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 Gynaecologists and Obstetricians

ADDITIONAL INFORMATION This article has been co-published in Kardiologia Polska (doi:10.33963/KP.14904), Arterial Hypertension (doi:10.5603/AH.a2019.0011), and Ginekologia Polska (doi:10.5603/GP.2019.0074). The articles in Kardiologia Polska, Arterial Hypertension, and Ginekologia Polska are identical except for minor stylistic and spelling differences in keeping with each journal's style. Any citation can be used when citing this article.

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Arterial Hypertens. 2019, vol. 23, no. 3, pages: 117–182
DOI: 10.5603/AH.a2019.0011

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Translated by Karolina Kalisz

Abbreviations

ABPM — ambulatory blood pressure monitoring
ACE-I — angiotensin-converting enzyme inhibitor
AF — atrial fibrillation
AFI — amniotic fluid index
AFL — atrial flutter
AGA — appropriate for gestational age
AHI — apnea hypopnea index
AKI — acute kidney injury
ALT — alanine transaminase
ARB — angiotensin receptor blocker
ARR — aldosterone-to-renin ratio
AST — aspartate aminotransferase
AT — atrial tachycardia
BAV — bicuspid aortic valve
BMI — body mass index
BNP — B-nariuretic peptide
BP — blood pressure
Bpm — beats per minute
BPP — biophysical profile
CABG — coronary artery bypass graft
CAD — coronary artery disease
CKD — chronic kidney disease
CNS — central nervous system
CoA — coarctation of the aorta
CPAP — continuous positive airway pressure
CPR — cerebroplacental ratio
CTG — cardiotocography
CV — cardiovascular
DBP — diastolic blood pressure
DIC — disseminated intravascular coagulation
DM — diabetes mellitus
ECMO — extracorporeal membrane oxygenation
ECG — electrocardiography
EF — ejection fraction
ESC — European Society of Cardiology
ESH — European Society of Hypertension
EVA — early vascular ageing
FDA — Food and Drug Administration
FHR — foetal heart rate
FIGO — International Federation of Gynaecology and Obstetrics
FMD — fibromuscular dysplasia
FMF — Fetal Medicine Foundation
FPS — frame per second
GFR — glomerular filtration rate
HELLP — hemolysis, elevated liver enzymes, low platelet count
HT — hypertension
INR — international normalized ratio
i.v. — intravenous
IABP — intra-aortic balloon pump
ICD — implantable cardioverter-defibrillator
IUFD — intrauterine fetal death
IUGR — intra-uterine growth restriction
IVF — in vitro fertilisation
LBBB — left bundle branch block
LBW — low birth weight
LDH — lactate dehydrogenase
LQTS — long QT syndrome
LVAD — left ventricular assist device
LVEF — left ventricular ejection fraction
MAP — mean arterial pressure
MCA — middle cerebral artery
MCS — mechanical circulatory support
MDT — multidisciplinary team
MRA — mineralocorticoids renceptor antagonist
MRAs — mineralocorticoids renceptor antagonists
MRI — magnetic resonance imaging
NSTEMI — non-ST elevation myocardial infarction
NT-BNP — N-terminal pro-BNP
NTS — non-stress-test
OGTT — oral glucose tolerance test
OSA — obstructive sleep apnoea
p.o. — per os
PA — primary aldosteronism
PAPP-A — pregnancy associated placental protein
PCI — percutaneous coronary intervention
PE — pre-eclampsia
PI — pulsatility index
PlGF — placental growth factor
PPCM — peripartum cardiomyopathy
PPGL — pheochromocytoma and paraganglioma
PREVEND — Prevention of Renal and Vascular End-Stage Diseae
P-SCAD — pregnancy associated with spontaneous coronary artery dissection
PTNT — Polish Society of Hypertension
RAAS — renin–angiotensin–aldosterone system
SBP — systolic blood pressure
SCAD — spontaneous coronary artery dissection
SDB — sleep-disordered breathing
SGA — small for gestational age
SmPC — summary of medicinal product characteristics
STEMI — ST elevation myocardial infarction
STV — short-term variation
SVT — supraventricular tachycardia
TGF-β — transforming growth factor β
TSH — thyroid stimulating hormone
TTE — transthoracic echocardiography
UA — umbilical artery
US — ultrasound
VEGF — vascular endothelial growth factor
VF — venrticular fibrillation)
VT — ventricular tachycardia)
WCD — wearable cardioverter-defibrillator
WHO — World Health Organisation
WPW — Wolff-Parkinson-White syndrome

1. Introduction

This document is the first joint expert opinion of three medical societies on hypertension in pregnancy. It aims at presenting the management of hypertension in pregnancy, with particular emphasis on pathophysiological differences, clinical manifestation and sequelae of pregnancy-induced hypertension and pre-eclampsia. 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. Hypertension (HT) in pregnancy affects 6–10% of pregnancies in the United States and Europe. Women with chronic HT (1–5% of the general population) have a higher risk of pre-eclampsia (PE) than women without pre-existing HT (17–25% *vs.* 3–5%, respectively). Furthermore, 7–20% 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 foetal health and life. According to the WHO, HT and its complications are among the leading causes of mortality in pregnancy in developed countries (approx. 16%) [9–11].

Hypertension 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 foetal 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 foetus. Each year, PE causes over 500 thousand foetal 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 two 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/hypertension or by societies of obstetrics and gynaecology [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.

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 categorised 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

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 favour 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 non-randomized studies
Level C	The consensus of opinion of the experts and/or small studies, retrospective studies, registries

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 colour-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 (Tab. 2.2).

3. Definitions and the classification of HT in pregnancy

Based on the differences in pathophysiology, clinical manifestation and management, HT during pregnancy can be divided into two distinct conditions (Fig. 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,
  — pre-eclampsia.

It should be noted that the two conditions are not mutually exclusive, that is, a woman with chronic HT may develop PE — **PE superimposed on chronic (pre-existent) HT**.

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

It is emphasized that the cut-off 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 blood pressure drop occurs at 16–18 gestational weeks, which may mask chronic HT, and the BP only returns to pre-conception values in the third trimester. Additionally, pre-conceptive BP values are often unknown [14]. Regardless of the above, physiological pregnancy is associated with a blood pressure 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 blood pressure in pregnancy.

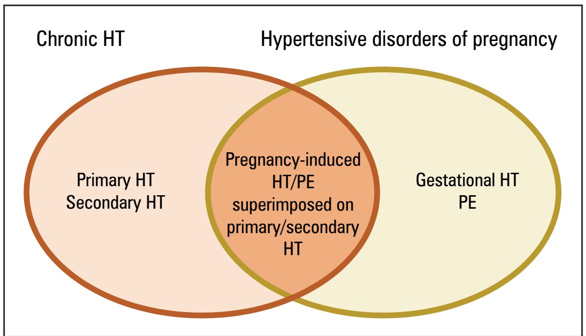

Figure 3.1. Classification of hypertension (HT) in pregnancy according to [1, 4]

4. Management of HT 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 foetal 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.

Table 3.1. Definitions and classification of HT in pregnancy [1–3]

Condition	Definition	Maternal outcomes	Fetal/Perinatal outcomes
Chronic HT	Hypertension 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. E.g. increased risk of PE, Caesarean 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 haematological 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 pre-existent HT
PE	New onset of HT after 20 gestational weeks plus new onset proteinuria and/or maternal kidney injury, maternal liver injury, neurological symptoms, haemolysis or thrombocytopenia and/or IUGR	High risk of complications, including death	High risk of complications, e.g. IUGR and IUFD
PE superimposed on chronic HT	PE in women with chronic HT	High risk of complications, including death	High risk of complications, e.g. 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	Hypertension diagnosed in the 2nd and 3rd trimester, usually based on office readings, which resolves within a few hours	Increased risk of pregnancy-induced HT and PE	
Hypertension not elsewhere classified	Any HT diagnosed after 20 gestational weeks should be considered pregnancy-induced HT if there is no data regarding pre-conception BP values		

4.1. Treatment of HT 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 blood pressure monitoring or home blood pressure (Fig. 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) (Tab. 4.1) [1,8]. Considering the need to develop practical guidelines which ensure standardised management, we recommend that every 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 (Fig. 4.2). The preferred quantitative method has not been clearly determined. In an outpatient setting, the protein:creatinine ratio in the morning urine sample or 24-hour urine collection may be considered (Tab. 4.1).

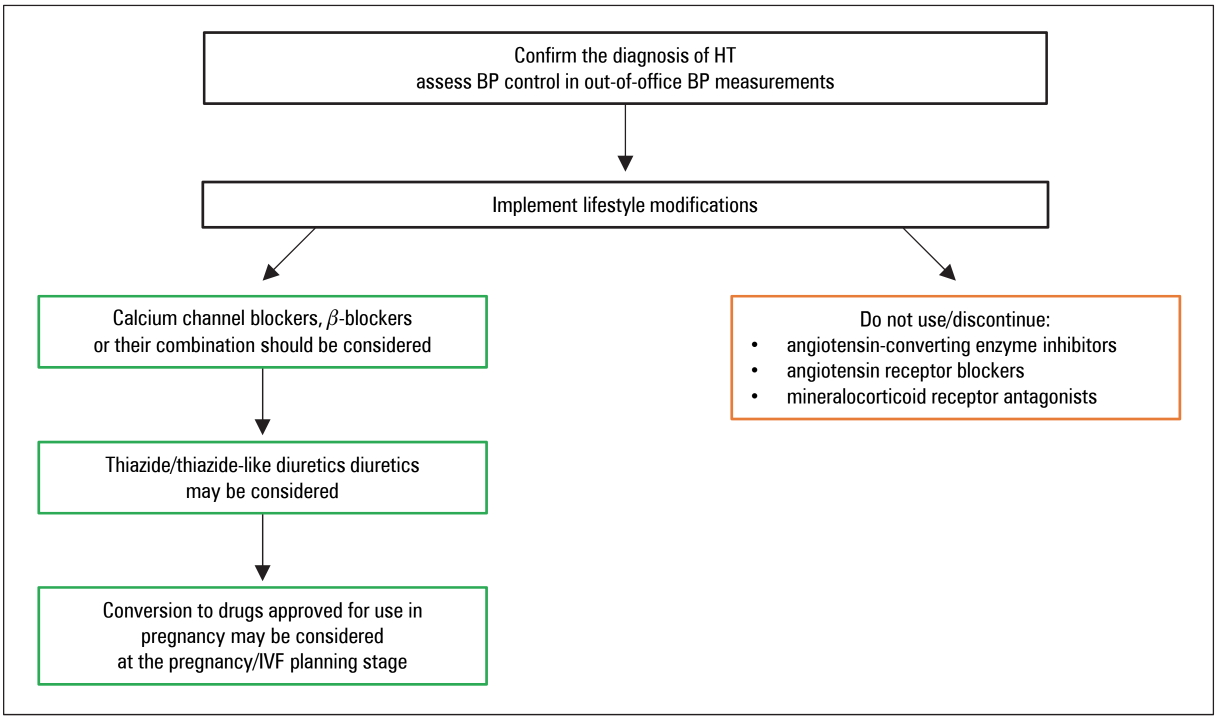

Figure 4.1. Management of hypertension (HT) in women at reproductive age

Table 4.1. Qualitative and quantitative assessment of proteinuria in women at reproductive age and pregnant women as per [2]

Method	Significant proteinuria cut-off
Qualitative methods	
Urinalysis	Qualitative assessment of proteinuria >15–30 mg/dL*
Strip test	Assessing the strip colour change by comparing it to a colour 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 hr urine collection	Proteinuria > 300 mg

*depending on the method

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 eGFR), liver function tests (AST, ALT), TSH, 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] (Tab. 4.2).

Due to their younger age, women planning to conceive may develop HT secondary to chronic kidney disease (e.g. vesicoureteral reflux, glomerulonephritis), renal artery stenosis from fibromuscular dysplasia, pheochromocytoma, coarctation of the aorta or primary aldosteronism. Secondary HT affects about 0.2% of all pregnancies and is diagnosed in 2–5% of all pregnant women with HT treated in highly specialist centres [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 in order 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.

4.2. Treatment of HT 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

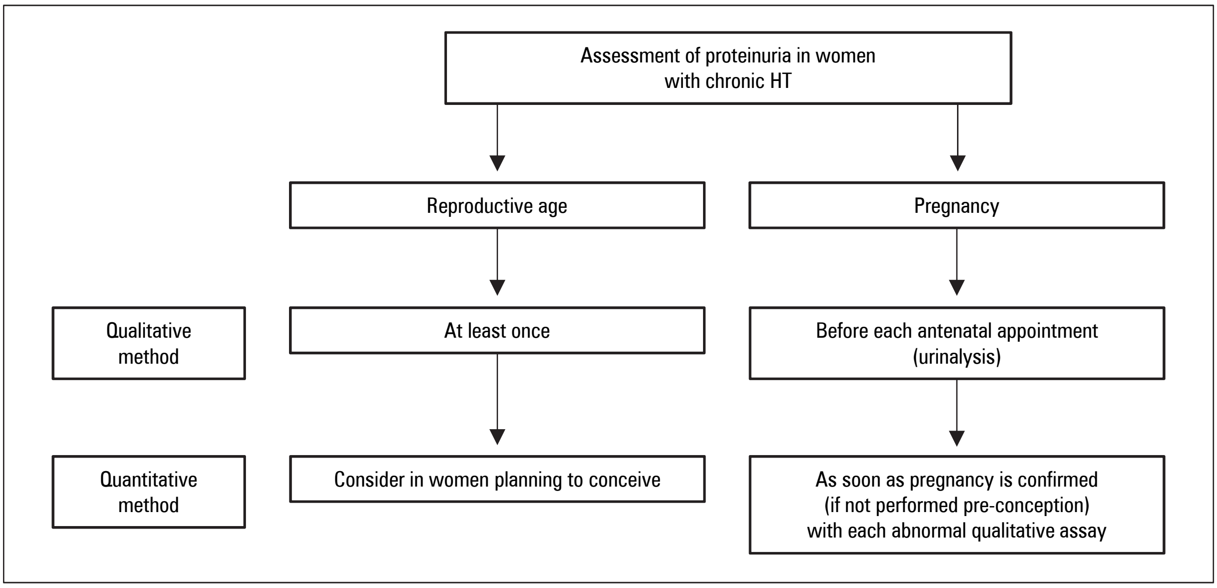

Figure 4.2. Assessment of proteinuria in women during the preconception, pregnancy and postpartum period

Table 4.2. Symptoms and test findings suggestive of secondary hypertension (HT) and screening for secondary HT — according to PTNT 2019 [3, 4]

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, haematuria, 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	Hypokalaemia (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) Hypokalaemia	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)	Hyperglycaemia	Incidental finding of an adrenal (or sometimes extra-adrenal) lesion	Plasma or urinary fractionated metanephrine

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Table 4.2. Symptoms and test findings suggestive of secondary hypertension (HT) and screening for secondary HT — according to PTNT 2019 [3, 4]

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	
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 3 sign and rib notching is seen in chest radiograms	Echocardiographic abnormalities	Echocardiography

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

to affect foetal 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, haemodynamic 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 (ACEI), angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA) 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, chronic kidney disease, primary aldosteronism). If these drug classes are used, patients should be informed about their potential teratogenic potential 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 (CCB) should be preferred for the management of hypertensive emergency in women at reproductive age.

Out of the 5 basic classes of hypotensive drugs, calcium channel blockers (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 (Fig. 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 two-drug combinations of anti-

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
Angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), renin inhibitors and mineralocorticoid receptor antagonists (MRA) are not recommended in women at reproductive age	Level B
Beta-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

hypertensive medications, which are well tolerated, effective, known to reduce cardiovascular risk and can be used in women at reproductive age, include dihydropyridine calcium channel blocker and β-blocker, calcium channel blocker and Thiazide/ /thiazide-like diuretics (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 (Fig. 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 favourable 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 measurements

5.1.1. Blood pressure measurements in pregnancy

The office BP readings taken using a validated, automatic blood pressure 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 measure-

Table 5.1. Techniques of office and home BP measurement in pregnant women, according to PTNT 2019 (modified) [3, 4]

Office measurement	Home measurement
A validated automatic blood pressure monitor for office BP measurements in pregnancy	A validated automatic blood pressure 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 1st 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 2nd and 3rd 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 (e.g. 06.00 and 18.00, 07.00 and 19.00 etc.). 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 in the morning 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 blood pressure 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

ment 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 blood pressure monitors, for both office and out-of-office BP measurements, can be found at http://bhsoc.org/bp-monitors/bp-monitors/ [20].

24-hour BP monitoring should be considered in the following clinical scenarios:

- to rule out white coat hypertension;
- 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 and/or diastolic BP is ≥ 90 mm Hg. HT in pregnancy is defined as mild (BP of 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 two separate occasions should be considered. 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 (Fig. 5.1) [1, 14]. Most women less than 20 weeks pregnancy should be counselled by a general practitioner, cardiologist or by 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 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 blood pressure ≥ 135 mm Hg systolic and/or ≥ 85 mm Hg diastolic obtained in 24-hour BP monitoring and home BP measurements;
- mean nocturnal blood pressure ≥ 120 mm Hg systolic and/or ≥ 70 mm Hg diastolic obtained in 24-hour BP monitoring.

5.1.3. Assessing the dynamics of BP changes in pregnancy

There is no optimum 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 two 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 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 1–2-minute interval in the morning and 2 consecutive readings at 1–2-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 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 HT

Women with chronic HT should be provided multidisciplinary care involving a consultant obstetrician/gynaecologist and a consultant cardiologist/clinical hypertension 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 presentation of the pregnant woman, the presence of proteinuria and routine laboratory test findings (including eGFR). Following a confirmation of pregnancy by the con-

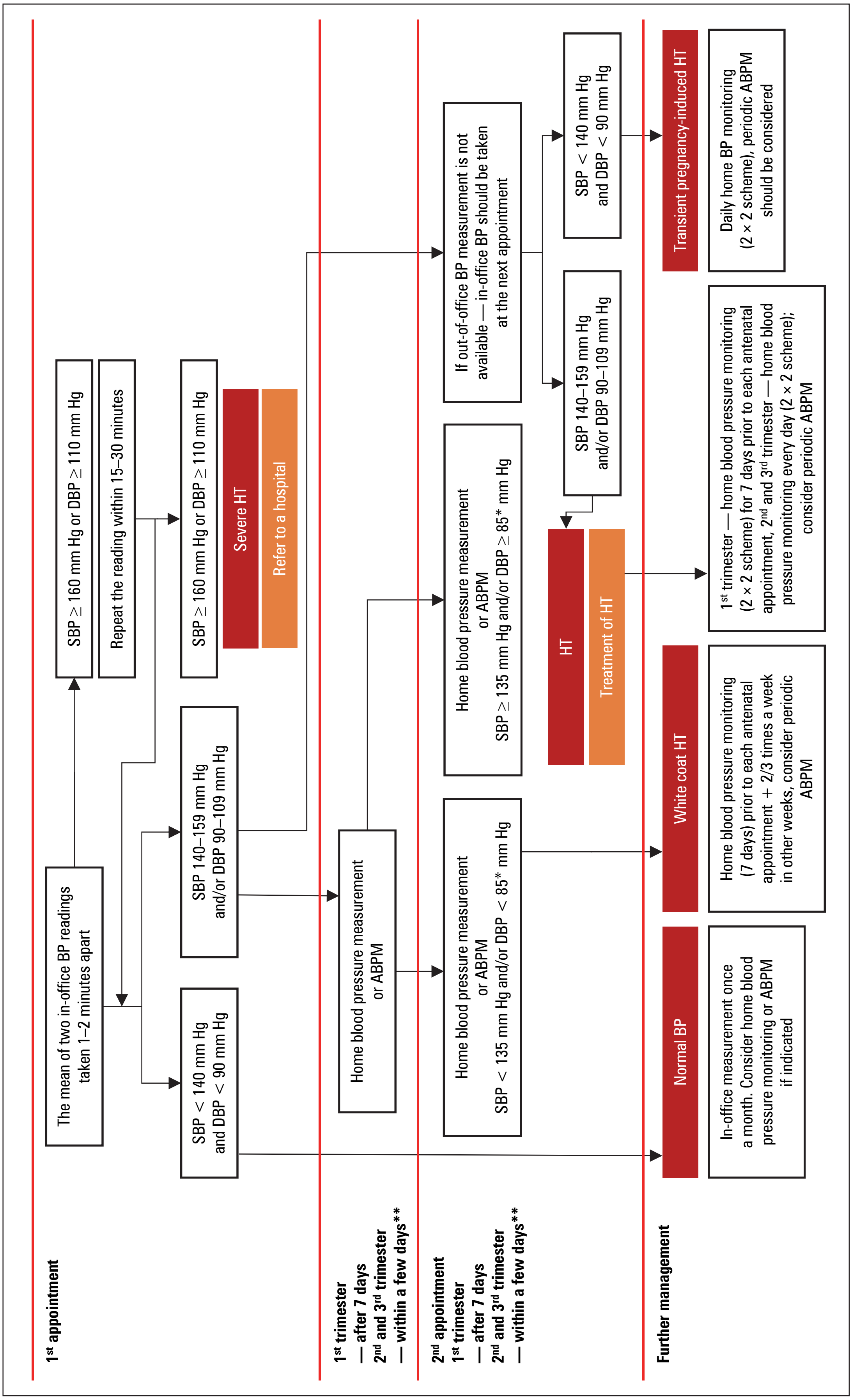

Figure 5.1. Diagnosis of hypertension (HT) and blood pressure (BP) measurements in pregnancy. *Mean of home BP monitoring or mean of daily ABPM; **Depending on the clinical presentation and next appointment availability

