Consensus Document

Management of hypertensive disorders in pregnancy: a Position Statement of the European Society of Hypertension Working Group 'Hypertension in Women'

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Hypertensive disorders in pregnancy (HDP), remain the leading cause of adverse maternal, fetal, and neonatal outcomes. Epidemiological factors, comorbidities, assisted reproduction techniques, placental disorders, and genetic predisposition determine the burden of the disease. The pathophysiological substrate and the clinical presentation of HDP are multifarious. The latter and the lack of well designed clinical trials in the field explain the absence of consensus on disease management among relevant international societies. Thus, the usual clinical management of HDP is largely empirical. The current position statement of the Working Group 'Hypertension in Women' of the European Society of Hypertension (ESH) aims to employ the current evidence for the management of HDP, discuss the recommendations made in the 2023 ESH guidelines for the management of hypertension, and shed light on controversial issues in the field to stimulate future research.

Keywords: assisted reproduction, cardiovascular risk, gestational hypertension, hypertension, hypertensive disorders in pregnancy, preeclampsia, pregnancy outcomes, pregnancy

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACR, albumin to creatinine ratio; AIPE, Italian Association of Preeclampsia; ART, assisted reproductive technology; ASPRE, Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention; BP, blood pressure; BUMP, Blood Pressure Monitoring in High-Risk Pregnancy to Improve the Detection and Monitoring of Hypertension; CHAP, Chronic Hypertension and Pregnancy; CHIPS, Control of Hypertension in Pregnancy Study; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESH, European Society of Hypertension; FEIRI, European/International Fibromuscular Dysplasia Registry; FET, frozen–thawed embryo transfer; FIVET, Fertilization in Vitro and Embryo Transfer; FMD, fibromuscular dysplasia; FMF, Fetal Medicine Foundation; HBPM, home blood pressure monitoring; HDP, hypertensive disorders in pregnancy; HELLP, hemolysis, elevated liver enzymes, low platelets; i.v., intravenous; ICSI, Intra-Cytoplasmic Sperm Injection; ISSHP, International Society for the Study of Hypertension in Pregnancy; IUGR, intrauterine growth restriction; IUI, intrauterine insemination; IVF, in-vitro fertilization; PIERS, Preeclampsia Integrated Estimate of Risk; PLGF, placental growth factor; PPGL, pheochromocytoma/paraganglioma; sFlt-1, soluble fms-like tyrosine kinase-1; STRIDE-BP, Science and Technology for Regional Innovation and Development in Europe – Blood Pressure

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INTRODUCTION

Hypertensive disorders in pregnancy (HDP) have an incidence of approximately 10% worldwide and are a major cause of maternal, fetal, and neonatal morbidity and mortality [1]. Maternal risks include placental abruption, stroke, pulmonary edema, thromboembolic events, renal failure, multiple organ failure, and disseminated intravascular coagulation. The fetus is at high risk of intrauterine growth restriction (IUGR; 25% of cases of preeclampsia), prematurity (27% of cases of preeclampsia), and intrauterine death (4% of cases of preeclampsia). Premature newborns are also exposed to prolonged high-level neonatal care, postnatal death, and higher cardiovascular risk later in life [2].

The clinical management of HDP remains, by and large, empirical because of scarce clinical research in the field and the suboptimal outcome reporting across different studies [3]. Moreover, the expert opinion recommendations in different guidelines related to HDP are not only characterized by areas of general agreement but also with significant dissimilarities potentially associated with great variability in decision-making [4]. Areas of major consensus between the international guidelines for managing pregnancy-related hypertensive disorders include the use of automated blood pressure (BP) measurement with validated devices, implementation of a dipstick to assess proteinuria followed by quantitative confirmation, adoption of the broader definition of preeclampsia, clear recommendation for the use of aspirin to prevent preeclampsia in high-risk and moderate-risk women, recognition that sustained hypertension in pregnancy should be treated, irrespective of the severity, the use of magnesium sulfate to prevent complications of preeclampsia, prompt delivery for term preeclampsia, and acknowledgment of heightened future cardiovascular risk in women with a history of preeclampsia. In contrast, areas of major disagreement between the guidelines are the components of the broad definition of preeclampsia are often unspecified, fetal manifestations or biomarkers are not widely endorsed, the definition of severe preeclampsia remains controversial, the choice of drugs in mild or severe hypertension, as well as the thresholds to initiate treatment and the BP targets to achieve, remain unclear [4].

