP measurement; Home BP measurement (7-day home BP monitoring according to the 2×2 scheme) Consider ABPM	Evaluation and intensification of non-pharmacological and pharmacological cardiovascular risk reduction strategies	Waist circumference and BMI Glucose metabolism and lipid profile assessment depending on previous findings (not less often than every 2 years); serum creatinine level

Abbreviations: ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; CV, cardiovascular; HT, hypertension; OGTT, oral glucose tolerance test; PE, preeclampsia

should be advised in women with a history of pregnancy-induced HT or PE. Lifestyle modification needs to be particularly emphasized.[231] Importantly, the presented data indicate that women with a history of pregnancy-induced HT or PE should be screened for cardiovascular diseases relatively short after the delivery, as the incidence of HT, diabetes, and lipid disorder as well as a risk of cardiovascular events and cardiovascular death increase significantly from middle age (40–60 years) onwards. The management of women with a history of pregnancy-induced HT or PE has been outlined in TABLE 9.1.

10. Impact of gestational hypertension and / or preeclampsia on children's long-term health

Gestational HT and / or PE are among the main risk factors for prematurity and IUGR. Both prematurity and IUGR are associated with LBW, being significant risk factors for cardiovascular disease, metabolic syndrome, and type 2 diabetes mellitus in adult life. Prematurity is a significant independent risk factor for CKD. As a result of reduced nephron mass (total nephron number), CKD additionally predisposes an individual to develop HT, while HT is the main risk factor for the progress to end-stage CKD.

Estimates indicate that HT was diagnosed in 7.3% of prematurely born children at the age of 3, whereas the expected prevalence of HT at this age is 1% to 2%. HT was diagnosed in 6% to 25% of preterm children assessed at the age of 6 to 12 years, and in 16% of teenagers assessed at the age of 13 to 18 years, whereas the estimated prevalence of HT in the general population of 18-year-olds is about 10%. The risk of HT increases with age and is particularly high in children born before 33 gestational weeks. Population studies show a higher risk of HT in both appropriate for gestational age (AGA) and SGA prematurely born children, with a higher risk found in boys than in girls.[232-234]

A systematic review and meta-analysis of studies assessing the association between preterm birth (<37 weeks), very LBW (<1500 g), and systolic BP in later life are noteworthy. BP was measured in children, adolescents, and adults born preterm. The controls were age-matched individuals born full-term. The meta-analysis included 10 studies (1342 individuals born preterm or with very LBW and 1758 individuals born full-term). The mean age on assessment was 17.8 years (6.3–22.4 years). Individuals born prematurely or with very LBW had systolic BP higher by about 2.5 mm Hg than that born full-term. The difference was even higher (3.8 mm Hg) in 5 selected studies. The authors concluded that children born prematurely or with a very LBW have moderately higher BP and may have a higher risk of HT later in life. In the era of dynamic progress in neonatology, the view that prevention of HT should be extended to include individuals

TABLE 10.1 Blood pressure standards for 2-week-old neonates born between 26 and 44 gestational weeks

Gestational age	95 cc [mm Hg]	99 cc [mm Hg]
44 gestational weeks		
SBP	105	110
DBP	68	73
MAP	80	85
42 gestational weeks		
SBP	98	102
DBP	65	70
MAP	76	81
40 gestational weeks		
SBP	95	100
DBP	65	70
MAP	75	80
38 gestational weeks		
SBP	92	97
DBP	65	70
MAP	74	79
36 gestational weeks		
SBP	87	92
DBP	65	70
MAP	72	71
34 gestational weeks		
SBP	85	90
DBP	55	60
MAP	65	70
32 gestational weeks		
SBP	83	88
DBP	55	60
MAP	62	69
30 gestational weeks		
SBP	80	85
DBP	55	60
MAP	65	68
28 gestational weeks		
SBP	75	80
DBP	50	54
MAP	58	63
26 gestational weeks		
SBP	72	77
DBP	50	56
MAP	57	63

Abbreviation: DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure

born prematurely or with very LBW is rightful and proper.[235]