DIAGNOSIS OF HYPERTENSION AND BLOOD PREASURE MEASUREMENTS IN PREGNANCY — RECOMMENDATIONS

Using validated, automatic blood pressure 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 — *see* 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 hypertension • 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

*Depending on the clinical presentation and next appointment availability

sultant gynaecologist, it is recommended to perform basic tests including liver enzyme tests (AST, ALT, LDH), liver function tests (INR, bilirubin and albumin levels), serum creatinine, sodium, potassium and quantitative urine protein test at the first appointment with a consultant cardiologist/clinical hypertension 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 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 (Tab. 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

DIAGNOSTIC TESTS IN PREGNANT WOMEN WITH HYPERTENSION — RECOMMENDATIONS

Following a confirmation of pregnancy by the consultant gynaecologist, 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 hypertension specialist	Level C
Routine screening for proteinuria is recommended in each pregnant woman prior to each antenatal appointment (Fig. 4.2 and Table 5.2)	Level B

Table 5.2. Diagnostic investigations in pregnant women with chronic HT and suggested appointment frequency

	1st trimester (up to 12 gestational weeks)	2nd trimester (13–26 gestational weeks)	3rd trimester (27–42 gestational weeks)
Frequency of antenatal appointments	≥ Once a month**	≥ Once a month**	Depending on the maternal and foetal condition
Routine antenatal care	Up to 10 gestational weeks: • office blood pressure • out-of-office blood pressure • full blood count • fasting blood glucose • urinalysis • other*	15–20 gestational weeks, 21–26 gestational weeks: • office blood pressure • out-of-office blood pressure • full blood count • urinalysis • other* 24–26 gestational weeks: • OGTT	27–32, 33–37, 38–39 gestational weeks: • office blood pressure • out-of-office blood pressure • full blood count • urinalysis • other*
Fetal growth and wellbeing assessment	11–13+6 gestational weeks: • ultrasound, possible individual risk assessment for pre-eclampsia (including but not limited to uterine artery Doppler, *see* Figure 6.2), screening for trisomy, foetal anatomy assessment	18–22 gestational weeks: • ultrasound, anomaly/ anatomy scan, foetal growth assessment, placental position evaluation	28–32 gestational weeks: • ultrasound, foetal growth assessment, ruling out SGA, intensive surveillance after 34 gestational weeks
Frequency of hypertension and cardiology appointments	≥ Once a month**	≥ Once a month**	≥ Once a month**
Diagnostic investigations as a part of specialist outpatient cardiac/ hypertension 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 blood pressure • out-of-office blood pressure Each appointment: • office blood pressure • 7-day home blood pressure monitoring or ABPM prior to appointment Between the appointments: • home BP measurements	Each appointment: • office blood pressure • consider ABPM prior to appointment Between the appointments: • home BP measurements (2 × 2 scheme)	28. and 34. gestational weeks: • serum creatinine levels, electrolytes, liver enzymes Each appointment: • office blood pressure • consider ABPM prior to appointment Between the appointments: • home BP measurements

*As per the Minister of Health regulation; ** 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

excretion, serum haemoglobin 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 haemodynamic conditions, which affects the echocardiographic image of the heart (Tab. 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

ECHOCARDIOGRAPHY IN PREGNANT WOMEN WITH HYPERTENSION — RECOMMENDATIONS

The transthoracic echocardiography should be considered in pregnant women with HT 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 5.3. 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 and pulmonary 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

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 (e.g. dyspnoea or abnormal heart murmur) in all pregnant women with cardiovascular disease, including HT [2].

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 colour 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 foetus 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 < 0.7 and minimizing the duration of exposure, especially with foetal Doppler ultrasound in the first trimester [31]. Nevertheless, it should be emphasized that Doppler imaging is considered safe as long as the embryo/foetus 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 imaging, gadolinium contrast media are listed as a Class C drug by the U.S. Food and Drug Administration, which means that they should not be routinely used for MRI imaging 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 (e.g. pheochromocytoma) even with non-contrast-enhanced scans [34, 35].

Diagnostic imaging using ionizing radiation is usually considered potentially harmful to the developing foetus. Nevertheless, it should be emphasized that the risk for the foetus depends on the radiation dose and pregnancy stage at the time of the procedure. Foetal exposure to radiation dose below 50 mGy even in the first trimester is not considered harmful to the foetus. It should be noted that a computed tomography 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 foetus is not directly exposed to the radiation beam. For example, computed tomography of the pulmonary circulation is associated with foetal exposure to 0.01–0.1 mGy, whereas the ionizing radiation dose exceeding 100 mGy is considered harmful to the foetus [37]. Similarly, foetal 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 magnetic resonance imaging (MRI) are not associated with the risk to the foetus 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, computed tomography (CT) scan, or nuclear medicine imaging techniques is at a dose much lower than the exposure associated with foetal 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 foetal or maternal outcome [29].

5.5. Assessing foetal wellbeing

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

5.5.1. Foetal movement counting

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

5.5.2. Cardiotocographic foetal monitoring

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

5.5.3. Foetal growth and amniotic fluid volume monitoring

Ultrasonography is a crucial aspect of foetal wellbeing assessment. The aim is to assess foetal anatomy and growth, amniotic fluid volume as well as to confirm normal placental location. Placental insufficiency secondary to PE often leads to intrauterine growth restriction (IUGR), which is associated with a high risk of iatrogenic preterm birth and prematurity [41]. All foetal biometry parameters should fall in the range of 2 standards deviations from the

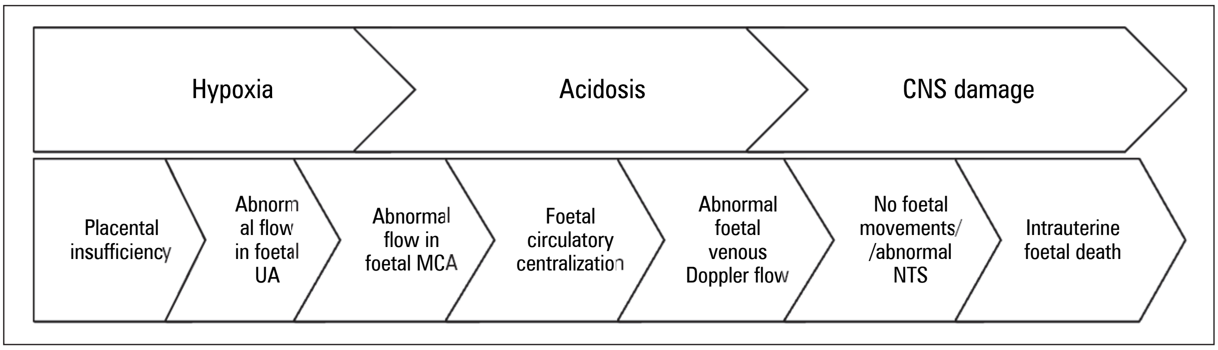

Figure 5.2. The effect of placental insufficiency on foetal circulation

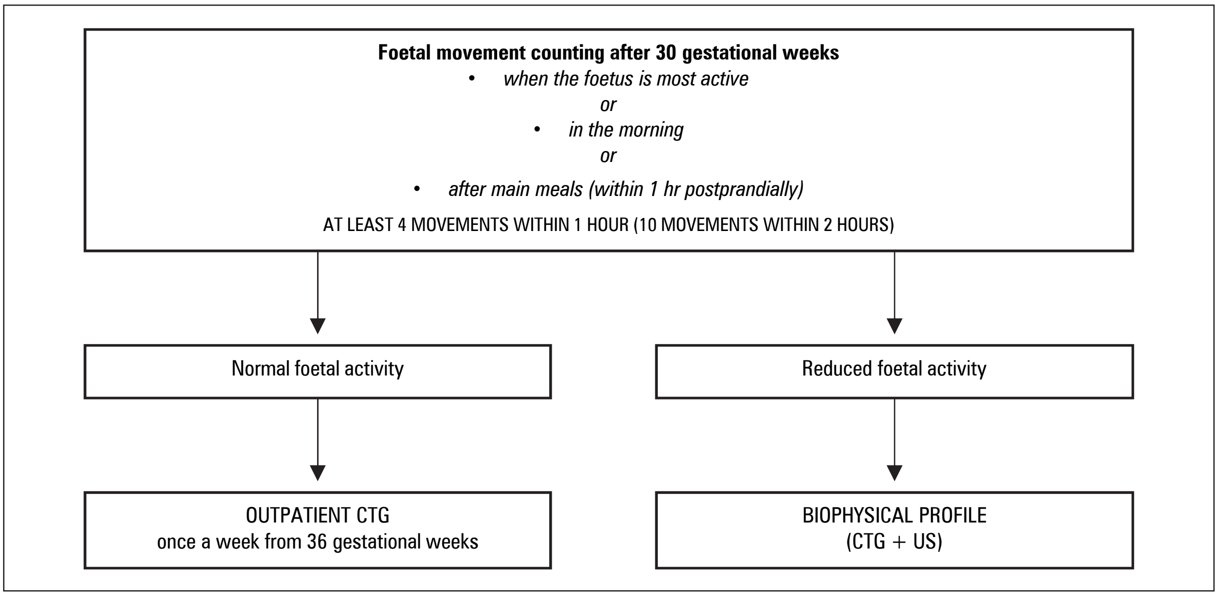

Figure 5.3. Foetal movement monitoring in patients with hypertension

ASSESSING FOETAL WELLBEING — RECOMMENDATIONS

Foetal wellbeing surveillance as per the algorithm shown in Figure 5.4 is recommended in patients with HT and PE	Level C
It is recommended to escalate foetal wellbeing surveillance upon sudden changes to a maternal health condition	Level C

normal mean for gestational age. The diagnosis of intrauterine growth restriction should prompt the clinician to assess the blood flow in the middle cerebral artery of the foetus 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 foetal biophysical profile

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

5.5.5. Foetal blood flow assessment

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

5.6. Preconception planning and obstetric care in patients with pre-existent HT

The aim of obstetric care in women with HT is to reduce the risk of maternal and foetal complications, as well as to achieve the lowest possible neonatal morbidity and mortality. This can be achieved

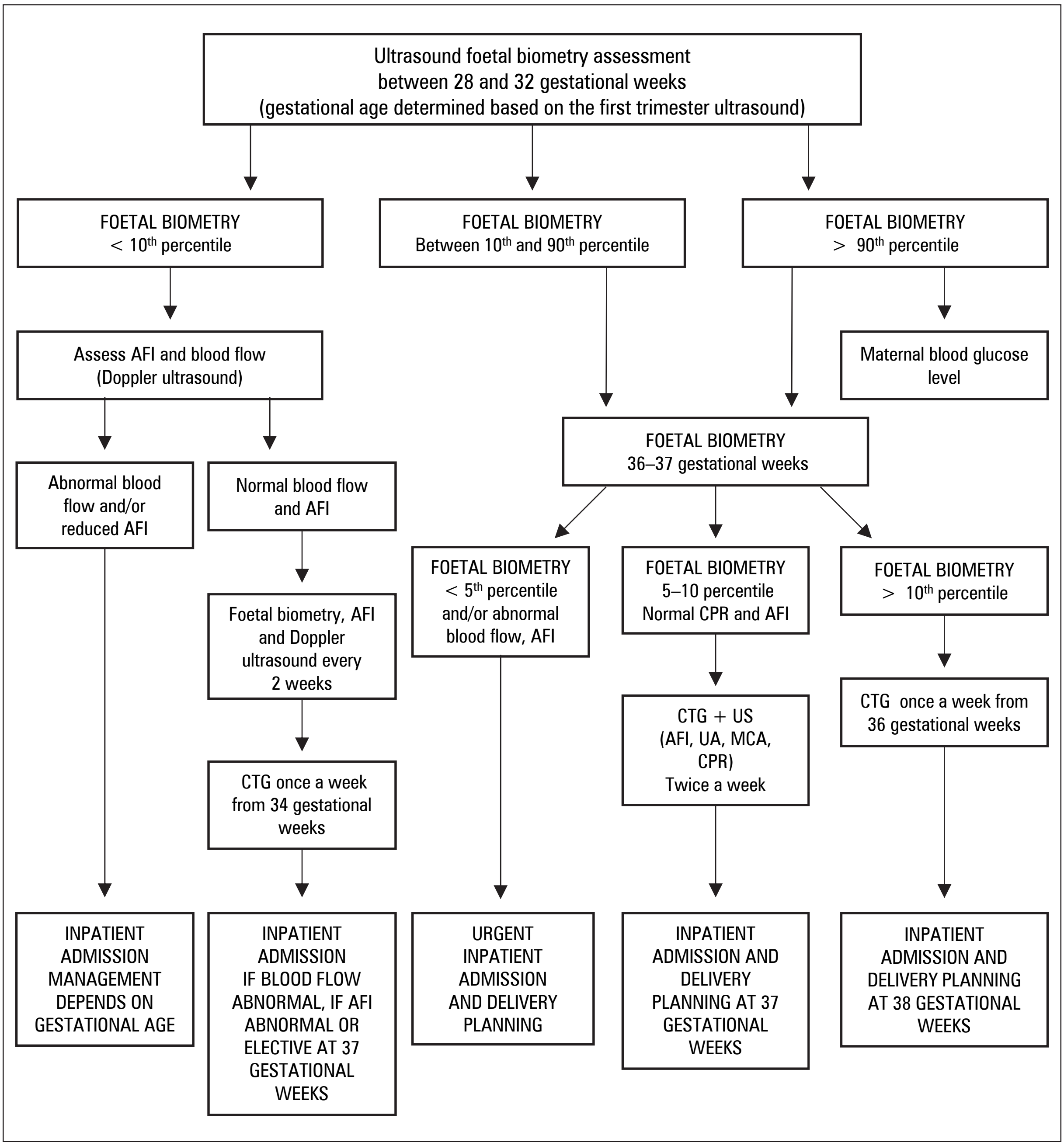

Figure 5.4. Assessing foetal wellbeing in women with hypertension (HT)

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 (Tab. 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 three antihypertensive medications as well as in women with secondary HT without treatment addressing the underlying cause of HT (*see* Chapter 4.2 and Tab. 4.2). A patient with suspected secondary HT should be assessed by a consultant clinical hypertension specialist or nephrologist (depending on creati-

Table 5.4. Obstetric assessment of women with chronic hypertension (HT) 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, dyslipidaemia, 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 accidents
Recommended diagnostic investigations	As discussed in Chapter 4.1

nine level and suspected chronic kidney disease) as a part of preconception care [6]. Medication review should be carried out as a part of preconception care — *see* Chapter 4.3. Birth defect prevention, primarily of the central nervous system, with 400–800 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 pre-existent obesity should be about 800 μg [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), foetal mortality (perinatal mortality is 3–4 × 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 foetal development [9]. At the same time, using hypotensive drugs in a woman with chronic HT may potentially adversely affect the foetus. Patients with uncomplicated chronic HT have a higher risk of Caesarean section, perinatal haemorrhage 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 > 35 y.o.;
- BP > 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, chronic kidney disease, 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 oedema, retinopathy, intracerebral haemorrhage or acute kidney injury [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 neonates and intraventricular haemorrhage [8]. Patients with chronic kidney disease, 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 pre-existent left ventricular

PRECONCEPTION PLANNING AND OBSTETRIC CARE IN PATIENTS WITH PRE-EXISTENT 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 hypertension without treatment addressing the underlying cause of hypertension	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 hypertension 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

heart failure 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 foetal complications, delivery is recommended after 38 gestational weeks. Hospital referral is recommended in patients with systolic BP ≥ 160 mm Hg or diastolic BP ≥ 110 mm Hg [1, 14]. Hospital referral should also be considered upon the onset of symptoms suggestive of PE (Tab. 6.2 and 6.3).

The incidence and sequelae of maternal and foetal 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 foetal medicine consultant, with multidisciplinary input from consultant cardiologist/clinical hypertension specialist and other consultants, if indicated.

5.7. Treatment of hypertension in pregnant women

5.7.1. Non-pharmacological management of hypertension in pregnant women

Lifestyle modifications, including behavioural changes improving foetal 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 foetal development, e.g. due to the effect of carbon monoxide contained in tobacco smoke, which binds to haemoglobin and reduces foetal oxygen supply [56].

The teratogenic effect of alcohol on the foetus was first described back in the 1960s. The recommendations of the International Federation of Gynaecology 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, 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 high 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, e.g. 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 to the preconception period. According to FIGO, based on American guidelines, the recommended weight gain during pregnancy in women with normal pre-pregnancy BMI (18.5–25 kg/m^2) is 11.5–16.0 kg. The recommended weight gain in overweight and obese women is 7–11.5 kg and 5–9 kg, respectively [54, 58].

A physically active adult with a body weight of about 70 kg needs about 2.5 litres of water per day (range from 1.5 to 3 litres, including about 700 ml of water contained in food). Pregnant and breastfeeding women should increase their daily water intake by about 300 ml and 600–800 ml, respectively. The daily recommended water intake in the second/third trimester and during breastfeeding is 3 litres and 3.8 litres, respectively. In the first trimester, the daily water requirement is the same as in a non-pregnant woman, i.e. 2.7 litres [59].

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

Daily intake of caffeinated beverages should be limited to not more than 200 mg of caffeine (one 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 foetal outcomes (e.g. 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 systolic and/or ≥ 90 mm Hg diastolic for the treatment of chronic and pregnancy-induced HT in all pregnant women.

The ESC guidelines of 2018 [2] recommend higher BP threshold for the initiation of antihypertensive drug treatment in pregnant women with uncomplicated chronic HT (≥ 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, pre-existing HT with the superimposition of gestational HT or HT with subclinical hypertension-mediated organ damage (BP threshold ≥ 140/≥ 90 mm Hg). The majority of studies (almost 50 studies) conducted to date, including Control of Hypertension in Pregnancy Study (CHIPS) described below, which evaluated the efficacy and safety of antihypertensive drug treatment in pregnancy, assumed the diastolic BP threshold of ≥ 90 mm Hg for the initiation of antihypertensive drug treatment. Fewer studies used systolic blood pressure thresholds for the initiation of antihypertensive treatment with the systolic BP threshold of ≥ 140 mm Hg (Fig. 5.5) assumed by the vast majority (almost 30) of them [64–66].

Patients with systolic BP ≥ 160 mm Hg or diastolic BP ≥ 110 mm Hg obtained in multiple consecutive measurements taken within 15–30 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 an SBP ≥ 170 mm Hg or DBP ≥ 110 mm Hg an emergency in a pregnant woman. However, following the recommendations of gynaecological societies and the Regulation of the Minister of Health, we decided to assume a lower threshold for hypertensive emergency (SBP ≥ 160 mm Hg/DBP ≥ 110 mm Hg) [1, 5, 6, 14].

Overzealous blood pressure control should be avoided as it may lead to placental hypoperfusion and this will compromise the foetus.

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

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

The composite primary endpoint was pregnancy loss or high-level neonatal care for > 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 systolic and 85.3 mm Hg diastolic, as compared to 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 > 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 *vs.* 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 (haemolysis, 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 < 10th percentile as well as a lower risk of delivery < 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, which 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 (DBP of 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 81–85 mm Hg [65, 67, 68]. However, there are no studies to evaluate the optimum target SBP range. The latest International Society for the Study

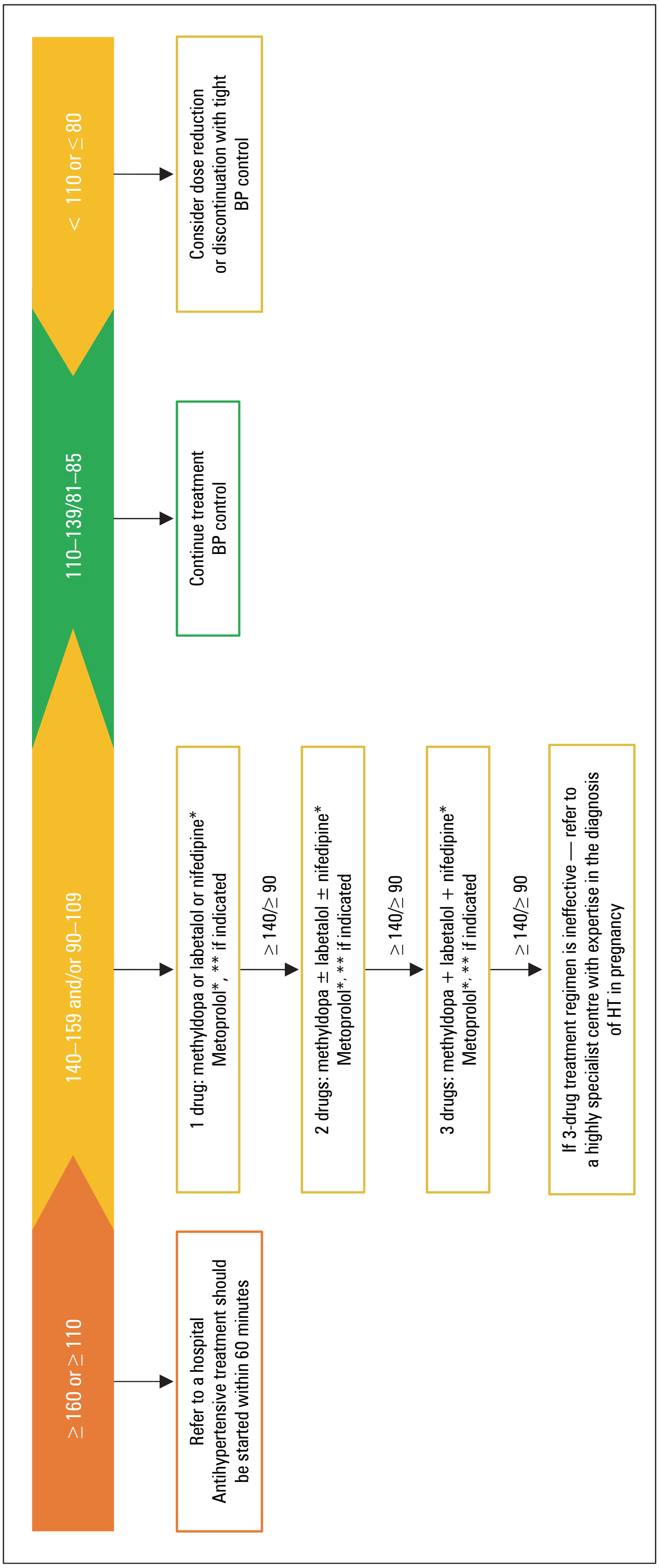

Figure 5.5. Principles of antihypertensive treatment in pregnancy. *Extended release formulation; **Do not combine metoprolol and labetalol

of Hypertension in Pregnancy (ISSHP) guidelines recommend the range of 110–139 mm Hg as the target SBP [1]. We consider it appropriate to assume the same range of target SBP values in antihypertensive treatment in pregnant women.