In the 2023 European Society of Hypertension (ESH) guidelines for managing hypertension [5], several important pregnancy-related issues were addressed, and new recommendations were offered with their class of recommendation and level of evidence. The present statement aims to establish the willingness of the ESH Working Group 'Hypertension in Women' to shed light on practical problems related to hypertension management during pregnancy by expanding on the pregnancy-related topic of the 2023 ESH guideline recommendations [5].

DEFINITION AND GRADING

Hypertension in pregnancy is defined as SBP at least 140 mmHg and/or DBP at least 90 mmHg. At variance with BP grading in the general population, hypertension in pregnancy is classified as mild (SBP/DBP, 140–159/90–109 mmHg) or severe (SBP/DBP at least 160/110 mmHg) based on office BP measurements [5,6]. The previous definition of a hypertensive emergency in pregnancy at levels at least 170/110 mmHg for SBP/DBP should be abandoned, and all women with new-onset confirmed severe hypertension should be hospitalized for immediate evaluation and treatment [7,8].

CLASSIFICATION OF HYPERTENSIVE DISORDERS IN PREGNANCY

Considering pathophysiological, clinical, and management differences, HDP can be divided into two distinct phenotypes [5]. The *first* is preexisting (chronic) hypertension that precedes pregnancy or is diagnosed before the 20th week of pregnancy. It usually persists for more than 6 weeks after delivery and, depending on the cause, can be classified as essential or secondary hypertension. For preexisting hypertension, based on discrepancies between office and out-of-office BP values before or during the first half of pregnancy, we also recognize the importance of diagnosing or ruling out white-coat or masked hypertension. The *second* phenotype is gestational hypertension, which develops after 20 weeks of pregnancy and usually resolves within 6 weeks after delivery. Gestational hypertension also has two types: preeclampsia and transient hypertension (Table 1).

It should be noted that preexisting and gestational hypertension are conditions not clinically exclusive to each other and, at times, may overlap. Thus, a woman with preexisting hypertension may develop preeclampsia (i.e. superimposed preeclampsia to preexisting hypertension). Among women with preexisting hypertension, almost 25% will develop superimposed preeclampsia [9]. In these women, the diagnosis is made when a *de novo* development of proteinuria is detected, or other maternal organ or uteroplacental dysfunctions develop after 20 weeks of gestation, and it is usually associated with an abrupt or progressive BP elevation. Finally, we recognize antenatally unclassifiable hypertension when BP is first recorded after 20 weeks of gestation and hypertension is diagnosed. Thus, reassessment is necessary at or after 6 weeks postpartum. If hypertension resolves, it should be retrospectively classified as gestational hypertension, whereas if hypertension persists, it should be retrospectively classified as one of the subcategories within HDP. We emphasize that the 20th week of pregnancy is the arbitrary limit to define HDP and should be used as an orientation point only, whereas a definite diagnosis should be guided by clinical judgment and biomarkers (see next sections). Classification of HDP is further hampered by the fact that maximum physiological reduction in blood pressure occurs at 16–22 weeks of pregnancy, with a return to prepregnancy BP values during the third trimester. Accordingly, a normal BP during the second trimester without known prepregnancy or first-trimester BP values may mask preexisting hypertension. Of note, based on empirical observations, women with a diagnosis of preexisting hypertension may enter pregnancy without hypertensive BP levels and continue to have normal BP during puerperium. Thus, the diagnosis of preexisting hypertension may be questioned after the end of puerperium. Figure 1 presents an overview of HDP.

TABLE 1. Classification of hypertensive disorders in pregnancy

A. Preexisting (chronic) hypertension
Hypertension either preceding pregnancy or developing before 20 weeks gestation, usually persisting for more than 6 weeks postpartum, and may be associated with proteinuria.
1. primary hypertension
2. secondary hypertension
3. white-coat hypertension
4. masked hypertension

B. Gestational hypertension
Hypertension develops after 20 weeks gestation and usually resolves within 6 weeks postpartum.

Transient gestational hypertension
Usually detected in the clinic but then settles with repeated BP measurements taken over several hours, it is associated with a 40% risk of developing true gestational hypertension or preeclampsia in the remainder of the pregnancy, thus requiring careful follow-up.

Preeclampsia is gestational hypertension accompanied by one or more of the following new-onset conditions at or after 20 weeks gestation:
– Proteinuria (urinary albumin excretion in a 24 h urine sample >0.3 g/day or UACR in a random spot urine sample >30 mg/mmol (0.3 mg/mg)
Other maternal organ dysfunction
Acute kidney injury (serum creatinine ≥90 mmol/l; 1 mg/dl)
Liver involvement (elevated ALT or AST >0.67 μkat/l; >40 U/l; with or without right upper quadrant or epigastric abdominal pain)
– Neurological complications (e.g. eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata)
– Hematological complications (platelet count <150 000/ml, DIC, hemolysis)
– Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth)

C. Preexisting hypertension plus superimposed preeclampsia
Preexisting hypertension associated with any of the above maternal organ dysfunctions consistent with preeclampsia or a further increase in BP with new-onset proteinuria

D. Antenatally unclassifiable hypertension
When BP is first recorded after 20 weeks gestation, and hypertension is diagnosed, reassessment is necessary at or after 42 days postpartum. If hypertension resolves, it should be reclassified as gestational hypertension, whereas if hypertension persists, it should be reclassified as preexisting hypertension.