There was a negative correlation between the gestational age at birth and birth weight, and the risk of CKD. At the age of 7 to 8 years the prevalence of glomerular hyperfiltration assessed as microalbuminuria ranged between 8% and 12% in prematurely born children as compared with 0% to 2.1% in the age-matched general population. It is estimated that the risk of CKD in children born before 32 gestational weeks without additional complications is 1.7-fold higher than in the general population. Due to impaired renal compensatory mechanisms associated with reduced nephron mass (see below), the risk of CKD increases significantly in preterm neonates with AKI. CKD was found in this group in 10% of children within 1 to 3 years following neonatal AKI.[236]

10.1. Pathogenesis of hypertension associated with prematurity and low birth weight

Multiple interrelated factors contribute to the pathogenesis of HT in prematurely born individuals, both AGA and SGA. Four main disorders were identified, which involve mechanisms leading to BP elevation. These include[236]:

- Impaired nephrogenesis and reduced nephron number
- Microdamage of the CNS and sympathetic nervous system upregulation
- The consequences of perinatal metabolic programming, including late metabolic effects of IUGR, postnatal pharmacological and nutritional treatment with associated body composition abnormalities and metabolic syndrome
- Early vascular ageing resulting in increased arterial stiffness, reduced production of vasodilators by arterial endothelium and reduced placental microcirculation

10.1.1. Reduced nephron mass

The main cause of reduced nephron mass is impaired nephrogenesis, which physiologically lasts until the end of the 36th gestational week. Preterm birth is associated with a reduced nephron endowment (reduced nephron mass). A lower number of nephrons impairs renal ability to compensate for additional injurious agents (toxins, drugs, infections, metabolic factors) leading to AKI. Regardless of the above, preterm birth is associated with an increased risk of neonatal AKI, due to the additional morbidity associated with prematurity. Additionally, both AGA and SGA preterm children present with metabolic disorders of varying severity due to fetal metabolic programming under intrauterine stress. These factors additionally affect kidney function in later years and usually manifest clinically in prepuberty. The first abnormality associated with reduced nephron endowment is glomerular hyperfiltration, which is the key contributor

to CKD progression and HT. Alongside glomerular hyperfiltration, a reduced nephron endowment (evaluated clinically in ultrasound as kidney volume or kidney length) is associated with salt sensitivity in preterm children. It is particularly pronounced in SGA children and can be observed as early as in 10-year-olds.

10.1.2. Sympathetic nervous system upregulation in children born prematurely and with low birth weight

The mean BP elevation, as well as decreased BP amplitude and heart rate, were demonstrated during 24-hour BP monitoring in preterm neonates.[232]

10.1.3. Metabolic programming

Preterm infants, and especially SGA, are exposed to increased cortisol levels, which is one of the main factors causing metabolic programming, that is, a shift to accumulating energy in visceral fat. According to the metabolic programming concept, if high-calorie nutrition is available, children with LBW, especially SGA, preferentially partition excess energy from food in visceral adipose tissue. This is accompanied by a relative reduction in muscle mass. As a result, they are uniquely susceptible to metabolic disorder manifesting as insulin resistance, elevated triglyceride levels, the tendency for hyperuricemia, and elevated BP. In this context, it is important to achieve adequate body weight with hypercaloric diet quickly in premature and / or SGA neonates.

10.1.4. Early vascular aging

Preterm children, both AGA and SGA, have a smaller caliber of retinal arteries at the age of 6. The differences were most significant in SGA children, who demonstrated the fastest weight gain in the first 24 months of life. Accelerated senescence of cord blood endothelial progenitor cells of premature neonates was also observed. Prematurely born individuals (both AGA and SGA) had increased arterial stiffness and higher BP. However, their presence was significantly modified by additional risk factors such as obesity and metabolic disorder.