If SBP is < 110 mm Hg or DBP is ≤ 80 mm Hg, treatment de-escalation should be considered, whereas if SBP is > 140 mm Hg or DBP is > 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. 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 blood pressure < 140/90 mm Hg without antihypertensive medication, group 2, with blood pressure < 140/90 mm Hg with antihypertensive medication and group 3, with systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg despite antihypertensive medication. In group 3, there was a significantly higher incidence of severe HT, preterm PE with onset at < 37 weeks of gestation and IUGR than in group 1. In group 2, the incidence of these outcome measures was nonsignificantly higher than in group 1 and lower than in group 3 [69]. 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 blood pressure values [70]. The results of both studies support the conclusion that the need for antihypertensive treatment in the first trimester (when blood pressure 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 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, were conducted within the first two decades of the 21st century. The most commonly assessed drugs were methyldopa, labetalol and nifedipine, which were used in over 3 thousand women. They were compared with placebo, no intervention and other antihypertensive drugs (including comparisons between the three abovementioned 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 one 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 to other antihypertensive drugs supports their use as preferred treatment of HT in pregnant women (Fig. 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 2–3 times a day *p.o.*, up to a daily dose of 2 g (max daily dose of 3 g) [14].

Labetalol is a selective α1-adrenergic and non-selective 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 *p.o.*, 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 foetal 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, hypoglycaemia 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 (e.g. metoprolol) are preferred [2]. Out of four studies evaluating metoprolol in pregnant women with HT, three used metoprolol tartrate and one 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 foetal growth is carefully monitored for the potential adverse effect of treatment.

Calcium channel blockers are a class of antihypertensive drugs with a favourable 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 calcium channel blockers), 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 calcium channel blockers in pregnant women, i.e. 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 calcium channel blockers 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 *p.o.* The most common adverse effects of nifedipine include excessive blood pressure lowering, headaches, dizziness, flushing and peripheral oedema.

Verapamil, a non-dihydropyridine calcium channel blocker, was used in pregnant women, especially those with arrhythmia, in a few studies [89, 90]. There is no sufficient data regarding its maternal and foetal 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 *p.o.* 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 α-2 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 are a lupus-like syndrome, palpitations, headaches and flushing. It is not available in Poland [1–8].

Alpha-blockers act as antagonists on α-adrenergic receptors located in smooth muscle cells of blood vessels. Individual substances have variable selectivity for $\alpha 1$ and $\alpha 2$ 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, angiotensin-converting enzyme ACE inhibitors (ACEI) 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 pre-conception is controversial. We do not recommend diuretics in pregnancy due to possible oligohydramnios and foetal electrolyte imbalance [75]. Spironolactone has been shown to adversely affect foetal 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 blood pressure 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 two drugs, followed by three 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, the patient should be referred to a specialist centre 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 centres, medical societies and organisations worldwide, treatment recommendations are still discrepant with no uniform treatment algorithm [1, 2, 4, 8, 95]. In the absence of large, multicentre, 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 blood pressure measurements (*see* Chapter 5.1) must be ensured.
- In patients with SBP ≥ 160 mm Hg and/or DBP ≥ 110 mm Hg as well as those with eclampsia or PE (*see* Chapter 6.2.3) even with lower blood pressure values, hospital referral needs to be made [1].
- Regardless of concomitant complications of HT in pregnancy, any patient with blood pressure ≥ 160/110 mm Hg 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

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 litres and 3.8 litres, respectively. The daily recommended water intake in the first trimester is 2.7 litres	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 blood pressure thresholds for the initiation of antihypertensive treatment are SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg	Level B
The recommended blood pressure 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

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 blood pressure	Level C
Antihypertensive medications recommended for treatment of hypertensive emergencies include labetalol *i.v.*, nifedipine *p.o.* and hydralazine *i.v.*	Level C
The 25% reduction in the mean arterial blood pressure, followed by a further blood pressure 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, e.g. amount sufficient for the treatment of 1–2 patients, for the immediate needs of the ward	Level C

be considered (Tab. 5.5). BP values should be closely monitored (reduction in BP values should not delay hospitalization).

- Blood pressure reduction should be monitored, preferably with direct arterial blood pressure (DABP) monitoring. Antihypertensive treatment in a hypertensive emergency should aim at a 25% reduction in the mean arterial blood pressure, followed by a further blood pressure reduction to < 160/110 mm Hg within minutes/ /hours [8]. Too rapid blood pressure lowering may cause serious maternal and foetal complications. In hypertensive urgencies, blood pressure lowering should be achieved within hours/days.
- In women with severe HT, the intensive antihypertensive treatment aims at achieving BP < 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 blood pressure reduction to < 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 foetal vital signs. Alongside blood pressure 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 h, and even every 4–8 h with significant haematological and/or biochemical abnormalities and haemorrhagic complications [96]. In patients with PE, diagnosis and monitoring of target-organ damage are crucial in assessing the indications for delivery. Monitoring foetal 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 (Tab. 5.5 and 5.6) share the following common characteristics:
  - — high efficacy and rate of blood pressure 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 blood pressure 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 summarised in Table 5.7.
- A possibility to immediately end the pregnancy in selected situations (*see* Chapter 6.3) should be available.
- Treatment of multi-organ complications, ideally by the multidisciplinary team including consultant gynaecologist-obstetrician, consultant cardiologist, clinical hypertension specialist, consultant anaesthesiologist, 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 oedema [8].
- In order to avoid pulmonary oedema, the intravenous and oral fluid intake should be limited in patients with PE [8].

Table 5.5. Anti-hypertensive drugs used for emergency blood pressure (BP) lowering

Anti-hypertensive drugs used for emergency BP lowering in pregnant women (first-choice)		
Medications	Characteristics, indications, contraindications, adverse effects, limitations of use	Level
Labetalol* *i.v.*, (2, 4, 95)	Fast onset of action Should be avoided in women with asthma or heart failure May cause neonatal bradycardia	A
Hydralazine* *i.v.* (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 gynaecologists Recommended in women with bradycardia (HR < 60 bpm) Avoid in women with chronic headaches	A
Nifedipine *p.o.* (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
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 labour, delivery route, potential general anaesthesia and maternal general condition		
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		
Medical	Characteristics, indications, contraindications, adverse effects, limitations of use	Level
Nitroglycerin *i.v.* (2, 4, 8)	Concomitant pulmonary oedema	B
Labetalol* *p.o.* (95, 96)	Contraindications as for the *i.v.* formulation Oral formulation may be used before peripheral venous cannulation or if venous access is not available Dosage — *see* Table 5.6	B
Urapidil *i.v.* (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* *i.v.* (2, 4, 95)	Recurrent HT with high BP values A drug of last resort Risk of cyanide and thiocyanate intoxication	B

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

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

Medication	**Onset of action**	**Duration of action**	**Dose**
Labetalol *i.v.*	5–10 min	3–6 h	20 mg *i.v.* for 2 min, followed by 20–80 mg *i.v.* 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 *p.o.*			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 *p.o.* If no antihypertensive effect, another 200 mg dose can be administered after 30 minutes. If no antihypertensive effect or poor tolerance of *p.o.* formulation, an alternative is to administer 50 mg *i.v.* for 5 minutes. Repeated 200 mg doses every 10 minutes. Intravenous administration can be continued as an infusion
Hydralazine *i.v.*	5 min		5 mg *i.v.*, repeated doses of 5–10 mg *i.v.* every 30 mins, a maximum dose of 20 mg
Nitroglycerine *i.v.*	2–5 min	30 min	Initial *i.v.* infusion of 5 μg/min can be increased every 3–5 min up to the maximum dose of 100 μg/min

→

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

Medication	Onset of action	Duration of action	Dose
Urapidil *i.v.*	3–5 min	4–6 h	10–50 mg as an *i.v.* 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 SmPC

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 *i.v.* 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 *i.v.* administration involves an initial 4 g injection followed by a continuous infusion of 1g/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, i.e. in a setting where haemodynamic 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	

6. Management of pregnancy-induced hypertension and pre-eclampsia

6.1. Pathogenesis of pregnancy-induced hypertension and pre-eclampsia

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 remodelling [97]. Physiologically, human extravillous trophoblasts penetrate decidual veins and lymphatics before remodelling 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 to its size before conception. The development of uteroplacental circulation ensures normal intervillous space perfusion. In the early stage of pre-eclampsia, trophoblastic cells only invade the intradecidual portion of the spiral arteries, without the remodelling of myometrial segments of the spiral arteries. Furthermore, patients with PE have fewer spiral arteries and their luminal diameter is halved as compared to 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 pre-eclampsia. 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 (TGF-β) are the key proangiogenic factors, whereas the soluble fms-like tyrosine kinase-1 (sFlt 1) and soluble TGF-β coreceptor, endoglin (sEng), 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, sFlt 1 and sEng [100]. The increased blood pressure 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 (PAPP-A) [101]. Furthermore, agonistic autoantibodies against the angiotensin II type 1 receptor (AT1) and up-regulated expression of AT1 receptor in the placenta have also been described in PE. An increase in many components of the circulating renin–angiotensin system (RAAS) seems to have a significant effect on blood pressure elevation, proteinuria and inflammatory cytokine stimulation. Based on the time of onset, clinical course and differences in foetal outcomes, early-onset PE and late-onset PE have been distinguished. The early-onset PE developing before 34 gestational weeks affects ~10% of cases and is often accompanied by intrauterine growth restriction and chronic foetal hypoxia, which may lead to intrauterine death. The early-onset PE is also associated with high dynamics of blood pressure elevation, proteinuria and maternal multi-organ complications. As a result, premature delivery is often necessary, because only this intervention can stop further damage and resolve the symptoms.

6.2. Risk assessment, prevention and diagnosis of pre-eclampsia

6.2.1. Assessing the risk of pre-eclampsia

The current state of medical knowledge makes it possible to identify women at high risk of pre-eclampsia. 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 aetiology, 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 pre-eclampsia 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), as well as biochemical methods (serum markers) (Fig. 6.1). According to the recommendation of the Foetal Medicine Foundation (FMF), 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

Table 6.1. Risk factors for pre-eclampsia (PE)

Risk factors for PE	
Moderate risk	**High risk**
First pregnancy	HT in previous pregnancies
Maternal age > 40 y.o.	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

weeks). The pulsatility index (PI) is then calculated for the right and left uterine artery. Abnormal placental perfusion, reflected in an elevated pulsatility index of uterine arteries, is considered one of the causes of PE. To calculate the pulsatility index (PI), it is necessary to determine the maximum systolic velocity (S), maximum diastolic velocity (D) and the mean flow velocity (V_{mean}). The pulsatility index 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 will be. 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 pulsatility index (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 pulsatility index is used for calculating the risk of PE in the algorithm developed by the Foetal Medicine Foundation, which is available online at https://foetalmedicine.org/research/assess/pre-eclampsia. The values of biochemical parameters, including a placental growth factor (PLGF) level, are also necessary for the calculation [110]. The calculation yields a number reflecting a specific risk for that individual patient. The FMF calculator also enables estimating the risk of intrauterine growth restriction. Risk of pre-eclampsia higher than **1:150** is usually considered an indication for aspirin prophylaxis. Screening based on risk factors, uterine artery flow parameters, MAP, as well as PAPP-A and PLGF levels enables identification of 95% of cases of early pre-eclampsia with a false positive rate of 10% [111]. The PE management algorithm based on risk stratification is shown in Figure 6.1.

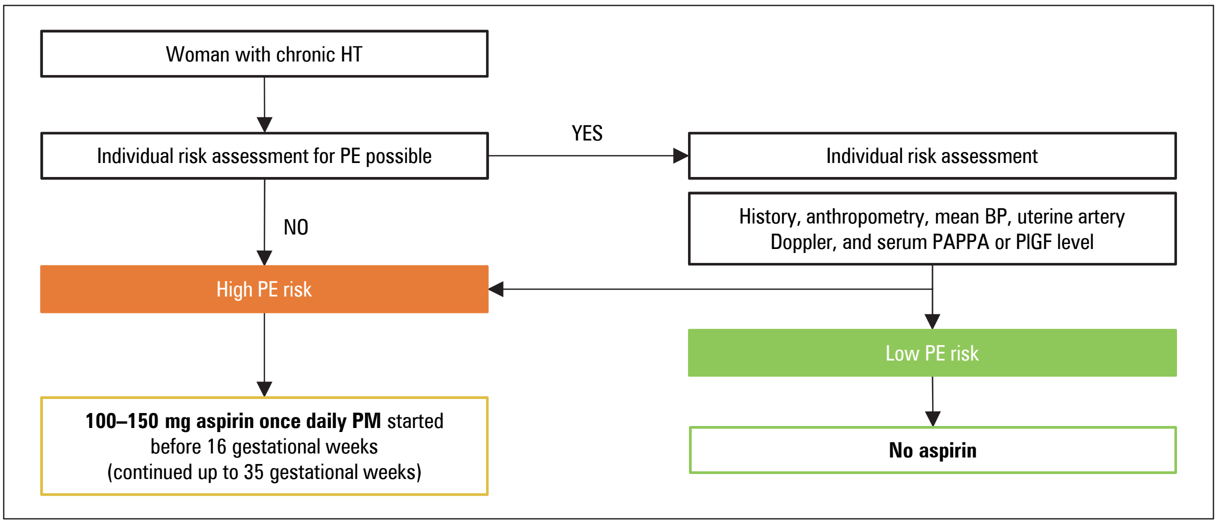

Figure 6.1. Assessing the risk of pre-eclampsia (PE)

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 pulsatility index (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 placental growth factor (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 pre-eclampsia. Within 4 weeks following the assessment, 80% of women with the sFlt-1/PLGF ratio above a derived cut-off developed PE, as compared to only 7% of those with the sFlt-1/PLGF ratio below a derived cut-off [113, 114]. The sFlt-1/PLGF ratio < 38 virtually rules out the onset of PE within the next seven days [115, 116].

6.2.2. Prevention of pre-eclampsia

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, i.e. before the uterine spiral artery remodelling ends, significantly reduces the risk of pre-eclampsia [117, 118]. The comprehensive, multicentre Aspirin versus Placebo in Pregnancies at High Risk for Preterm Pre-eclampsia (ASPRE) study confirmed that aspirin showed an 80% and a 63% reduction in the risk of developing PE < 34 weeks and < 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 100–150 mg aspirin dose taken *p.o.* at bedtime is recommended [120]. Aspirin is undoubtedly the best prevention in women at high risk for preterm pre-eclampsia, identified using the risk calculation algorithm based on biophysical and biochemical parameters (Fig. 6.1). However, where individual risk assessment is not possible, aspirin prophylaxis should be considered in all patients with at least one high-risk factor or at least two moderate risk factors (Tab. 6.1).

6.2.3. Diagnosis of pre-eclampsia

Pre-eclampsia 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 blood pressure 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 h. 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 summarised in Table 6.3.

6.3. Management of gestational hypertension and pre-eclampsia

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 foetus. 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 one in ten 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].

Pre-eclampsia, 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, foetal and neonatal mortality and morbidity. Pre-eclampsia may progress to eclampsia with stroke and seizures, life-threatening central nervous system conditions. Pregnancy-induced HT is also associated with other serious complications such as disseminated intravascular coagulation, liver damage, the HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome or premature placental abruption.

Based on the time of onset, clinical course and differences in foetal 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 intrauterine growth restriction and chronic foetal hypoxia, which may lead to intrauterine death [123]. The early-onset PE is also associated with high dynamics of blood pressure elevation, proteinuria and maternal multi-organ 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 disor-

PREVENTION OF PRE-ECLAMPSIA IN PREGNANT WOMEN WITH HYPERTENSION — RECOMMENDATIONS

A single 100–150 mg aspirin dose taken *p.o.* 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 personalised 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 1:150	

Table 6.2. Diagnostic criteria of pre-eclampsia according to the ISSHP [1]

Pregnancy-induced hypertension developing after 20 gestational weeks coexisting with one or more of the following new onset conditions*:
• Proteinuria (quantitative method — Table 4.1) • Acute kidney injury (creatinine ≥ 1 mg/dL or ≥ 90 μmol/L) • Liver involvement (elevated transaminases, e.g. AST or ALT > 40 IU/L) and/or severe right upper quadrant or epigastric pain • Haematological complications (PLT count < 150,000/μL, DIC, haemolysis) • Neurological complications (e.g. 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)

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

Table 6.3. Signs and symptoms of pre-eclampsia

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

der, 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 foetal size is normal, although foetal 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.

Hypertension 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 be 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 SBP ≥ 160 mm Hg and/or DBP ≥ 110 mm Hg;
- monitoring and recording home blood pressure — 2 measurements in the morning and 2 measurements in the evening (Tab. 5.1);
- maternal biochemical blood and urine tests (Tab. 5.2);
- foetal ultrasound in order to assess foetal growth.

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

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

Diuretics should not be used in women with pre-eclampsia and gestational hypertension, due to an increased risk of placental abruption.

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II-receptor blockers are contraindicated during pregnancy [126, 127].

Atenolol is not recommended during pregnancy due to its reported adverse effect on foetal growth [128].

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

Foetal ultrasound for foetal growth assessment should be performed at least once every four weeks. The diagnosis of intrauterine growth restriction with abnormal blood flow parameters in uteroplacental and fetoplacental circulation is an indication for in-patient admission and intensive foetal wellbeing surveillance (Fig. 5.4)

In women with uncomplicated pregnancy-induced hypertension with no other concomitant maternal abnormality, normal laboratory test findings and normal foetal biometry, foetal wellbeing should be assessed with outpatient cardiotocography once a week from 36 gestational weeks onwards (Fig. 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 blood pressure values [129].

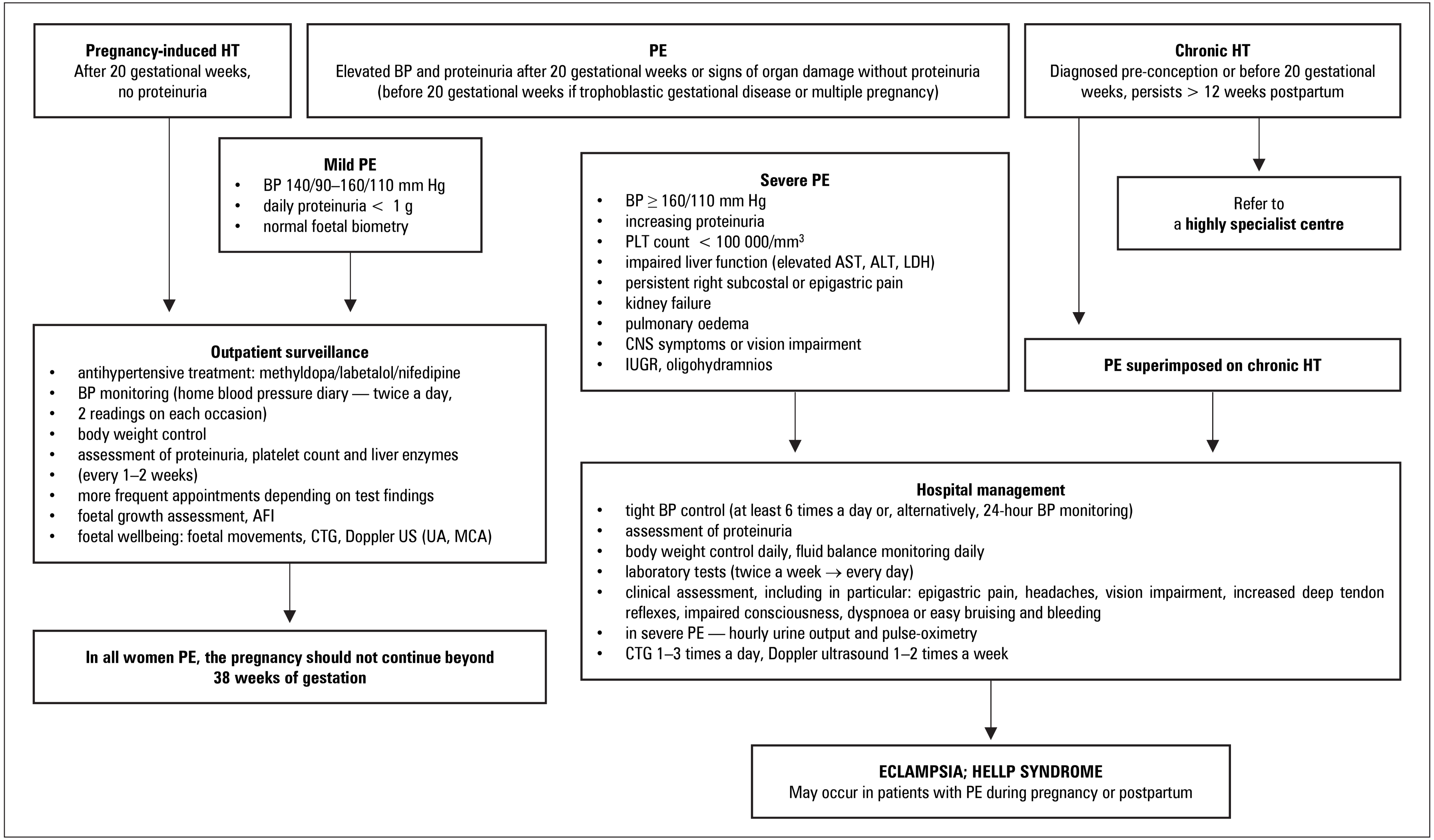

Figure 6.2. Perinatal care for women with gestational hypertension (HT) and pre-eclampsia (PE)

MANAGEMENT OF PRE-ECLAMPSIA — 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 foetal 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 foetal maturation is recommended	Level A
Magnesium sulphate in an intravenous infusion to prevent seizures and for foetal 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 foetal life-threatening emergency	Level C

6.3.2. Management of pre-eclampsia

The diagnosis of PE is an indication for hospital referral and for the following actions to be taken (Fig. 6.3):
- maternal surveillance including:
  - — blood pressure measurement at least 4 times a day,
  - — monitoring diuresis and protein excretion in 24 hr 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;
- in women with severe HT, the intensive antihypertensive treatment aims at achieving BP < 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 h urine collection is above 3.5 g, anticoagulant prophylaxis using low molecular weight heparins (LMWH) 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 foetal neuroprotection [130, 131];
- if a delivery before 34 gestational weeks is needed, a short (48-hour) course of antenatal glucocorticoid (betamethasone or dexamethasone in a total dose of 24 mg) therapy for foetal maturation should be administered [132];
- foetal wellbeing surveillance including:
  - — foetal movement counting every day,
  - — cardiotocography at least once a day,
  - — foetal ultrasound for foetal growth assessment every 2 weeks,
  - — additionally, if intrauterine growth restriction is confirmed, Doppler ultrasound should be performed in order to assess fetoplacental blood flow and biophysical profile of the foetus. Depending on the findings, it should be repeated at least once a week.

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

Emergency delivery is indicated in women with pre-eclampsia:
- after 37 gestational weeks [133];
- before 37 gestational weeks, if:
  - — the SBP is above 160 mm Hg systolic blood pressure and DBP 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 foetal life-threatening emergency,
  - — there is intrauterine foetal 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

MANAGEMENT OF LIFE-THREATENING EMERGENCIES IN PREGNANT WOMEN WITH HYPERTENSION

SEVERE PRE-ECLAMPSIA / PRE-ECLAMPSIA

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

24–34 gestational weeks
- conservative management with intensive maternal and foetal surveillance in a highly specialist perinatology centre
- course of steroids (24 mg/48 h — betamethasone)
- magnesium sulphate ($MgSO_4$) (4–6 g *i.v.* 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/foetal deterioration

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 foetal condition, gestational age, and cervical ripening

Postpartum
- aggressive treatment and monitoring
- antihypertensive treatment — BP up to 150/100 mm Hg
- seizure prevention — magnesium sulphate ($MgSO_4$) *i.v.* 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 *i.v.* (max. 30 mg),
- magnesium sulphate ($MgSO_4$). 4–6 g *i.v.* 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 ($MgSO_4$) *i.v.* 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 — haemolysis: 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 *i.v.* 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** (24mg/48h – betamethasone)
- **magnesium sulphate** ($MgSO_4$) (4–6 g *i.v.* within the first 30 minutes followed by an infusion at 1 g/h continued for up to 48 hours)

Before27 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
- foetal deterioration

Figure 6.3. Management of life-threatening emergencies in pregnant women with hypertension (HT)

have detrimental clinical consequences, leading to the sudden onset of severe, refractory or malignant HT, acute kidney injury 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 one study in a small sample [142].

7.1.1. Definition of fibromuscular dysplasia

FMD is an idiopathic, segmental, non-inflammatory and non-atherosclerotic 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 hypertension, 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 hypertension or malignant HT;
- refractory HT;
- a small kidney in patients without known uropathy;
- abdominal murmur without obvious features of atherosclerosis;
- FMD affecting at least one 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 at the 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 (MRA), computed tomography angiography (CTA) and digital subtraction angiography (DSA) 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 revascularisation 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 revascularisation or those without indications for revascularisation should be monitored clinically, with biochemical tests and diagnostic imaging. Doppler ultrasound of renal arteries should be performed in women after angioplasty due to renal artery stenosis secondary to FMD who plan to conceive in order to rule out restenosis [143].

Antihypertensive treatment in women with FMD should follow principles presented in Chapter 5.7. A 75–100 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 one 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 ar-

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 revascularisation 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* and aneurysms, if indicated, is recommended prior to conception	Level C

*In arteries other than renal

tery 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 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, primary aldosteronism is diagnosed by demonstrating that aldosterone levels in an individual are not affected by the factors, which physiologically mediate its secretion [145, 146]. The detailed guidance on the diagnosis and treatment of PA has been provided in the PTNT Recommendations of 2019 [3].

Pregnancy is associated with physiological changes to the activity of the RAAS [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 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 mineralocorticoid receptor antagonist, favourably 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 4.2. There are only limited data regarding the clinical presentation of PA in pregnant women. Classical symptoms, such as hypokalaemia and dysregulated blood pressure 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 hypokalaemia or incidental finding of an adrenal tumour.

7.2.3. Screening for primary aldosteronism

The key screening for primary aldosteronism 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 hypokalaemia. 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 renin-angiotensin-aldosterone system; 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].

7.2.4. Confirming the diagnosis of primary aldosteronism

In Poland, the saline suppression test (SST) and the captopril challenge test (CCT) 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 two main causes of PA. According to the guidelines, computed tomography 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 MRAs are recommended in patients with bilateral adrenal hyperplasia. The initial daily dose of spironolactone should be 12.5–25 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 feminising 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 foetus 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 foetal outcomes. A potentially adverse effect of spironolactone-induced natriuresis on intrauterine growth has been postulated [2, 147–149].

Eplerenone is a newer, selective mineralocorticoid receptor antagonist, 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 primary aldosteronism. There is no evidence to support the adverse effect of eplerenone on the foetus. 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 eplere-

MANAGEMENT OF SUSPECTED PRIMARY ALDOSTERONISM IN WOMEN AT REPRODUCTIVE AGE AND IN PREGNANCY — RECOMMENDATIONS

The determination of the renin-to-aldosterone ratio (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

none in breast milk is believed to be negligible and too low to affect the infant, it should be considered in breastfeeding women who need antimineralocorticoid treatment, provided that the above limitations have been taken into account [147–149].

7.3. Catecholamine-secreting tumours

7.3.1. Definition

Catecholamine-secreting adrenal tumours are referred to as pheochromocytoma, whereas other chromaffin cell-derived tumours, 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 foetus. Early diagnosis in pregnancy and appropriate treatment reduce the maternal and foetal mortality to < 5% and < 15%, respectively [151–154].

Only a small portion of maternal catecholamines are transferred to foetal circulation. Furthermore, foetuses have high catecholamine clearance, which ensures their low levels in foetal circulation. Transient catecholamine peaks in women with PPGL may adversely affect the uteroplacental circulation causing vasoconstriction, which may lead to placental abruption and foetal 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 delilvery. PPGL should be suspected in pregnant women with refractory HT [152].

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

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

7.3.3. Diagnosis of PPGL

Plasma or urinary fractionated metanephrines (normetanephrine and metanephrine measured separately) are the most useful and the most sensitive biochemical assays 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 (VMA) 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 the reproductive age prior to conception in order to rule out PPGL.

7.3.4. Treatment of PPGL

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

MANAGEMENT OF SUSPECTED PPGL 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

can then be performed either as a combined procedure with the Caesarean section or after the delivery. The Caesarean 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 two times a day to the maximum daily dose of 1 mg per body weight kg *p.o.* in 2–3 divided doses) or doxazosin (in doses increased gradually from 2 mg to the maximum daily dose of 32 mg *p.o.* in 1–2 divided doses) are used for 2–3 weeks prior to surgery. As phenoxybenzamine passes through the placenta, neonatal surveillance for hypotonia and respiratory failure is recommended during for the first few days after birth. About 1% of phenoxybenzamine passes to human breast milk. The FDA considers phenoxybenzamine the pregnancy category C drug. Due to its more favourable 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 calcium channel blocker (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. Hypotonia 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 foetal wellbeing surveillance continued throughout the treatment. As a part of preoperative management, it is important to address hypovolaemia by ensuring an adequate supply of sodium and fluids in order 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 phentolamine administered *i.v.*, usually at the dose of 2–5 mg, and repeated if necessary.

7.4. Coarctation of the aorta

Coarctation of the aorta (CoA) accounts for 5–10% 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 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]. 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.

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

Coarctation of the aorta (CoA) accounts for 5–10% 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]. Patients with CoA generally tolerate pregnancy well. A higher incidence of PE and higher miscarriage rate were reported in pregnant women after a previous correction of 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 centre.

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 sino-tubular junction (STJ). 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 > 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 blood pressure 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) magnetic resonance imaging 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 40–45mm, vaginal delivery with spinal anaesthesia and a shortened second stage should be considered. Delivery by Caesarean section may be considered in women with the diameter of the aorta between 40–45 mm and should be considered in women with the diameter of the aorta > 45 mm [2].

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 anaesthesia and a shortened second stage should be considered. Delivery by Caesarean section may be considered in women with the diameter of the aorta between 40–45 mm and should be considered in women with the diameter of the aorta > 45 mm	Level C
Pregnancy is not recommended in patients with BAV and the diameter of the ascending aorta > 50 mm	Level C

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 (REM) sleep [162].

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 apnoea (OSA) in pregnancy depends on gestational age. OSA is estimated to affect several per cent of pregnant women during the first trimester, as compared to almost 30% during the third trimester [164]. Diagnostic criteria of SDB assumed for adult populations also apply to pregnant women. Based on them, mild apnoea, defined as AHI (apnoea-hypopnea index, that is, the mean number of apnoea and hypopnea events per hour of sleep) of < 15 is diagnosed the most commonly [164].

7.6.2. Pathogenesis of obstructive sleep apnoea in pregnancy

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

7.6.3. Maternal and foetal complications of obstructive sleep apnoea

Patients with apnoea 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 apnoea causes intrauterine growth restriction. However, it has been demonstrated that SDB in pregnant women is an independent risk factor for neonatal heart failure and respiratory failure (or cardiorespiratory arrest), which require postnatal resuscitation and/or neonatal intensive care [168, 169].

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

Diagnosis and assessing the severity of obstructive sleep apnoea should be based on objective evaluation with cardiorespiratory polygraphy or polysomnography [170, 171].

7.6.5. Treatment of obstructive sleep apnoea in pregnancy

The current guidelines do not recommend specific treatment of SDB in pregnant women. A few studies have shown partial efficacy of behavioural treatments in sleep apnoea 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 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 (CPAP) devices offer better efficacy.

7.7. Kidney disease

7.7.1. Chronic kidney disease

Chronic kidney disease (CKD) significantly increases the risk of HT in pregnant women [172]. HT affects about 20–50% 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 lead to HT [174].

It can be assumed that, as it is true for the CKD in non-pregnant 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 foetal complications increases. At the same time, maternal and perinatal outcomes are likely to be worse. PE, eclampsia, prematurity and low birth

Non-invasive treatments (positional therapy, mandibular advancement devices, CPAP) are recommended in pregnant women with diagnosed OSA	Level B
For the sake of foetal 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

weight 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. 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 [177].

The eGFR cannot be calculated in pregnant women with commonly used formulas, such as the MDRD (Modification of Diet in Renal Disease) formula or the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula [6]. Therefore, the severity of CKD in pregnant women is primarily based on the pre-conception 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 foetal complications. It is necessary to determine the stage of kidney disease pre-conception, urinary protein (preferably albumin) excretion in 24hr 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 blood pressure — 2 measurements in the morning and 2 measurements in the evening) is necessary for pregnant women with CKD. A 24-hour ambulatory blood pressure monitoring should also be considered [176].

Target BP in pregnant women with CKD is similar to the target BP in pregnant women without CKD, i.e. the target DBP in pregnant women with HT and CKD should be 81–85 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 non-pregnant women, such as ACEI, angiotensin receptor blockers and mineralocorticoid receptor antagonists, are prohibited in pregnant women with CKD. Since methyldopa is largely excreted by the kidneys, the Summary of Product Characteristics (SmPC) 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 8–12 hours and with the eGFR < 30 mL/min/1.73 m^2 the interval between the doses be extended to 12–25 hours. Dialysis removes methyldopa; therefore, a booster dose of 250 mg is recommended to prevent blood pressure 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 oedema, mainly secondary to nephrotic syndrome [30]. However, as the first line intervention in peripheral oedema, 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 100–150 mg before 16 gestational weeks. This reduces the risk of PE, prematurity and intrauterine growth restriction [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 body weight kg [175, 180]. However, there are no recommendations as to the salt intake in pregnant women with HT and CKD. Anaemia 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

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 oedema, 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 haemoglobin 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 haemodialysis) with maternal serum urea level of about 100 mg/dL (15 mmol/L).	Level C

iron, vitamin B12 and folic acid deficiency [181]. Erythropoiesis-stimulating agents (ESAs) may be considered in pregnant women with CKD after normalising 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. Haemoglobin levels in pregnant women should be maintained within the range of 10–11 g/L. However, ESAs should be used with great caution in pregnant women, as they may contribute to the blood pressure increase, especially when the treatment was too aggressive and the haemoglobin level increased too rapidly or above the recommended value, i.e. 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 haemodialysis in a pregnant woman are determined based clinical assessment (e.g. 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 haemodialysis [181]. It is now believed that the haemodialysis should be started in pregnant women with serum urea level of about 100 mg/dL (15 mmol/L). The minimum duration of haemodialysis in patients with no residual diuresis, both those started on haemodialysis during pregnancy and those who have already been on haemodialysis at conception should be 36 hours/week. It is necessary to maintain serum urea levels of 60–90 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 personalised approach in patients previously treated with peritoneal analysis. The conversion to haemodialysis 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 5–15% of patients [186–188]. Premature ventricular contractions (PVC) usually originating from the ventricular outflow tract occur in more than 50% of patients referred for 24-hour ECG registration 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 15–20 degrees to the left causes changes to the ST segment and the 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 10–15 beats per minute as compared to the non-pregnant state, which is a physiological phenomenon, but it may hinder the diagnosis of heart failure 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 1/3 of affected pregnant women. Exacerbation of pre-existent arrhythmia in pregnancy occurs in another 30-40% of affected pregnant women [2]. Arrhythmia in pregnancy significantly increases the risk of gestational and perinatal complications and may lead to the development of foetal congenital anomalies [190].

7.8.3. Diagnosis of arrhythmia pre-conception and in pregnancy

The ESC guidelines recommend electrocardiography (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 atrial fibrillation or flutter.

Women with arrhythmia present both pre-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 three 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.

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 foetus, 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.safefoetus.com prior to starting pharmacological treatment of a pregnant woman.

It should be noted that non-vitamin K oral anticoagulation drugs are contraindicated during pregnancy [193].

Women with congenital long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) 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 centre should be considered in women with poorly tolerated or refractory supraventricular tachycardia. 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 7.1 A–D.

The ESC guidelines recommend electrocardiography (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.safefoetus.com* is recommended prior to starting pharmacological treatment of a pregnant woman	Level C
Beta-blockers are recommended during pregnancy and postpartum in women with long QT syndrome (LQTS) or catecholaminergic polymorphic ventricular tachycardia (CPVT)	Level C
Ablation guided by electroanatomical mapping in an experienced centre 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

7.9. Acute coronary syndromes

7.9.1. Aetiology and epidemiology

The risk of myocardial infarction in pregnancy is 3–4 times higher than in age-matched non-pregnant women [2]. Risk factors include maternal age, HT, diabetes, obesity, smoking, hyperlipidaemia, eclampsia, multiple gestation, thrombophilia, cocaine misuse, and perinatal haemorrhage or infection [2]. Spontaneous coronary artery dissection (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 spontaneous coronary artery dissections. 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: non-iatrogenic and non-traumatic intimal tear or spontaneous vasa vasorum rupture. In both mechanisms, intramural haemorrhage 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 oestrogen levels leading to loss of normal corrugation of elastic fibres, 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 dyspnoea, nausea or abdominal pain. An electrocardiogram is in keeping with myocardial infarction with (STEMI, 57–85% of cases) or without (NSTEMI, 15–43% of cases) ST elevation [2, 200, 201]. P-SCAD may cause cardiogenic shock or cardiac arrest. Compared to non-pregnant 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 1/3 of patients [201].

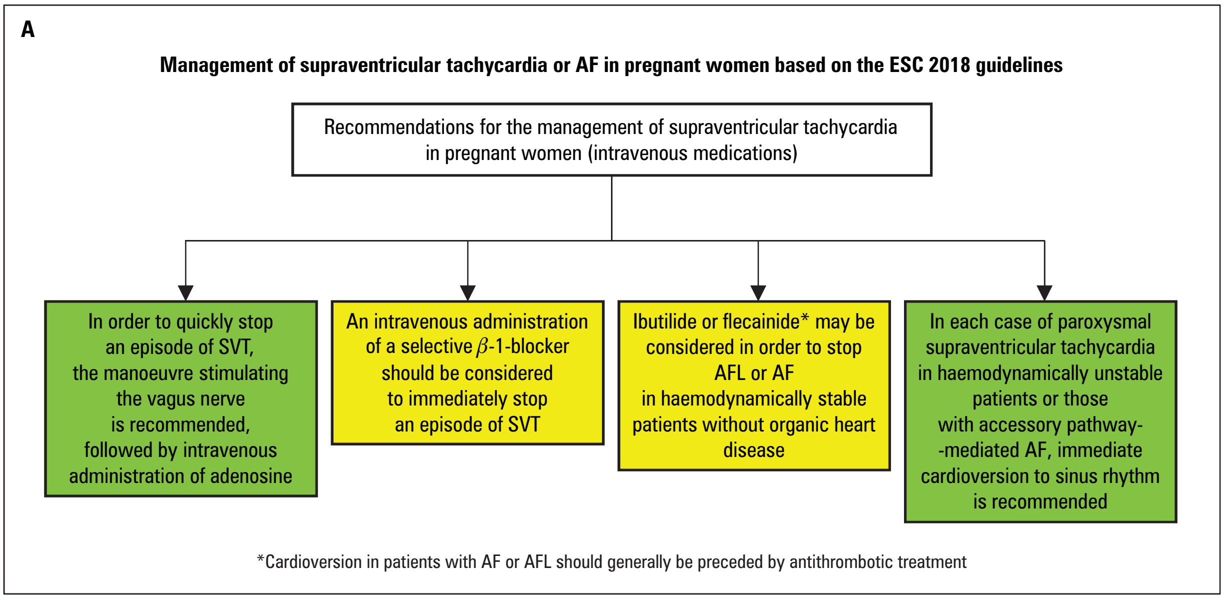

Figure 7.1A. Management of arrhythmia in pregnancy

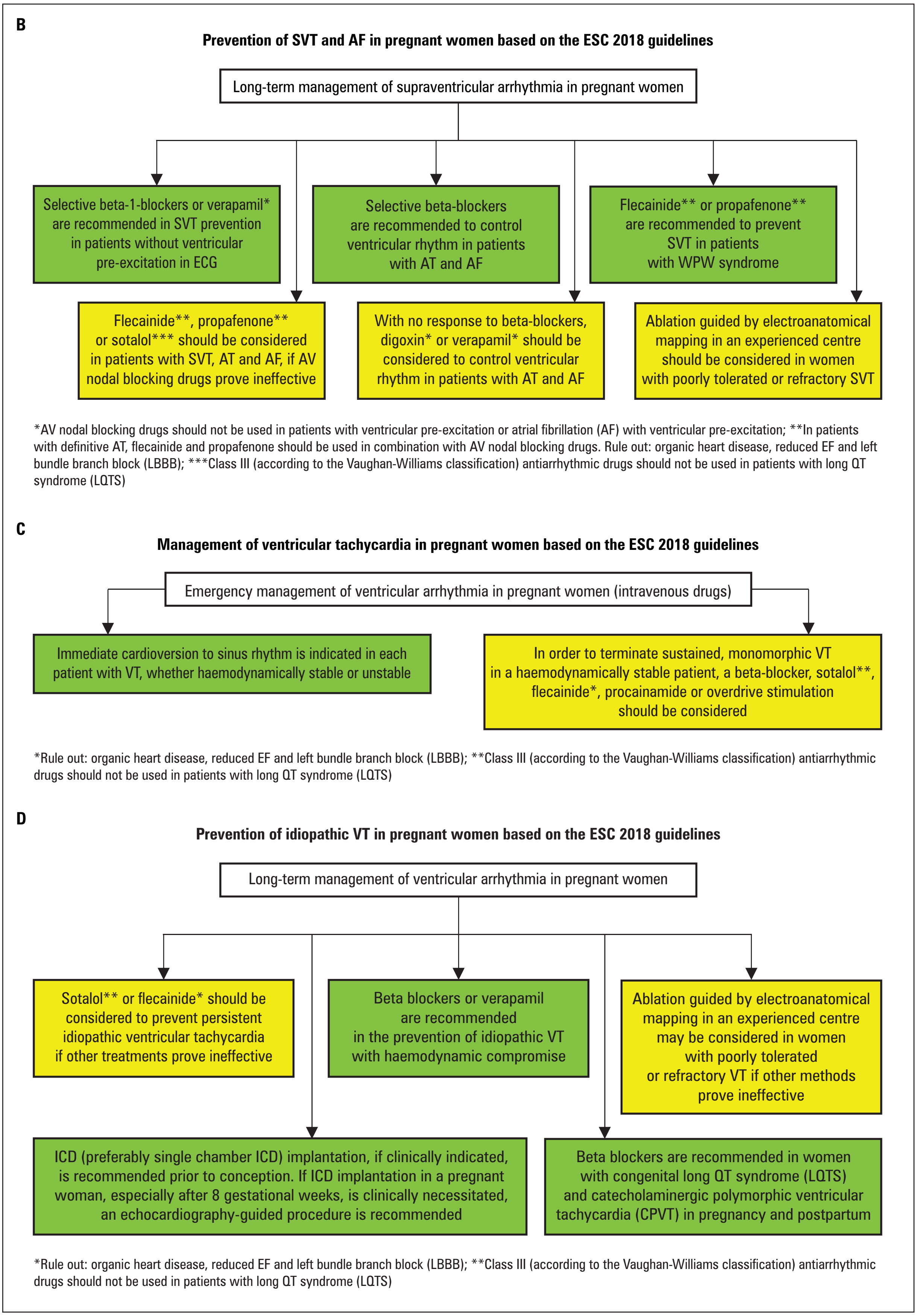

Figure 7.1B–D. Management of arrhythmia in pregnancy

7.9.4. Diagnosis

The diagnosis of SCAD is made based on clinical presentation and coronary angiography findings. Five types of spontaneous coronary artery dissection 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 (IVUS) or optical coherent tomography of coronary arteries are additionally needed to confirm the diagnosis of SCAD [197, 198].