10.2. Recommendations for early diagnosis of hypertension in preterm and / or small for gestational age neonates

Recommendations for post-discharge care in preterm neonates, both AGA and SGA, aimed at early diagnosis of HT are expert recommendations and represent class of recommendation I, level of evidence C. In Poland, this issue was discussed in the 2018 Recommendations of the Pediatric Section of the Polish Society of Hypertension and as a chapter in the "Standards of outpatient care for preterm neonates" and recommended by the Polish Neonatal Society and the Polish Pediatric Society.[237]

10.2.1. Screening for hypertension in the post-discharge care of preterm neonates (born before 33 gestational weeks)

Children with HT diagnosed prior to discharge from the neonatal ward should be consulted and provided with specialist care in a pediatric HT center. Further diagnostic and therapeutic management should be based on the current pediatric recommendations of the Polish Society of Hypertension (2018) and the European Society of Hypertension (2016).[238,239]

Children with concomitant renal and urinary tract pathology should remain under the care of a highly specialist pediatric nephrology, hypertension, and urology center. This will enable early treatment planning to address both urinary tract abnormalities and the need for renoprotective treatment.

Children presenting as normotensive prior to discharge from the neonatal ward should have BP measured at every medical appointment. Automated BP measurement on the right arm is recommended as the basic method in children up to 3 years of age. Elevated BP found on automated measurement should be confirmed with the auscultatory method.[239-241] A referral to a pediatric HT center is indicated in children presenting with HT. Due to the complex pathogenesis of HT in prematurely born children and concomitant neuroimmune abnormalities (see CHAPTER 10.1), a referral to a university pediatric center with HT department / unit is recommended in such cases.

10.2.2. Definition of hypertension in newborns and infants

As the first weeks of life are associated with significant BP changes additionally depending on the gestational age, the BP standards developed for neonates born between 26 and 44 gestational weeks should be used for the diagnosis of HT in newborns (TABLE 10.1). In older infants and children up to 3 years of age, the standards outlined in The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents of the National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescent should be used. In children above 36 months of age, the applicable standards will depend on the measurement technique. As an automated BP measurement is most frequently used and recommended for screening, the norms developed in the OLA and OLAF studies should be used.[239,242]

Elevated BP found on the measurement with an automated oscillometric device should be confirmed with the auscultatory method. Just as in older children, the diagnosis of HT is based on the finding of BP above the 95th percentile determined for age in 3 measurements.

The classification of BP in prematurely born children is the same as in the general population and should be consistent with the recommendations of the Polish Society of Hypertension.

10.2.3. Blood pressure measurement in newborns and infants

BP measurement with an automated oscillometric device on the right arm is recommended in post-discharge care. Cuff length encircling at least 80% to 100% of arm circumference, and cuff width-to-arm circumference ratio of 0.45 to 0.55 is recommended.

The automated oscillometric device should offer cuff pressure of 120 mm Hg at the onset of deflation. For technical reasons, reliable BP readings can only be obtained with the auscultatory method if the child's arm circumference is suitable for using appropriate cuff and the child is calm during the measurement. Therefore, BP measurement should be taken in calm (preferably asleep) infants, 15 to 30 minutes after the feed, avoiding measurements during or shortly after treatments, bathing or changing. The cuff should be placed first and the measurement should be taken after a 5- to 10-minute wait. Elevated BP found on the first measurement should be confirmed with subsequent measurements.

It is recommended to take several measurements at several-dozen-second long intervals.

SUPPLEMENTARY MATERIAL

Supplementary material as well as references and the Polish version of the paper are available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

DISCLAIMER The position statement represent the views of the authors and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating. The authors and societies are not responsible in the event of any contradiction, discrepancy, and/or ambiguity between the position statement and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the position statement fully into account when exercising their clinical judgment as well as in the determination and the implementation of preventive, diagnostic, or therapeutic medical strategies.

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REFERENCES

For references, see Supplementary material at www.mp.pl/kardiologiapolska.

APPENDIX 1 **Seven-day home blood pressure monitoring chart**

		In the morning (before medications, before breakfast)				In the evening (before medications, before a meal)			
Day	Date	Time	Systolic BP	Diastolic BP	Heart rate	Time	Systolic BP	Diastolic BP	Heart rate
1									
2									
3									
4									
5									
6									
7									
2 consecutive readings should be taken each time (2 in the morning and 2 in the evening)									