7.9.5. Treatment

The diagnostic management of chest pain in pregnant women is similar to that in non-pregnant women and is shown in Figure 7.2A. The management of myocardial infarction in pregnant women is no 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 non-invasive approach should be considered (class of recommendation IIa, level of evidence C) [2]. However, given the predominant non-atherosclerotic aetiology of acute coronary syndromes (P-SCAD), the optimum management strategy for patients with P-SCAD needs to be discussed separately. It is currently believed that non-invasive 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 ischaemia, invasive treatment should be considered. The percutaneous coronary intervention (PCI) with stenting is the method of choice which effectively restores normal coronary blood flow in about half of cases [200, 203]. The

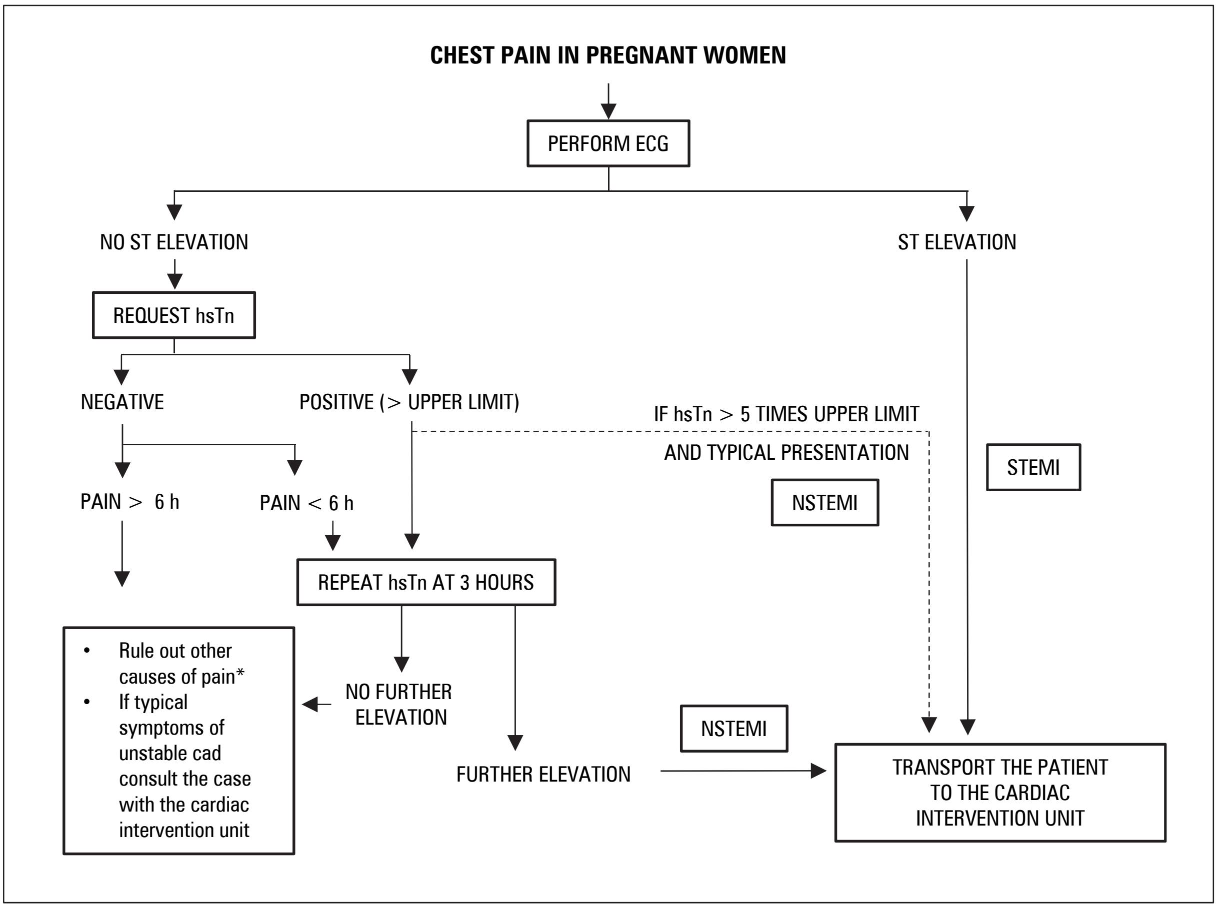

Figure 7.2.A. Management of chest pain in pregnant women; *E.g. pulmonary embolism, aortic dissection, GERD, muskuloskeletal disorder, pericarditis or myocarditis

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 ischaemia	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 optimisation of ionising 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

coronary artery bypass grafting (CABG) 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 assistant device (LVAD), the extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pump (IABP) 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 gynaecologist-obstetrician, consultant anaesthesiologist, 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, angiotensin converting enzyme inhibitors, mineralocorticoid receptor antagonists) 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 0-4%, and the mean left ventricular ejection fraction was about 50%. Although long-term prognosis is favourable, there is a 10-20% 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 (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery. The diagnosis can only be confirmed in the absence of a pre-existent cardiovascular disease as a key pre-requisite. 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 (STAT-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 symp-

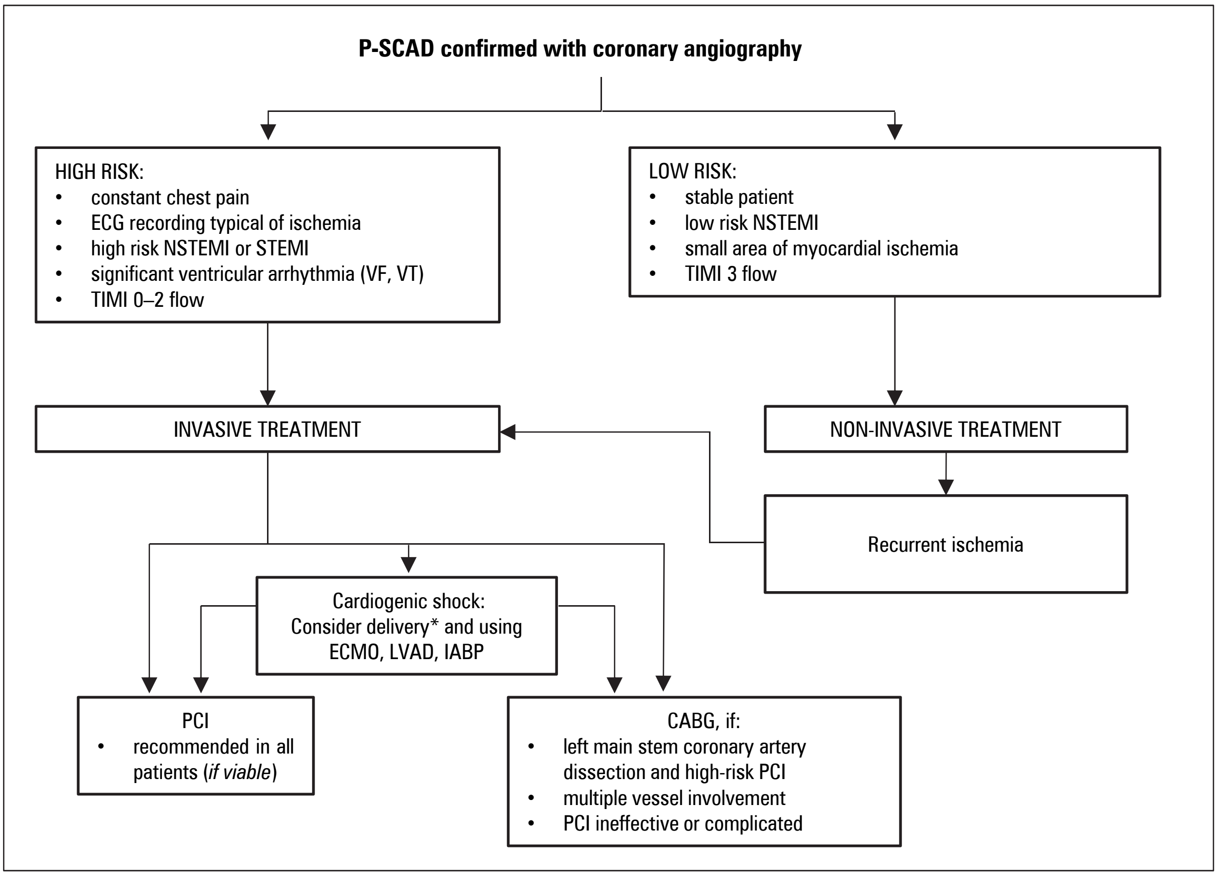

Figure 7.2.B. Treatment algorithm for the pregnancy-associated spontaneous coronary artery dissectiont; *MDT management including consultant cardiologist, consultant gynaecologist, consultant neonatologist, consultant anaesthesiologist and consultant cardiac surgeon

toms 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-BNP) and echocardiography are recommended in women with dyspnoea, who present with congested lung fields, peripheral oedema 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 (Fig. 7.3) [207].

Haemodynamically stable patients should be treated according to the recommendations for treatment of chronic and acute heart failure developed by the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy [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

The evaluation of the left ventricular ejection fraction (LVEF) during transthoracic echocardiography and serum B-natriuretic peptide (BNP) or N-terminal pro-BNP (NT-BNP) 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 EF < 35% and/or those treated with bromocriptine	Level C

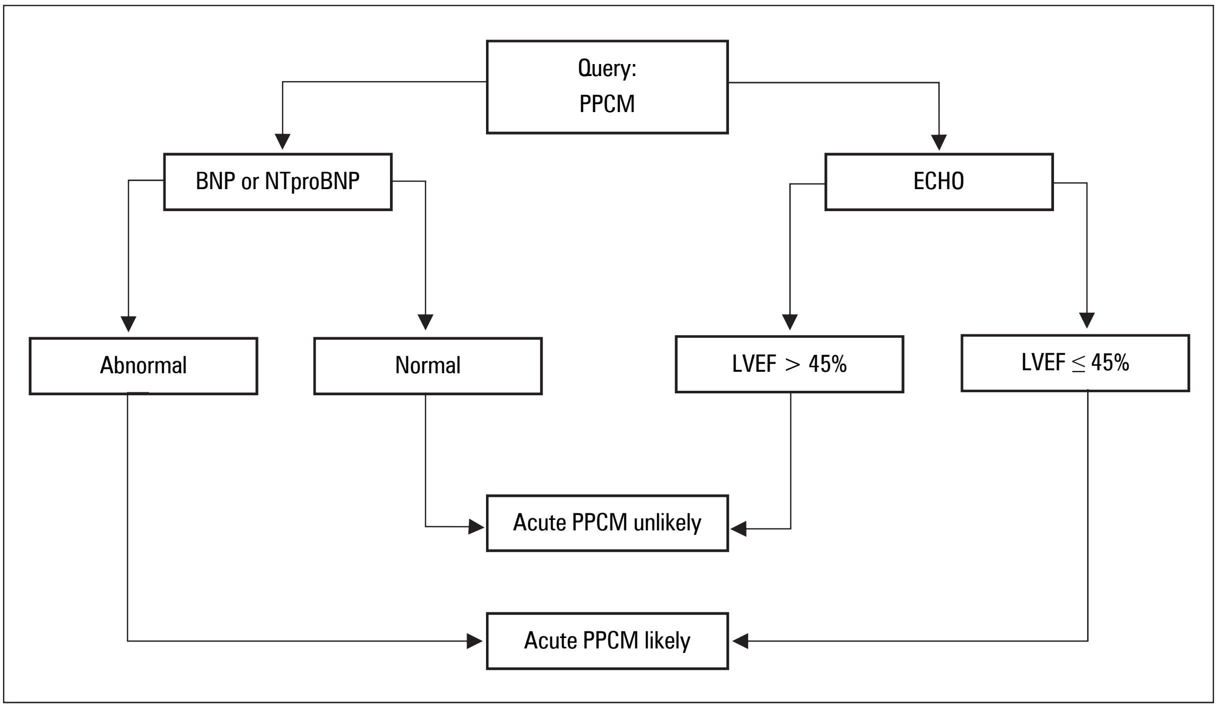

Figure 7.3. Diagnostic algorithm for peripartum cardiomyopathy (PPCM)

Poland), nitrates and possibly (sparingly) diuretics are recommended. Vaginal delivery is preferred in stable patients.

After delivery, ACEI/ARB and β-blockers in maximum tolerated doses are recommended. Furthermore, mineralocorticoids (eplerenone) are recommended in women with EF < 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 ≤ 35% or those treated with bromocriptine [2, 206]. In haemodynamically unstable patients (SBP < 90 mm Hg, O_2 saturation < 90%, lactates > 2 mmol/L), treatment with levosimendan (0.1 μg/kg/minute for 24 h) or mechanical circulatory support (MCS) devices such as intra-aortic balloon pump (IABP) or transcutaneous temporary ventricular support device (e.g. Impella) with or without ECMO [206] is recommended. Caesarean section is the preferred delivery method in unstable patients with PPCM [209]. In patients with persistently low EF < 35% despite optimal medical therapy, wearable cardioverter-defibrillator (WCD), implantable cardioverter-defibrillator (ICD), 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 3–6 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, in order 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.

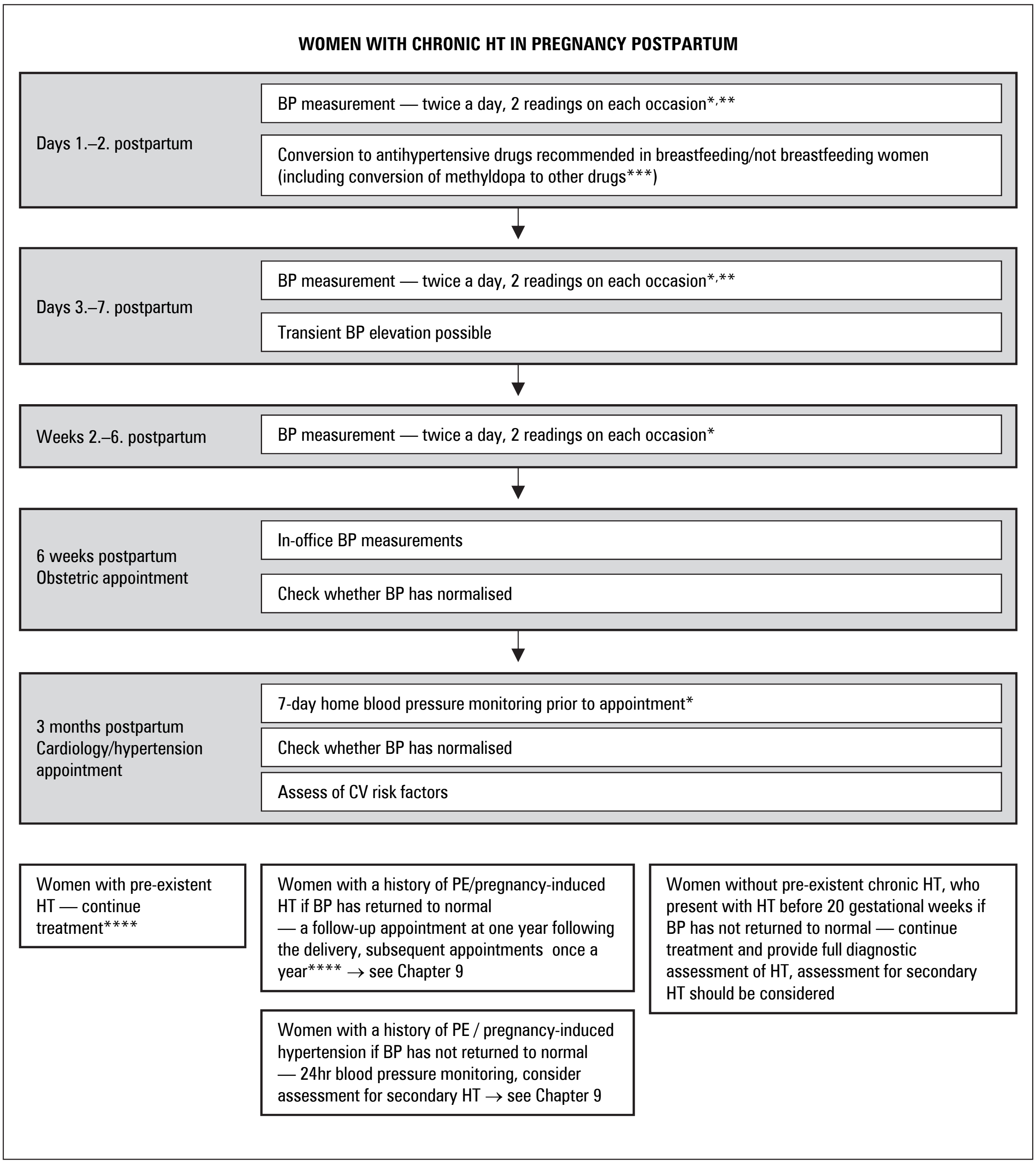

Figure 8.1. Postpartum management of women with hypertension (HT) during pregnancy; *or more frequently, depending on clinical presentation; **4 times a day if admitted as an inpatient; ***do not discontinue methyldopa; ****appointment frequency should be determined based on clinical presentation

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]. Beta-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

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 blood pressure 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

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 amlodipine seems a reasonable choice if extended-release nifedipine is unavailable. The data on the safety of verapamil in breastfeeding women is contradictory.

Angiotensin-converting enzyme inhibitors 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. Some guidelines only recommend enalapril. There are special indications for using ACEI in breastfeeding women with heart failure and peripartum cardiomyopathy. 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 US National Library of Medicine National Institute of Health and updated on an ongoing basis.

9. Management of women with a history of gestational hypertension, pre-eclampsia and other gestational complications

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

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 body mass index, higher BP values and pre-existent abnormal lipid profile preconception as compared to women without gestational HT or PE [217].

9.1.1. The risk of hypertension in women with a history of gestational hypertension and pre-eclampsia

It was shown that women with a history of pregnancy-induced hypertensive disorder had a higher risk of HT than in 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 25–32-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 normalise post-partum 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 6–12 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].

9.1.2. Gestational hypertension and pre-eclampsia 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 Nord Trøndelag Health Study (HUNT) showed that women with a history of pregnancy-induced HT or PE in their first pregnancy had a higher pre-conception body mass index, waist circumference, blood pressure, heart rate, as well as glucose and triglyceride levels as compared to 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 Prevention of Renal and Vascular End-Stage Disease (PREVEND) 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 to women without pregnancy-induced HT [222]. This indicates the need to monitor blood pressure, 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 pre-eclampsia 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 multi-slice computed tomography indicated that the frequency of coronary artery calcium score ≥ 95th percentile determined for the general population aged 45–55 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 to those 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 pre-eclampsia 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 to 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 two large meta-analyses. The risk of PE remained significant even after adjustment for conventional cardiovascular risk factors [227, 228].

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 blood pressure has not normalised postpartum	Level C
Both office and out-of-office blood pressure measurements are recommended in women with a history of pregnancy-induced HT or PE	Level C

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, low birth weight, stillbirth. These complications should be ascertained as a part of taking history to determine cardiovascular risk factor in women [229].

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

The studies discussed above indicate a significant association between pregnancy-induced hypertension and/or PE, and cardiovascular risk in later life [230]. Regular monitoring of cardiovascular risk factors, including regular blood pressure measurements, 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 indicates 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 pre-eclampsia on children's long-term health

Gestational HT and/or PE are among the main risk factors for prematurity and intrauterine growth restriction. Both prematurity and intrauterine growth restriction are associated with low birth weight, 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 chronic kidney disease (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 1–2%. HT was diagnosed in 6 to 25% of preterm children assessed at the age of 6–12 years, and in 16% of

Table 9.1. Management of women with a history of gestational hypertension/pre-eclampsia (HT/PE)

Time point	Speciality	BP measurement	Actions	Assessments
6 weeks after delivery	Obstetrics	Office BP measurement Home BP measurement (Fig. 8.1)	Educate on high cardiovascular risk Refer to cardiologist/hypertension specialist	Depending on the clinical presentation
3 months after delivery	Cardiology/ /hypertension	Office BP measurement Home BP measurement (Fig. 8.1) Consider ABPM	CV risk determination CV risk assessment Patient education on the need and possibility to address modifiable cardiovascular risk factors (non-pharmacological 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/ /hypertension	Office BP measurement Home BP measurement (7-day home blood pressure 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 OGTT Lipid profile Serum creatinine and uric acid levels
Once a year	Cardiology/ /hypertension	Office BP measurement Home BP measurement (7-day home blood pressure 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

teenagers assessed at the age of 13–18 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 small for gestational age (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 low birth weight (< 1500 g) and SBP in later life are noteworthy. Blood pressure 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 low birth weight 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 low birth weight had SBP 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 conclude that children born prematurely or with a very low birth weight have moderately higher blood pressure 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 born prematurely or with very low birth weight 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 7–8 years the prevalence of glomerular hyperfiltration assessed as microalbuminuria ranged between 8% and 12% in prematurely born children as compared to 0–2.1% in the age-matched general population. It is estimated that the risk of CKD in children born < 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 acute kidney injury (AKI). CKD was found in this group in 10% of children within 1–3 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 blood pressure elevation. These include [236]:

- impaired nephrogenesis and reduced nephron number;
- micro-damage of the central nervous system and sympathetic nervous system upregulation;
- the consequences of perinatal metabolic programming, including late metabolic effects of intrauterine growth restriction, postnatal pharmacological and nutritional treatment with associated body composition abnormalities and metabolic syndrome, as well as
- early vascular ageing (EVA) resulting in increased arterial stiffness, reduced the 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 foetal 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, i.e. a shift to accumulating energy in visceral fat. According to the metabolic programming concept, if high-calorie nutrition is available, children with low birth weight, 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 blood pressure. 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 calibre of retinal arteries at the age of 6. The differences were the 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 Paediatric 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 Paediatric Society [237].

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

Children with HT diagnosed prior to discharge from the neonatal ward should be consulted and provided with specialist care in a paediatric hypertension centre. Further diagnostic and therapeutic management should be based on the current paediatric 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 paediatric nephrology, hypertension and urology centre. 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 blood pressure 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 paediatric hypertension centre 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 paediatric centre with hypertension 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 blood pressure 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 (Tab. 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

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

→

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]
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

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 three 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

Blood pressure measurement with an automated oscillometric device on the right arm is recommended in post-discharge care. Cuff length encircling at least 80–100% of arm circumference, and cuff width–to–arm circumference ratio of 0.45 to 0.55 are 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, blood pressure measurement should be taken in calm (preferably asleep) infants, 15–30 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 5–10-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.

Appendix 1. 7-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 blood pressure**	**Diastolic blood pressure**	**Heart rate**	**Time**	**Systolic blood pressure**	**Diastolic blood pressure**	**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)									

1. Bramham K, Parnell B, Nelson-Piercy C et al. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ 2014; 348: g2301.
2. Brown MA, Magee LA, Kenny LC et al. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. Hypertension 2018; 72: 24–43.
3. Williams B, Mancia G, Spiering W et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39: 3021–3104.
4. Tykarski A, Narkiewicz K, Gaciong Z et al. Zasady postępowania w nadciśnieniu tętniczym — 2015 rok. Wytyczne Polskiego Towarzystwa Nadciśnienia Tętniczego. Nadciśnienie Tętnicze w Praktyce 2015; 1: 1–70.
5. Cornette J, Ruys TP, Rossi A et al. Hemodynamic adaptation to pregnancy in women with structural heart disease. Int J Cardiol 2013; 168: 825–831.

References

1. Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2018; 13(1): 291–310, doi: 10.1016/j.preghy.2018.05.004, indexed in Pubmed: 29803330.
2. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018; 39(34): 3165–3241, doi: 10.1093/eurheartj/ehy340, indexed in Pubmed: 30165544.
3. Tykarski A, Narkiewicz K, Gaciong Z, et al. Zasady postępowania w nadciśnieniu tętniczym 2019. Wytyczne Polskiego Towarzystwa Nadciśnienia Tętniczego. Nadciśnienie Tętnicze w Praktyce. 2019; 5(1): 1–86.
4. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39(33): 3021–3104, doi: 10.1093/eurheartj/ehy339, indexed in Pubmed: 30165516.
5. Zhou M, Daubresse M, Stafford RS, et al. National trends in the ambulatory treatment of hypertension in the United States, 1997–2012. PLoS One. 2015; 10(3): e0119292, doi: 10.1371/journal.pone.0119292, indexed in Pubmed: 25738503.
6. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013; 122(5): 1122–1131, doi: 10.1097/01.AOG.0000437382.03963.88, indexed in Pubmed: 24150027.
7. Lowe SA, Bowyer L, Lust K, et al. The SOMANZ Guidelines for the Management of Hypertensive Disorders of Pregnancy 2014. Aust N Z J Obstet Gynaecol. 2015; 55(1): 11–16, doi: 10.1111/ajo.12253, indexed in Pubmed: 25308532.
8. Magee LA, Pels A, Helewa M, et al. Canadian Hypertensive Disorders of Pregnancy Working Group. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. J Obstet Gynaecol Can. 2014; 36(5): 416–441, indexed in Pubmed: 24927294.
9. Mounier-Vehier C, Amar J, Boivin JM, et al. Hypertension and pregnancy: expert consensus statement from the French Society of Hypertension, an affiliate of the French Society of Cardiology. Fundamental & Clinical Pharmacology. 2016; 31(1): 83–103, doi: 10.1111/fcp.12254.
10. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014; 2(6): e323–e333, doi: 10.1016/S2214-109X(14)70227-X, indexed in Pubmed: 25103301.
11. Gillon TER, Pels A, von Dadelszen P, et al. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. PLoS One. 2014; 9(12): e113715, doi: 10.1371/journal.pone.0113715, indexed in Pubmed: 25436639.
12. Bramham K, Parnell B, Nelson-Piercy C, et al. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ. 2014; 348: g2301, doi: 10.1136/bmj.g2301, indexed in Pubmed: 24735917.
13. Chahine KM, Sibai BM. Chronic hypertension in pregnancy: new concepts for classification and management. Am J Perinatol. 2019; 36(2): 161–168, doi: 10.1055/s-0038-1666976, indexed in Pubmed: 29986344.
14. ACOG Practice Bulletin No. 203 Summary: Chronic hypertension in pregnancy. Obstet Gynecol. 2019; 133(1): 215–219, doi: 10.1097/AOG.0000000000003021, indexed in Pubmed: 30575669.
15. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001; 104(5): 515–521, indexed in Pubmed: 11479246.
16. Brown MA. Is there a role for ambulatory blood pressure monitoring in pregnancy? Clin Exp Pharmacol Physiol. 2014; 41(1): 16–21, doi: 10.1111/1440-1681.12106, indexed in Pubmed: 23651133.
17. Brown MA, Buddle ML, Martin A. Is resistant hypertension really resistant? Am J Hypertens. 2001; 14(12): 1263–1269, indexed in Pubmed: 11775136.
18. Malha L, August P. Secondary hypertension in pregnancy. Curr Hypertens Rep. 2015; 17(7): 53, doi: 10.1007/s11906-015-0563-z, indexed in Pubmed: 26068655.
19. Bello NA, Miller E, Cleary K, et al. Out of office blood pressure measurement in pregnancy and the postpartum period. Curr Hypertens Rep. 2018; 20(12): 101, doi: 10.1007/s11906-018-0901-z, indexed in Pubmed: 30361886.
20. Brown MA, Roberts L, Davis G, et al. Can we use the Omron T9P automated blood pressure monitor in pregnancy? Hypertens Pregnancy. 2011; 30(2): 188–193, doi: 10.3109/10641955.2010.507854, indexed in Pubmed: 20846049.
21. Prejbisz A, Kabat M, Januszewicz A. Pomiary ciśnienia tętniczego poza gabinetem lekarskim. Metody, interpretacja i zastosowanie w praktyce. Medycyna Praktyczna, Kraków 2017.
22. Feldman D. Blood pressure monitoring during pregnancy. Blood Pressure Monitoring. 2001; 6(1): 1–7, doi: 10.1097/00126097-200102000-00001.
23. Phelan LK, Brown MA, Davis GK, et al. A prospective study of the impact of automated dipstick urinalysis on the diagnosis of preeclampsia. Hypertens Pregnancy. 2004; 23(2): 135–142, doi: 10.1081/PRG-120028289, indexed in Pubmed: 15369647.
24. Cade TJ, Gilbert SA, Polyakov A, et al. The accuracy of spot urinary protein-to-creatinine ratio in confirming proteinuria in pre-eclampsia. Aust N Z J Obstet Gynaecol. 2012; 52(2): 179–182, doi: 10.1111/j.1479-828X.2011.01409.x, indexed in Pubmed: 22335428.
25. Waugh J, Hooper R, Lamb E, et al. Spot protein-creatinine ratio and spot albumin-creatinine ratio in the assessment of pre-eclampsia: a diagnostic accuracy study with decision-analytic model-based economic evaluation and acceptability analysis. Health Technol Assess. 2017; 21(61): 1–90, doi: 10.3310/hta21610, indexed in Pubmed: 29064366.
26. Redman CWG. Hypertension in pregnancy: the NICE guidelines. Heart. 2011; 97(23): 1967–1969, doi: 10.1136/heartjnl-2011-300949, indexed in Pubmed: 21990386.
27. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1–39.e14, doi: 10.1016/j.echo.2014.10.003, indexed in Pubmed: 25559473.
28. Cornette J, Ruys TPE, Roos-Hesselink JW, et al. Hemodynamic adaptation to pregnancy in women with structural heart disease. Int J Cardiol. 2013; 168(2): 825–831, doi: 10.1016/j.ijcard.2012.10.005, indexed in Pubmed: 23151412.
29. Committee on Obstetric P. Committee Opinion No. 723: Guidelines for Diagnostic Imaging During Pregnancy and Lactation. Obstet Gynecol. 2017; 130(4): e210–e216.
30. Abramowicz J. Benefits and risks of ultrasound in pregnancy. Semin Perinatol. 2013; 37(5): 295–300, doi: 10.1053/j.semperi.2013.06.004.
31. American Institute of Ultrasound in Medicine. Statement on the Safe Use of Doppler Ultrasound During 11–14 week scans (or earlier in pregnancy). AIUM 2011, revised 2016 [cited 2018 31.07.2018]; Available from: www.aium.org/officialStatements.17.
32. Kanal E, Barkovich AJ, Bell C, et al. ACR guidance document on MR safe practices: 2013. J Magn Reson Imaging. 2013; 37(3): 501–530, doi: 10.1002/jmri.24011, indexed in Pubmed: 23345200.
33. Tirada N, Dreizin D, Khati NJ, et al. Imaging pregnant and lactating patients. Radiographics. 2015; 35(6): 1751–1765, doi: 10.1148/rg.2015150031, indexed in Pubmed: 26466183.
34. Albert TSE, Akahane M, Parienty I, et al. An international multicenter comparison of time-SLIP unenhanced MR angiography and contrast-enhanced CT angiography for assessing renal artery stenosis: the renal artery contrast-free trial. AJR Am J Roentgenol. 2015; 204(1): 182–188, doi: 10.2214/AJR.13.12022, indexed in Pubmed: 25539255.

35. Bekiesińska-Figatowska M, Romaniuk-Doroszewska A, Brągoszewska H, et al. Diagnostic imaging of pregnant women. The role of magnetic resonance imaging. Pol J Radiol. 2017; 82: 220–226, doi: 10.12659/PJR.900071, indexed in Pubmed: 28507642.
36. Sjösten N, Nabi H, Westerlund H, et al. Effect of depression onset on adherence to medication among hypertensive patients: a longitudinal modelling study. J Hypertens. 2013; 31(7): 1477–84; discussion 1484, doi: 10.1097/HJH.0b013e32836098d1, indexed in Pubmed: 23666419.
37. Abushouk AI, Sanei Taheri M, Pooransari P, et al. Pregnancy screening before diagnostic radiography in rmergency department; an educational review. Emerg. 2017; 5(1): e60, indexed in Pubmed: 28894775.
38. RSNA Statement on Safety of the Developing Fetus in Medical Imaging During Pregnancy. Reviewed: 04.03.2018. [cited: 05.08.2018]; Available from: www.rsna.org/uploadedFiles/RSNA/Content/Role_based_pages/Media/RSNA-Imaging-During-Pregnancy-Statement.
39. Bocking AD. Assessment of fetal heart rate and fetal movements in detecting oxygen deprivation in-utero. Eur J Obstet Gynecol Reprod Biol. 2003; 110 Suppl 1: S108–S112, indexed in Pubmed: 12965098.
40. Practice bulletin no. 145: antepartum fetal surveillance. Obstet Gynecol. 2014; 124(1): 182–192, doi: 10.1097/01.AOG.0000451759.90082.7b, indexed in Pubmed: 24945455.
41. Bartsch E, Medcalf KE, Park AL, et al. High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016; 353: i1753, doi: 10.1136/bmj.i1753, indexed in Pubmed: 27094586.
42. Baschat AA. Planning management and delivery of the growth-restricted fetus. Best Pract Res Clin Obstet Gynaecol. 2018; 49: 53–65, doi: 10.1016/j.bpobgyn.2018.02.009, indexed in Pubmed: 29606482.
43. Manning FA, Snijders R, Harman CR, et al. Fetal biophysical profile score. VI. Correlation with antepartum umbilical venous fetal pH. Am J Obstet Gynecol. 1993; 169(4): 755–763, indexed in Pubmed: 8238129.
44. Turan S, Turan OM, Berg C, et al. Computerized fetal heart rate analysis, Doppler ultrasound and biophysical profile score in the prediction of acid-base status of growth-restricted fetuses. Ultrasound Obstet Gynecol. 2007; 30(5): 750–756, doi: 10.1002/uog.4101, indexed in Pubmed: 17688309.
45. Thompson RS, Trudinger BJ. Doppler waveform pulsatility index and resistance, pressure and flow in the umbilical placental circulation: an investigation using a mathematical model. Ultrasound Med Biol. 1990; 16(5): 449–458, indexed in Pubmed: 2238251.
46. Hecher K, Bilardo CM, Stigter RH, et al. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet Gynecol. 2001; 18(6): 564–570, doi: 10.1046/j.0960-7692.2001.00590.x, indexed in Pubmed: 11844190.
47. Weiner CP. The relationship between the umbilical artery systolic/diastolic ratio and umbilical blood gas measurements in specimens obtained by cordocentesis. Am J Obstet Gynecol. 1990; 162(5): 1198–1202, indexed in Pubmed: 2187351.
48. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Folic acid for the prevention of neural tube defects: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009; 150(9): 626–631, indexed in Pubmed: 19414842.
49. Ruager-Martin R, Hyde MJ, Modi N. Maternal obesity and infant outcomes. Early Hum Dev. 2010; 86(11): 715–722, doi: 10.1016/j.earlhumdev.2010.08.007, indexed in Pubmed: 20846795.
50. Zetterström K, Lindeberg SN, Haglund B, et al. Maternal complications in women with chronic hypertension: a population-based cohort study. Acta Obstet Gynecol Scand. 2005; 84(5): 419–424, doi: 10.1111/j.0001-6349.2005.00508.x, indexed in Pubmed: 15842204.
51. Ananth CV, Savitz DA, Bowes WA, et al. Influence of hypertensive disorders and cigarette smoking on placental abruption and uterine bleeding during pregnancy. Br J Obstet Gynaecol. 1997; 104(5): 572–578, indexed in Pubmed: 9166200.
52. Sibai BM, Lindheimer M, Hauth J, et al. Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med. 1998; 339(10): 667–671, doi: 10.1056/NEJM199809033391004, indexed in Pubmed: 9725924.
53. Cruz MO, Gao W, Hibbard JU. Obstetrical and perinatal outcomes among women with gestational hypertension, mild preeclampsia, and mild chronic hypertension. Am J Obstet Gynecol. 2011; 205(3): 260.e1–260.e9, doi: 10.1016/j.ajog.2011.06.033, indexed in Pubmed: 22071056.
54. Hanson M, Bardsley A, De-Regil L, et al. The International Federation of Gynecology and Obstetrics (FIGO) recommendations on adolescent, preconception, and maternal nutrition: "Think Nutrition First". Int J Gynecol Obstet. 2015; 131: S213, doi: 10.1016/s0020-7292(15)30023-0.
55. Sochaczewska D, Czeszyńska Maria B, Konefał H, et al. Assessment of relationship between cord blood cotinine levels and some factors of perinatal hypoxia. Ginekol Pol. 2009; 80(12): 920–926, indexed in Pubmed: 20120937.
56. Polańska K, Hanke W. Influence of smoking during pregnancy on children's health – overview of epidemiologic studies. Przegl Epidemiol. 2005; 59(1): 117–123, indexed in Pubmed: 16013417.
57. Kociszewska-Najman B, Pietrzek B, Mazanowska N, et al. Fetal alcohol spectrum disorder. Breastfeeding and alcohol. Ginekologia i Perinatologia Praktyczna. 2017; 2(4): 93–109.
58. Antoniou T, Camacho X, Yao Z, et al. Comparative effectiveness of angiotensin-receptor blockers for preventing macrovascular disease in patients with diabetes: a population-based cohort study. CMAJ. 2013; 185(12): 1035–1041, doi: 10.1503/cmaj.121771, indexed in Pubmed: 23836857.
59. Niemiec T, Dębski R, Kotarski J, et al. The statement of Polish Gynaecologic Society experts concerning drinking water consumption in women in reproductive age, pregnancy and breast feeding. Ginekol Pol. 2009; 80(7): 538–47.
60. EFSA NDA Panel. EFSA Panel on Dietetic Products NaA. Scientific opinion on the safety of caffeine. EFSA Journal. 2015; 13: 4102.
61. Koletzko B, Cremer M, Flothkötter M, et al. Diet and lifestyle before and during pregnancy. Practical recommendations of the Germany-wide healthy start: young family network. Geburtshilfe Frauenheilkd. 2018; 78(12): 1262–1282, doi: 10.1055/a-0713-1058, indexed in Pubmed: 30655650.
62. Aune D, Schlesinger S, Henriksen T, et al. Physical activity and the risk of preterm birth: a systematic review and meta-analysis of epidemiological studies. BJOG. 2017; 124(12): 1816–1826, doi: 10.1111/1471-0528.14672, indexed in Pubmed: 28374930.
63. Magro-Malosso ER, Saccone G, Di Tommaso M, et al. Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2017; 96(8): 921–931, doi: 10.1111/aogs.13151, indexed in Pubmed: 28401531.
64. Abalos E, Duley L, Steyn DW, et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2001; 10(2): CD002252, doi: 10.1002/14651858.CD002252, indexed in Pubmed: 11406040.
65. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med. 2015; 372(5): 407–417, doi: 10.1056/NEJMoa1404595, indexed in Pubmed: 25629739.
66. Webster LM, Conti-Ramsden F, Seed PT, et al. Impact of antihypertensive treatment on maternal and perinatal outcomes in pregnancy complicated by chronic hypertension. A systematic review and meta-analysis. J Am Heart Assoc. 2017; 6(5), doi: 10.1161/JAHA.117.005526, indexed in Pubmed: 28515115.
67. Magee LA, von Dadelszen P, Singer J, et al. The CHIPS Randomized Controlled Trial (Control of hypertension in pregnancy study): Is severe hypertension just an elevated blood pressure? Hypertension. 2016; 68(5): 1153–1159, doi: 10.1161/HYPERTENSIONAHA.116.07862, indexed in Pubmed: 27620393.

68. , et al Pels A, Mol BWJ, Singer J, et al. Influence of gestational age at initiation of antihypertensive therapy. Hypertension. 2018; 71(6):1170–1177.
69. Nzelu D, Dumitrascu-Biris D, Nicolaides KH, et al. Chronic hypertension: first-trimester blood pressure control and likelihood of severe hypertension, preeclampsia, and small for gestational age. Am J Obstet Gynecol. 2018; 218(3): 337.e1–337.e7, doi: 10.1016/j.ajog.2017.12.235, indexed in Pubmed: 29305253.
70. Hoeltzenbein M, Beck E, Fietz AK, et al. Pregnancy outcome after first trimester use of methyldopa. A prospective cohort study. Hypertension. 2017; 70(1): 201–208, doi: 10.1161/HYPERTENSIONAHA.117.09110, indexed in Pubmed: 28533329.
71. Cockburn J, Moar VA, Ounsted M, et al. Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. Lancet. 1982; 1(8273): 647–649, indexed in Pubmed: 6121965.
72. Duan L, Ng A, Chen W, et al. β-blocker exposure in pregnancy and risk of fetal cardiac anomalies. JAMA Intern Med. 2017; 177(6): 885–887, doi: 10.1001/jamainternmed.2017.0608, indexed in Pubmed: 28418448.
73. Clark SM, Dunn HE, Hankins GDV. A review of oral labetalol and nifedipine in mild to moderate hypertension in pregnancy. Semin Perinatol. 2015; 39(7): 548–555, doi: 10.1053/j.semperi.2015.08.011, indexed in Pubmed: 26344738.
74. Yakoob MY, Bateman BT, Ho E, et al. The risk of congenital malformations associated with exposure to β-blockers early in pregnancy: a meta-analysis. Hypertension. 2013; 62(2): 375–381, doi: 10.1161/HYPERTENSIONAHA.111.00833, indexed in Pubmed: 23753416.
75. Pieper P. Use of medication for cardiovascular disease during pregnancy. Nature Reviews Cardiology. 2015; 12(12): 718–729, doi: 10.1038/nrcardio.2015.172.
76. Nakhai-Pour HR, Rey E, Bérard A. Antihypertensive medication use during pregnancy and the risk of major congenital malformations or small-for-gestational-age newborns. Birth Defects Res B Dev Reprod Toxicol. 2010; 89(2): 147–154, doi: 10.1002/bdrb.20238, indexed in Pubmed: 20437474.
77. Meidahl Petersen K, Jimenez-Solem E, Andersen JT, et al. β-blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population-based cohort study. BMJ Open. 2012; 2(4), doi: 10.1136/bmjopen-2012-001185, indexed in Pubmed: 22815467.
78. Bortolus R, Ricci E, Chatenoud L, et al. Nifedipine administered in pregnancy: effect on the development of children at 18 months. BJOG. 2000; 107(6): 792–794, indexed in Pubmed: 10847237.
79. Giannubilo SR, Bezzeccheri V, Cecchi S, et al. Nifedipine versus labetalol in the treatment of hypertensive disorders of pregnancy. Arch Gynecol Obstet. 2012; 286(3): 637–642, doi: 10.1007/s00404-012-2371-x, indexed in Pubmed: 22581388.
80. Gazzolo D, Visser GH, Russo A, et al. Pregnancy-induced hypertension, antihypertensive drugs and the development of fetal behavioural states. Early Hum Dev. 1998; 50(2): 149–157, indexed in Pubmed: 9483388.
81. Jannet D, Carbonne B, Sebban E, et al. Nicardipine versus metoprolol in the treatment of hypertension during pregnancy: a randomized comparative trial. Obstet Gynecol. 1994; 84(3): 354–359, indexed in Pubmed: 8058230.
82. Ahn HK, Nava-Ocampo AA, Han JY, et al. Exposure to amlodipine in the first trimester of pregnancy and during breastfeeding. Hypertens Pregnancy. 2007; 26(2): 179–187, doi: 10.1080/10641950701204554, indexed in Pubmed: 17469008.
83. Lawrence MR, Broughton Pipkin F. Some observations on the effects of a calcium channel blocker, nitrendipine, in early human pregnancy. Br J Clin Pharmacol. 1987; 23(6): 683–692, doi: 10.1111/j.1365-2125.1987.tb03102.x, indexed in Pubmed: 3300758.
84. Allen J, Maigaard S, Forman A, et al. Acute effects of nitrendipine in pregnancy-induced hypertension. Br J Obstet Gynaecol. 1987; 94(3): 222–226, indexed in Pubmed: 3567118.
85. Wide-Swensson DH, Ingemarsson I, Lunell NO, et al. Calcium channel blockade (isradipine) in treatment of hypertension in pregnancy: a randomized placebo-controlled study. Am J Obstet Gynecol. 1995; 173(3 Pt 1): 872–878, indexed in Pubmed: 7573260.
86. Weber-Schoendorfer C, Hannemann D, Meister R, et al. The safety of calcium channel blockers during pregnancy: a prospective, multicenter, observational study. Reprod Toxicol. 2008; 26(1): 24–30, doi: 10.1016/j.reprotox.2008.05.065, indexed in Pubmed: 18585452.
87. Sørensen HT, Czeizel AE, Rockenbauer M, et al. The risk of limb deficiencies and other congenital abnormalities in children exposed in utero to calcium channel blockers. Acta Obstet Gynecol Scand. 2001; 80(5): 397–401, indexed in Pubmed: 11328214.
88. Kurtzman JL, Thorp JM, Spielman FJ, et al. Do nifedipine and verapamil potentiate the cardiac toxicity of magnesium sulfate? Am J Perinatol. 1993; 10(6): 450–452, doi: 10.1055/s-2007-994629, indexed in Pubmed: 8267811.
89. Belfort MA, Anthony J, Buccimazza A, et al. Hemodynamic changes associated with intravenous infusion of the calcium antagonist verapamil in the treatment of severe gestational proteinuric hypertension. Obstet Gynecol. 1990; 75(6): 970–974, indexed in Pubmed: 1692982.
90. Anugu VR, Nalluri N, Asti D, et al. New-onset lone atrial fibrillation in pregnancy. Ther Adv Cardiovasc Dis. 2016; 10(4): 274–276, doi: 10.1177/1753944716644584, indexed in Pubmed: 27099243.
91. Ruys TPE, Maggioni A, Johnson MR, et al. Cardiac medication during pregnancy, data from the ROPAC. Int J Cardiol. 2014; 177(1): 124–128, doi: 10.1016/j.ijcard.2014.09.013, indexed in Pubmed: 25499355.
92. Bullo M, Tschumi S, Bucher BS, et al. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension. 2012; 60(2): 444–450, doi: 10.1161/HYPERTENSIONAHA.112.196352, indexed in Pubmed: 22753220.
93. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med. 2006; 354(23): 2443–2451, doi: 10.1056/NEJMoa055202, indexed in Pubmed: 16760444.
94. Magee LA, von Dadelszen P, Singer J, et al. Control of hypertension in pregnancy study randomised controlled trial-are the results dependent on the choice of labetalol or methyldopa? BJOG. 2016; 123(7): 1135–1141, doi: 10.1111/1471-0528.13568, indexed in Pubmed: 26259808.
95. Moroz LA, Simpson LL, Rochelson B. Management of severe hypertension in pregnancy. Semin Perinatol. 2016; 40(2): 112–118, doi: 10.1053/j.semperi.2015.11.017, indexed in Pubmed: 26726135.
96. Ryan R, McCarthy F. Hypertension in pregnancy. Obstetrics, Gynaecology & Reproductive Medicine. 2018; 28(5): 141–147, doi: 10.1016/j.ogrm.2018.03.003.
97. Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. JAMA. 2002; 287(24): 3183–3186, indexed in Pubmed: 12076198.
98. Matijevic R, Johnston T. In vivo assessment of failed trophoblastic invasion of the spiral arteries in pre-eclampsia. Br J Obstet Gynaecol. 1999; 106(1): 78–82, indexed in Pubmed: 10426264.
99. Meekins JW, Pijnenborg R, Hanssens M, et al. A study of placental bed spiral arteries and trophoblast invasion in normal and severe pre-eclamptic pregnancies. Br J Obstet Gynaecol. 1994; 101(8): 669–674, indexed in Pubmed: 7947500.
100. Brownfoot F, Kaitu'u-Lino T, Beard S, et al. sFlt-1 and soluble endoglin concentrations in serum vs plasma in preterm preeclampsia: Are they interchangeable for biomarker studies? Pregnancy Hypertens. 2017; 10: 18–21, doi: 10.1016/j.preghy.2017.07.138, indexed in Pubmed: 29153675.
101. Yliniemi A, Makikallio K, Korpimaki T, et al. Combination of PAPPA, fhCGβ, AFP, PlGF, sTNFR1, and maternal characteristics in prediction of early-onset preeclampsia. Clin Med Insights Reprod Health. 2015; 9: 13–20, doi: 10.4137/CMRH.S21865, indexed in Pubmed: 26106266.
102. Roberts L, Chaemsaithong P, Sahota DS, et al. Protocol for measurement of mean arterial pressure at 10-40weeks' gesta-

tion. Pregnancy Hypertens. 2017; 10: 155–160, doi: 10.1016/j.preghy.2017.08.002, indexed in Pubmed: 29153670.
103. Tan MY, Syngelaki A, Poon LC, et al. ASPRE trial: incidence of preterm pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm. Ultrasound Obstet Gynecol. 2018; 51(6): 738–742, doi: 10.1002/uog.19019, indexed in Pubmed: 29380918.
104. Velauthar L, Plana MN, Kalidindi M, et al. First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55,974 women. Ultrasound Obstet Gynecol. 2014; 43(5): 500–507, doi: 10.1002/uog.13275, indexed in Pubmed: 24339044.
105. Kleinrouweler CE, Bossuyt PMM, Thilaganathan B, et al. Value of adding second-trimester uterine artery Doppler to patient characteristics in identification of nulliparous women at increased risk for pre-eclampsia: an individual patient data meta-analysis. Ultrasound Obstet Gynecol. 2013; 42(3): 257–267, doi: 10.1002/uog.12435, indexed in Pubmed: 23417857.
106. Cnossen JS, Morris RK, ter Riet G, et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. CMAJ. 2008; 178(6): 701–711, doi: 10.1503/cmaj.070430, indexed in Pubmed: 18332385.
107. Papageorghiou A, Yu C, Erasmus I, et al. Assessment of risk for the development of pre-eclampsia by maternal characteristics and uterine artery Doppler. BJOG. 2005; 112(6): 703–709, doi: 10.1111/j.1471-0528.2005.00519.x.
108. Martin AM, Bindra R, Curcio P, et al. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11-14 weeks of gestation. Ultrasound Obstet Gynecol. 2001; 18(6): 583–586, doi: 10.1046/j.0960-7692.2001.00594.x, indexed in Pubmed: 11844193.
109. Yu CKH, Smith GCS, Papageorghiou AT, et al. An integrated model for the prediction of preeclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. Am J Obstet Gynecol. 2005; 193(2): 429–436, doi: 10.1016/j.ajog.2004.12.014, indexed in Pubmed: 16098866.
110. Poon LCY, Kametas NA, Maiz N, et al. First-trimester prediction of hypertensive disorders in pregnancy. Hypertension. 2009; 53(5): 812–818, doi: 10.1161/HYPERTENSIONAHA.108.127977, indexed in Pubmed: 19273739.
111. Poon LC, Nicolaides KH. Early prediction of preeclampsia. Obstet Gynecol Int. 2014; 2014: 297397, doi: 10.1155/2014/297397, indexed in Pubmed: 25136369.
112. Gallo DM, Wright D, Casanova C, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19-24 weeks' gestation. Am J Obstet Gynecol. 2016; 214(5): 619.e1–619.e17, doi: 10.1016/j.ajog.2015.11.016, indexed in Pubmed: 26627730.
113. Agrawal S, Cerdeira AS, Redman C, et al. Meta-analysis and systematic review to assess the role of soluble FMS-like tyrosine kinase-1 and placenta growth factor ratio in prediction of preeclampsia: the SaPPPhirE Study. Hypertension. 2018; 71(2): 306–316, doi: 10.1161/HYPERTENSIONAHA.117.10182, indexed in Pubmed: 29229743.
114. Zeisler H, Llurba E, Chantraine F, et al. Soluble FMS-like tyrosine kinase-1-to-placental growth factor ratio and time to delivery in women with suspected preeclampsia. Obstet Gynecol. 2016; 128(2): 261–269, doi: 10.1097/AOG.0000000000001525, indexed in Pubmed: 27399996.
115. Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016; 374(1): 13–22, doi: 10.1056/NEJMoa1414838, indexed in Pubmed: 26735990.
116. Dragan I, Georgiou T, Prodan N, et al. Screening for pre-eclampsia using sFlt-1/PlGF ratio cut-off of 38 at 30-37 weeks' gestation. Ultrasound Obstet Gynecol. 2017; 49(1): 73–77, doi: 10.1002/uog.17301, indexed in Pubmed: 27619203.
117. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol. 2018; 218(3): 287–293.e1, doi: 10.1016/j.ajog.2017.11.561, indexed in Pubmed: 29138036.
118. Bujold E, Roberge S, Nicolaides KH. Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation. Prenat Diagn. 2014; 34(7): 642–648, doi: 10.1002/pd.4403, indexed in Pubmed: 24799357.
119. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med. 2017; 377(7): 613–622, doi: 10.1056/NEJMoa1704559, indexed in Pubmed: 28657417.
120. Hermida RC, Ayala DE, Mojón A, et al. Ambulatory blood pressure control with bedtime aspirin administration in subjects with prehypertension. Am J Hypertens. 2009; 22(8): 896–903, doi: 10.1038/ajh.2009.83, indexed in Pubmed: 19407805.
121. Steegers EAP, von Dadelszen P, Duvekot JJ, et al. Pre-eclampsia. Lancet. 2010; 376(9741): 631–644, doi: 10.1016/S0140-6736(10)60279-6, indexed in Pubmed: 20598363.
122. Zhao M, Yin Y, Wei J, et al. Trophoblastic debris extruded from hydatidiform molar placentae activates endothelial cells: Possible relevance to the pathogenesis of preeclampsia. Placenta. 2016; 45: 42–49, doi: 10.1016/j.placenta.2016.07.007, indexed in Pubmed: 27577709.
123. Huppertz B. Trophoblast differentiation, fetal growth restriction and preeclampsia. Pregnancy Hypertens. 2011; 1(1): 79–86, doi: 10.1016/j.preghy.2010.10.003, indexed in Pubmed: 26104234.
124. Abalos E, Duley L, Steyn DW, et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2007; 1: CD002252.
125. Duley L, Henderson-Smart DJ, Meher S. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev. 2006(3): CD001449, doi: 10.1002/14651858.CD001449.pub2, indexed in Pubmed: 16855969.
126. Centers for Disease Control and Prevention (CDC). Postmarketing surveillance for angiotensin-converting enzyme inhibitor use during the first trimester of pregnancy--United States, Canada, and Israel, 1987-1995. MMWR Morb Mortal Wkly Rep. 1997; 46(11): 240–242, indexed in Pubmed: 9082178.
127. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med. 2006; 354(23): 2443–2451, doi: 10.1056/NEJMoa055202, indexed in Pubmed: 16760444.
128. Easterling TR, Carr DB, Brateng D, et al. Treatment of hypertension in pregnancy: effect of atenolol on maternal disease, preterm delivery, and fetal growth. Obstet Gynecol. 2001; 98(3): 427–433, indexed in Pubmed: 11530124.
129. Cruz MO, Gao W, Hibbard JU. What is the optimal time for delivery in women with gestational hypertension? Am J Obstet Gynecol. 2012; 207(3): e1–e6, doi: 10.1016/j.ajog.2012.06.009, indexed in Pubmed: 22831812.
130. Duley L, Gulmezoglu AM, Henderson-Smart DJ, et al. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane Database Syst Rev. 2010; 11: CD000025.
131. Marret S, Marpeau L, Zupan-Simunek V, et al. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial. BJOG. 2007; 114(3): 310–318, doi: 10.1111/j.1471-0528.2006.01162.x, indexed in Pubmed: 17169012.
132. Roberts D, Brown J, Medley N, et al. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006; 3(3): CD004454, doi: 10.1002/14651858.CD004454.pub2, indexed in Pubmed: 16856047.
133. Koopmans CM, Bijlenga D, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet. 2009; 374(9694): 979–988, doi: 10.1016/S0140-6736(09)60736-4, indexed in Pubmed: 19656558.
134. Plouin PF, Baguet JP, Thony F, et al. High prevalence of multiple arterial bed lesions in patients with fibromuscular dysplasia: The ARCADIA Registry (Assessment of Renal and Cervical Artery Dysplasia). Hypertension. 2017; 70(3): 652–658,

doi: 10.1161/HYPERTENSIONAHA.117.09539, indexed in Pubmed: 28716989.
135. Dobrowolski P, Januszewicz M, Klisiewicz A, et al. Echocardiographic assessment of left ventricular morphology and function in patients with fibromuscular dysplasia: the ARCADIA-POL study. J Hypertens. 2018; 36(6): 1318–1325, doi: 10.1097/HJH.0000000000001706, indexed in Pubmed: 29528871.
136. Gornik HL, Persu A, Adlam D, et al. First international consensus on the diagnosis and management of fibromuscular dysplasia. J Hypertens. 2019; 37(2): 229–252, doi: 10.1097/HJH.0000000000002019, indexed in Pubmed: 30640867.
137. Khan F, Ghani AR, Mackenzie L, et al. A rare presentation of fibromuscular dysplasia: postpartum vascular catastrophe and brief literature review. J Investig Med High Impact Case Rep. 2017; 5(3): 2324709617719917, doi: 10.1177/2324709617719917, indexed in Pubmed: 28815187.
138. Shoja T, Basman C, Jain S, et al. Postpartum sudden cardiac death after spontaneous coronary artery dissection in a patient with fibromuscular dysplasia. Cardiol Res. 2017; 8(6): 327–330, doi: 10.14740/cr587w, indexed in Pubmed: 29317976.
139. Kadian-Dodov D, Gornik HL, Gu X, et al. Dissection and aneurysm in patients with fibromuscular dysplasia: findings from the U.S. Registry for FMD. J Am Coll Cardiol. 2016; 68(2): 176–185, doi: 10.1016/j.jacc.2016.04.044, indexed in Pubmed: 27386771.
140. Touzé E, Southerland AM, Boulanger M, et al. Fibromuscular dysplasia and its neurologic manifestations: a systematic review. JAMA Neurol. 2018 [Epub ahead of print], doi: 10.1001/jamaneurol.2018.2848, indexed in Pubmed: 30285053.
141. Talarowska P, Dobrowolski P, Klisiewicz A, et al. High incidence and clinical characteristics of fibromuscular dysplasia in patients with spontaneous cervical artery dissection: The ARCADIA-POL study. Vasc Med. 2019; 24(2): 112–119, doi: 10.1177/1358863X18811596, indexed in Pubmed: 30739593.
142. Vance CJ, Taylor RN, Craven TE, et al. Increased prevalence of preeclampsia among women undergoing procedural intervention for renal artery fibromuscular dysplasia. Ann Vasc Surg. 2015; 29(6): 1105–1110, doi: 10.1016/j.avsg.2015.03.037, indexed in Pubmed: 26004957.
143. Berra E, Dominiczak AF, Touyz RM, et al. Management of a pregnant woman with fibromuscular dysplasia. Hypertension. 2018; 71(4): 540–547, doi: 10.1161/HYPERTENSIONAHA.118.10819, indexed in Pubmed: 29483231.
144. Kaszuba AM, Prejbisz A, Kądziela J, et al. Forty-two-year-old female patient with resistant hypertension, bilateral renal fibromuscular dysplasia and intracranial aneurysm. Postępy Kardiol Interwencyjnej. 2016; 12(4): 386–388, doi: 10.5114/aic.2016.63644, indexed in Pubmed: 27980558.
145. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2016; 101(5): 1889–1916, doi: 10.1210/jc.2015-4061, indexed in Pubmed: 26934393.
146. Young W, Calhoun D, Lenders J, et al. Screening for endocrine hypertension: an endocrine society scientific statement. Endocrine Reviews. 2017; 38(2): 103–122, doi: 10.1210/er.2017-00054.
147. Riester A, Reincke M. Progress in primary aldosteronism: mineralocorticoid receptor antagonists and management of primary aldosteronism in pregnancy. Eur J Endocrinol. 2015; 172(1): R23–R30, doi: 10.1530/EJE-14-0444, indexed in Pubmed: 25163723.
148. Morton A. Primary aldosteronism and pregnancy. Pregnancy Hypertens. 2015; 5(4): 259–262, doi: 10.1016/j.preghy.2015.08.003, indexed in Pubmed: 26597737.
149. Landau E, Amar L. Primary aldosteronism and pregnancy. Ann Endocrinol (Paris). 2016; 77(2): 148–160, doi: 10.1016/j.ando.2016.04.009, indexed in Pubmed: 27156905.
150. Kądziela J, Prejbisz A, Michałowska I, et al. A single-centre experience of the implementation of adrenal vein sampling procedure: the impact on the diagnostic work-up in primary aldosteronism. Kardiol Pol. 2017; 75(1): 28–34, doi: 10.5603/KP.a2016.0166, indexed in Pubmed: 27878800.
151. Lenders J, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2014; 99(6): 1915–1942, doi: 10.1210/jc.2014-1498.
152. Lenders JW. Pheochromocytoma and pregnancy: a deceptive connection. Eur J Endocrinol. 2012; 166(2): 143–150.
153. Weerd Kv, Noord Cv, Loeve M, et al. Endocrinology in pregnancy: pheochromocytoma in pregnancy: case series and review of literature. Eur J Endocrinol. 2017; 177(2): R49–R58, doi: 10.1530/eje-16-0920.
154. Wing L, Conaglen J, Meyer-Rochow G, et al. Paraganglioma in pregnancy: a case series and review of the literature. J Clin Endocrinol Metab. 2015; 100(8): 3202–3209, doi: 10.1210/jc.2015-2122.
155. Jozwik-Plebanek K, Peczkowska M, Klisiewicz A, et al. Pheochromocytoma presenting as takotsubo-like cardiomyopathy following delivery. Endocr Pract. 2014; 20(12): e233–e236.
156. Prejbisz A, Lenders J, Eisenhofer G, et al. Cardiovascular manifestations of phaeochromocytoma. J Hypertens. 2011; 29(11): 2049–2060, doi: 10.1097/hjh.0b013e32834a4ce9.
157. Eisenhofer G, Prejbisz A, Peitzsch M, et al. Biochemical diagnosis of chromaffin cell tumors in patients at high and low risk of disease: plasma versus urinary free or deconjugated o-methylated catecholamine metabolites. Clin Chem. 2018; 64(11): 1646–1656, doi: 10.1373/clinchem.2018.291369.
158. Canniffe C, Ou P, Walsh K, et al. Hypertension after repair of aortic coarctation. A systematic review. Int J Cardiol. 2013; 167(6): 2456–2461, doi: 10.1016/j.ijcard.2012.09.084.
159. Vriend J, Drenthen W, Pieper P, et al. Outcome of pregnancy in patients after repair of aortic coarctation. Eur Heart J. 2005; 26(20): 2173–2178, doi: 10.1093/eurheartj/ehi338.
160. Beauchesne L, Connolly H, Ammash N, et al. Coarctation of the aorta: outcome of pregnancy. J Am Coll Cardiol. 2001; 38(6): 1728–1733, doi: 10.1016/s0735-1097(01)01617-5.
161. McKellar S, MacDonald R, Michelena H, et al. Frequency of cardiovascular events in women with a congenitally bicuspid aortic valve in a single community and effect of pregnancy on events. Am J Cardiol. 2011; 107(1): 96–99, doi: 10.1016/j.amjcard.2010.08.061.
162. Wilson D, Barnes M, Ellett L, et al. Decreased sleep efficiency, increased wake after sleep onset and increased cortical arousals in late pregnancy. Aust N Z J Obstet Gynaecol. 2010; 51(1): 38–46, doi: 10.1111/j.1479-828x.2010.01252.x.
163. Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013; 177(9): 1006–1014, doi: 10.1093/aje/kws342.
164. Pien G, Pack A, Jackson N, et al. Risk factors for sleep-disordered breathing in pregnancy. Thorax. 2013; 69(4): 371–377, doi: 10.1136/thoraxjnl-2012-202718.
165. Macgillivray I, Campbell D. The Relevance of hypertension and oedema in pregnancy. Clinical and Experimental Hypertension. 2009; 2(5): 897–914, doi: 10.3109/10641968009037148.
166. Pilkington S, Carli F, Dakin MJ, et al. Increase in Mallampati score during pregnancy. Br J Anaesth. 1995; 74(6): 638–642, doi: 10.1093/bja/74.6.638.
167. Izci B. Sleep-disordered breathing and upper airway size in pregnancy and post-partum. Eur Respir J. 2006; 27(2): 321–327, doi: 10.1183/09031936.06.00148204.
168. Bourjeily G, Danilack V, Bublitz M, et al. 0474 A national cohort study of obstructive sleep apnea in pregnancy and adverse neonatal outcomes. Sleep. 2017; 40(suppl. 1): A177, doi: 10.1093/sleepj/zsx050.473.
169. Louis J, Auckley D, Miladinovic B, et al. Perinatal outcomes associated with obstructive sleep apnea in obese pregnant women. Obstet Gynecol. 2012: 1, doi: 10.1097/aog.0b013e31826eb9d8.
170. Higgins N, Leong E, Park CS, et al. The Berlin Questionnaire for assessment of sleep disordered breathing risk in parturients and non-pregnant women. Int J Obstet Anesth. 2011; 20(1): 22–25, doi: 10.1016/j.ijoa.2010.09.010.
171. Pengo M, Rossi G, Steier J. Obstructive sleep apnea, gestational hypertension and preeclampsia. Curr Opin Pulm Med. 2014; 20(6): 588–594, doi: 10.1097/mcp.0000000000000097.

172. Piccoli G, Cabiddu G, Attini R, et al. Hypertension in CKD pregnancy: a question of cause and effect (cause or effect? this is the question). Current Hypertension Reports. 2016; 18(5), doi: 10.1007/s11906-016-0644-7.
173. Hall M. Pregnancy in women with CKD: a success story. Am J Kidney Dis. 2016; 68(4): 633–639, doi: 10.1053/j.ajkd.2016.04.022.
174. Gonzalez Suarez ML, Kattah A, Grande JP, et al. Renal disorders in pregnancy: core curriculum 2019. Am J Kidney Dis. 2019; 73(1): 119–130, doi: 10.1053/j.ajkd.2018.06.006, indexed in Pubmed: 30122546.
175. Krane N, Hamrahian M. Pregnancy: kidney diseases and hypertension. Am J Kidney Dis. 2007; 49(2): 336–345, doi: 10.1053/j.ajkd.2006.10.029.
176. Zhang JJ, Ma XX, Hao Li, et al. A systematic review and meta-analysis of outcomes of pregnancy in ckd and ckd outcomes in pregnancy. Clinical Journal of the American Society of Nephrology. 2015; 10(11): 1964–1978, doi: 10.2215/cjn.09250914.
177. Bateman B, Bansil P, Hernandez-Diaz S, et al. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. Am J Obstet Gynecol. 2012; 206(2): 134.e1–134.e8, doi: 10.1016/j.ajog.2011.10.878.
178. Jesudason S, Mohammadi F, Fitzpatrick A. Managing pregnancy in chronic kidney disease: improving outcomes for mother and baby. Int J Womens Health. 2016; Volume 8: 273–285, doi: 10.2147/ijwh.s76819.
179. Piccoli G, Cabiddu G, Attini R, et al. Risk of adverse pregnancy outcomes in women with CKD. J Am Soc Nephrol. 2015; 26(8): 2011–2022, doi: 10.1681/asn.2014050459.
180. Alkhunaizi A, Melamed N, Hladunewich M. Pregnancy in advanced chronic kidney disease and end-stage renal disease. Current Opinion in Nephrology and Hypertension. 2015; 24(3): 252–259, doi: 10.1097/mnh.0000000000000119.
181. Wiles K, Nelson-Piercy C, Bramham K. Reproductive health and pregnancy in women with chronic kidney disease. Nature Reviews Nephrology. 2018; 14(3): 165–184, doi: 10.1038/nrneph.2017.187.
182. Cabiddu G, Castellino S, Gernone G, et al. Best practices on pregnancy on dialysis: the Italian Study Group on Kidney and Pregnancy. Journal of Nephrology. 2015; 28(3): 279–288, doi: 10.1007/s40620-015-0191-3.
183. Koulouridis I, Alfayez M, Trikalinos T, et al. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a metaregression analysis. Am J Kidney Dis. 2013; 61(1): 44–56, doi: 10.1053/j.ajkd.2012.07.014.
184. Hladunewich M, Schatell D. Intensive dialysis and pregnancy. Hemodialysis International. 2016; 20(3): 339–348, doi: 10.1111/hdi.12420.
185. Katritsis DG, Boriani G, Cosio FG, et al. European Heart Rhythm Association (EHRA) consensus document on the management of supraventricular arrhythmias, endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardiaca y Electrofisiologia (SOLAECE). EP Europace. 2017; 19(3): 465–511, doi: 10.1093/europace/euw444.
186. Vaidya VR, Arora S, Patel N, et al. Burden of arrhythmia in pregnancy. Circulation. 2017; 135(6): 619–621, doi: 10.1161/CIRCULATIONAHA.116.026681, indexed in Pubmed: 28154000.
187. Drenthen W, Pieper PG, Roos-Hesselink JW, et al. Outcome of pregnancy in women with congenital heart disease: a literature review. J Am Coll Cardiol. 2007; 49(24): 2303–2311, doi: 10.1016/j.jacc.2007.03.027, indexed in Pubmed: 17572244.
188. Upshaw CB. A study of maternal electrocardiograms recorded during labor and delivery. Am J Obstet Gynecol. 1970; 107(1): 17–27, indexed in Pubmed: 5443060.
189. Shotan A, Ostrzega E, Mehra A, et al. Incidence of arrhythmias in normal pregnancy and relation to palpitations, dizziness, and syncope. Am J Cardiol. 1997; 79(8): 1061–1064, indexed in Pubmed: 9114764.
190. Chang SH, Kuo CF, Chou IJ, et al. Outcomes associated with paroxysmal supraventricular tachycardia during pregnancy. Circulation. 2017; 135(6): 616–618, doi: 10.1161/CIRCULATIONAHA.116.025064, indexed in Pubmed: 28153999.
191. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace. 2015; 17(11): 1601–1687, doi: 10.1093/europace/euv319, indexed in Pubmed: 26318695.
192. Szumowski L, Szufladowicz E, Orczykowski M, et al. Ablation of severe drug-resistant tachyarrhythmia during pregnancy. J Cardiovasc Electrophysiol. 2010; 21(8): 877–882, doi: 10.1111/j.1540-8167.2010.01727.x, indexed in Pubmed: 20158563.
193. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016; 50(5): e1–e88, doi: 10.1093/ejcts/ezw313.
194. Rashba EJ, Zareba W, Moss AJ, et al. Influence of pregnancy on the risk for cardiac events in patients with hereditary long QT syndrome. LQTS Investigators. Circulation. 1998; 97(5): 451–456, indexed in Pubmed: 9490239.
195. Elkayam U, Jalnapurkar S, Barakkat MN, et al. Pregnancy-associated acute myocardial infarction: a review of contemporary experience in 150 cases between 2006 and 2011. Circulation. 2014; 129(16): 1695–1702, doi: 10.1161/CIRCULATIONAHA.113.002054, indexed in Pubmed: 24753549.
196. Faden MS, Bottega N, Benjamin A, et al. A nationwide evaluation of spontaneous coronary artery dissection in pregnancy and the puerperium. Heart. 2016; 102(24): 1974–1979, doi: 10.1136/heartjnl-2016-309403, indexed in Pubmed: 27411842.
197. Adlam D, Alfonso F, Maas A, et al. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. Eur Heart J. 2018; 39(36): 3353–3368, doi: 10.1093/eurheartj/ehy080, indexed in Pubmed: 29481627.
198. Hayes SN, Kim ESH, Saw J, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. Circulation. 2018; 137(19): e523–e557, doi: 10.1161/CIR.0000000000000564, indexed in Pubmed: 29472380.
199. Appleby CE, Barolet A, Ing D, et al. Contemporary management of pregnancy-related coronary artery dissection. A single-centre experience and literature review. Exp Clin Cardiol. 2009; 14(1): e8–ee16, indexed in Pubmed: 19492033.
200. Havakuk O, Goland S, Mehra A, et al. Pregnancy and the risk of apontaneous coronary artery dissection: an analysis of 120 contemporary cases. Circ Cardiovasc Interv. 2017; 10(3), doi: 10.1161/CIRCINTERVENTIONS.117.004941, indexed in Pubmed: 28302642.
201. Tweet MS, Hayes SN, Codsi E, et al. Spontaneous coronary artery dissection associated with pregnancy. J Am Coll Cardiol. 2017; 70(4): 426–435, doi: 10.1016/j.jacc.2017.05.055, indexed in Pubmed: 28728686.
202. Higgins GL, Borofsky JS, Irish CB, et al. Spontaneous peripartum coronary artery dissection presentation and outcome. J Am Board Fam Med. 2013; 26(1): 82–89, doi: 10.3122/jabfm.2013.01.120019, indexed in Pubmed: 23288285.
203. Tweet MS, Eleid MF, Best PJM, et al. Spontaneous coronary artery dissection: revascularization versus conservative therapy. Circ Cardiovasc Interv. 2014; 7(6): 777–786, doi: 10.1161/CIRCINTERVENTIONS.114.001659, indexed in Pubmed: 25406203.
204. Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. Lancet. 2006; 368(9536): 687–693, doi: 10.1016/S0140-6736(06)69253-2, indexed in Pubmed: 16920474.
205. Hilfiker-Kleiner D, Kaminski K, Podewski E, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell. 2007; 128(3): 589–600, doi: 10.1016/j.cell.2006.12.036, indexed in Pubmed: 17289576.

206. Bauersachs J, Arrigo M, Hilfiker-Kleiner D, et al. Current management of patients with severe acute peripartum cardiomyopathy: practical guidance from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. Eur J Heart Fail. 2016; 18(9): 1096–1105, doi: 10.1002/ejhf.586, indexed in Pubmed: 27338866.
207. Hilfiker-Kleiner D, Haghikia A, Nonhoff J, et al. Peripartum cardiomyopathy: current management and future perspectives. Eur Heart J. 2015; 36(18): 1090–1097, doi: 10.1093/eurheartj/ehv009, indexed in Pubmed: 25636745.
208. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure]. Kardiol Pol. 2016; 74(10): 1037–147.
209. Koenig T, Hilfiker-Kleiner D, Bauersachs J. Peripartum cardiomyopathy. Herz. 2018; 43(5): 431–437, doi: 10.1007/s00059-018-4709-z.
210. Bramham K, Nelson-Piercy C, Brown MJ, et al. Postpartum management of hypertension. BMJ. 2013; 346: f894, doi: 10.1136/bmj.f894, indexed in Pubmed: 23440270.
211. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. Hypertension. 2018; 72(1): 24–43.
212. Krause T, Lovibond K, Caulfield M, et al. Management of hypertension: summary of NICE guidance. BMJ. 2011; 343: d4891, doi: 10.1136/bmj.d4891, indexed in Pubmed: 21868454.
213. Manninen AK, Juhakoski A. Nifedipine concentrations in maternal and umbilical serum, amniotic fluid, breast milk and urine of mothers and offspring. Int J Clin Pharmacol Res. 1991; 11(5): 231–236, indexed in Pubmed: 1814844.
214. Sachs HC. Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. Pediatrics. 2013; 132(3): e796–e809, doi: 10.1542/peds.2013-1985, indexed in Pubmed: 23979084.
215. McManus RJ, Caulfield M, Williams B. NICE hypertension guideline 2011: evidence based evolution. BMJ. 2012; 344: e181, doi: 10.1136/bmj.e181, indexed in Pubmed: 22246269.
216. Aye CYL, Elmahi E, Boardman H, et al. Do young women need treatment for hypertension after pregnancy complications? J Am Heart Assoc. 2018; 7(10), doi: 10.1161/JAHA.118.009159, indexed in Pubmed: 29755037.
217. Romundstad PR, Magnussen EB, Smith GD, et al. Hypertension in pregnancy and later cardiovascular risk: common antecedents? Circulation. 2010; 122(6): 579–584, doi: 10.1161/CIRCULATIONAHA.110.943407, indexed in Pubmed: 20660802.
218. Stuart JJ, Tanz LJ, Missmer SA, et al. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development. An observational cohort study. Ann Intern Med. 2018; 169(4): 224–232, doi: 10.7326/M17-2740, indexed in Pubmed: 29971437.
219. Ditisheim A, Wuerzner G, Ponte B, et al. Prevalence of hypertensive phenotypes after preeclampsia. A prospective cohort study. Hypertension. 2018; 71(1): 103–109, doi: 10.1161/HYPERTENSIONAHA.117.09799, indexed in Pubmed: 29133363.
220. Podymow T, August P. Postpartum course of gestational hypertension and preeclampsia. Hypertens Pregnancy. 2010; 29(3): 294–300, doi: 10.3109/10641950902777747, indexed in Pubmed: 20670153.
221. Haug EB, Horn J, Markovitz AR, et al. Life course trajectories of cardiovascular risk factors in women with and without hypertensive disorders in first pregnancy. The HUNT study in Norway. J Am Heart Assoc. 2018; 7(15): e009250, doi: 10.1161/JAHA.118.009250, indexed in Pubmed: 30371249.
222. Groenhof TK, Zoet GA, Franx A, et al. Trajectory of cardiovascular risk factors after hypertensive disorders of pregnancy. Hypertension. 2019; 73(1): 171–178, doi: 10.1161/HYPERTENSIONAHA.118.11726, indexed in Pubmed: 30571544.
223. Zoet GA, Benschop L, Boersma E, et al. Prevalence of subclinical coronary artery disease assessed by coronary computed tomography angiography in 45- to 55-year-old women with a history of preeclampsia. Circulation. 2018; 137(8): 877–879, doi: 10.1161/CIRCULATIONAHA.117.032695, indexed in Pubmed: 29459475.
224. Zoet GA, Linstra KM, Bernsen ML, et al. Stroke after pregnancy disorders. Eur J Obstet Gynecol Reprod Biol. 2017; 215: 264–266, doi: 10.1016/j.ejogrb.2017.06.018, indexed in Pubmed: 28624311.
225. Skjaerven R, Wilcox AJ, Klungsøyr K, et al. Cardiovascular mortality after pre-eclampsia in one child mothers: prospective, population based cohort study. BMJ. 2012; 345: e7677, doi: 10.1136/bmj.e7677, indexed in Pubmed: 23186909.
226. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. Hypertension. 2010; 56(1): 166–171, doi: 10.1161/HYPERTENSIONAHA.110.150078, indexed in Pubmed: 20516394.
227. Bellamy L, Casas JP, Hingorani AD, et al. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007; 335(7627): 974, doi: 10.1136/bmj.39335.385301.BE, indexed in Pubmed: 17975258.
228. Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and future cardiovascular health: A systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2017; 10(2), doi: 10.1161/CIRCOUTCOMES.116.003497, indexed in Pubmed: 28228456.
229. Cortés YI, Catov JM, Brooks M, et al. History of adverse pregnancy outcomes, blood pressure, and subclinical vascular measures in late midlife: SWAN (Study of Women's Health Across the Nation). J Am Heart Assoc. 2017; 7(1), doi: 10.1161/JAHA.117.007138, indexed in Pubmed: 29288157.
230. Ahmed R, Dunford J, Mehran R, et al. Pre-eclampsia and future cardiovascular risk among women: a review. J Am Coll Cardiol. 2014; 63(18): 1815–1822, doi: 10.1016/j.jacc.2014.02.529, indexed in Pubmed: 24613324.
231. Spaan J, Peeters L, Spaanderman M, et al. Cardiovascular risk management after a hypertensive disorder of pregnancy. Hypertension. 2012; 60(6): 1368–1373, doi: 10.1161/HYPERTENSIONAHA.112.198812, indexed in Pubmed: 23071130.
232. Wolfenstetter A, Simonetti GD, Pöschl J, et al. Altered cardiovascular rhythmicity in children born small for gestational age. Hypertension. 2012; 60(3): 865–870, doi: 10.1161/HYPERTENSIONAHA.112.196949, indexed in Pubmed: 22733461.
233. Simonetti GD, Raio L, Surbek D, et al. Salt sensitivity of children with low birth weight. Hypertension. 2008; 52(4): 625–630, doi: 10.1161/HYPERTENSIONAHA.108.114983, indexed in Pubmed: 18695145.
234. Shah AB, Hashmi SS, Sahulee R, et al. Characteristics of systemic hypertension in preterm children. J Clin Hypertens. 2015; 17(5): 364–370, doi: 10.1111/jch.12528, indexed in Pubmed: 25775924.
235. de Jong F, Monuteaux MC, van Elburg RM, et al. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. Hypertension. 2012; 59(2): 226–234, doi: 10.1161/HYPERTENSIONAHA.111.181784, indexed in Pubmed: 22158643.
236. Luyckx VA, Perico N, Somaschini M, et al. A developmental approach to the prevention of hypertension and kidney disease: a report from the Low Birth Weight and Nephron Number Working Group. Lancet. 2017; 390(10092): 424–428, doi: 10.1016/S0140-6736(17)30576-7, indexed in Pubmed: 28284520.
237. Litwin M. Standard powypisowej, wczesnej diagnostyki nadciśnienia tętniczego u dzieci urodzonych przedwcześnie i obserwowanych do końca 3 r.ż. Standardy opieki ambulatoryjnej nad dzieckiem urodzonym przedwcześnie Zalecenia Polskiego Towarzystwa Neonatologicznego i Polskiego Towarzystwa Pediatrycznego. Media Press, Warszawa 2018.
238. Lurbe E, Agabiti-Rosei E, Cruickshank JK, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016; 34(10): 1887–1920, doi: 10.1097/HJH.0000000000001039, indexed in Pubmed: 27467768.
239. Litwin M, Niemirska A, Obrycki L, et al. Guidelines of the Pediatric Section of the Polish Society of Hypertension on diagnosis and treatment of arterial hypertension in children and adolescents. Arter Hypertens. 2018; 22(2): 45–73.
240. Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: diagnosis, management and outcome. Pediatr Nephrol. 2012; 27(1): 17–32, doi: 10.1007/s00467-010-1755-z, indexed in Pubmed: 21258818.

241. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017; 140(3), doi: 10.1542/peds.2017-1904, indexed in Pubmed: 28827377.

242. Kułaga Z, Litwin M, Grajda A, et al. OLAF Study Group. Oscillometric blood pressure percentiles for Polish normalweight school-aged children and adolescents. J Hypertens. 2012; 30(10): 1942–1954, doi: 10.1097/HJH.0b013e328356abad, indexed in Pubmed: 22828086