Modified from reference [5], with permission from Wolters Kluwer Health. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; DIC, disseminated intravascular coagulation.

As in the general population, the diagnosis of hypertension in pregnancy should be based on repeated office BP measurements, preferably complemented by out-of-office BP measurements. White-coat hypertension is characterized by increased office BP and normal BP out-of-office. It is more common in pregnancy than in the general population, with a mean prevalence of 30% of pregnant women with elevated BP [6,10]. However, not to be underestimated, the risk of preeclampsia and preterm birth is significantly higher in white-coat hypertension compared with normotension [11], although maternal and neonatal prognosis seems to be better than in chronic hypertension [12]. Transient gestational hypertension is usually detected in the clinic and settles with repeated BP measurements taken over several hours. However, it is associated with a 40% risk of developing true gestational hypertension or preeclampsia in the remainder of the pregnancy, thus requiring close clinical surveillance [10,13]. Masked hypertension refers to women without antihypertensive treatment with elevated BP values in out-of-office BP measurements associated with normal office BP measurements. This form of hypertension, though difficult to detect, should be suspected in patients with kidney dysfunction or other hypertension-mediated organ damage diagnosed prepregnancy or in the first half of pregnancy [6]. In those high-risk women, out-of-office BP measurements should be recommended; however, screening for masked hypertension should not be routinely performed because the prognostic value in pregnancy remains uncertain [14–16].

Preeclampsia: definition

Preeclampsia is a multifaceted disorder impacting both the mother and the fetus, highlighting the intricate interdependence of their physical conditions. It manifests abnormalities in both maternal and fetal clinical conditions. We recommend using the broader definition of preeclampsia previously proposed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) and endorsed by the 2023 ESH guidelines [5,6]. Accordingly, preeclampsia is gestational hypertension in the presence of one or more of the following new-onset conditions at or after 20 weeks of gestation: significant proteinuria [albumin to creatinine ratio (ACR) at least 30 mg/mmol or albuminuria at least 300 mg/24 h], maternal organ dysfunction [i.e. acute kidney injury (serum creatinine ≥1 mg/dl; 90 μmol/l); liver injury (elevated transaminases >40 U/l) with or without right upper quadrant or epigastric pain; neurological manifestations (convulsions, altered mental status, blindness, scotoma or headache); hematological manifestations (platelet count <150 000/μl, disseminated intravascular coagulation, hemolysis)]; and uteroplacental dysfunction (i.e. IUGR, abnormal umbilical artery Doppler waves or stillbirth). The combination of hemolysis, thrombocytopenia, and elevated transaminases defines the HELLP syndrome, and therefore, additional features of preeclampsia should be evaluated (Table 1) [5,6,17].

Preeclampsia: epidemiology

Preeclampsia occurs in 2–4% of pregnancies [18]. It is associated with almost 50 000 maternal deaths and a 10 times higher number of fetal or neonatal deaths every year worldwide [19]. Among risk factors for preeclampsia, socioeconomic status plays a pivotal role as women from low-income or middle-income countries have a three to four-fold greater risk of preeclampsia compared with higher income countries [20–22]. Regarding ethnic differences, Black and African-American, compared with Caucasian women, are at a 60% higher risk for preeclampsia [22]. In addition, women with preexisting hypertension have five times greater rates of preeclampsia compared with prepregnancy normotensive women [1]. At term, compared with preterm, preeclampsia is two times more frequent, but it is associated with lower rates of maternal or fetal and neonatal complications [20]. Clinicians should always consider preeclampsia as a serious disease with a rather unpredictable prognosis. In clinical practice, it is no longer recommended to use the previous classification of preeclampsia based on clinical features such as mild or severe or the stage of pregnancy at the diagnosis [i.e. early preterm (<34 weeks), preterm (34–37weeks), term (37–39 weeks and post-term >39weeks)] [6]. Although many cases of at-term preeclampsia may not lead to significant short-term complications for both the mother and newborn, consistent with the adage 'prompt delivery is the definitive treatment for preeclampsia,' increased long-term cardiovascular disease is a well known adverse consequence for women with

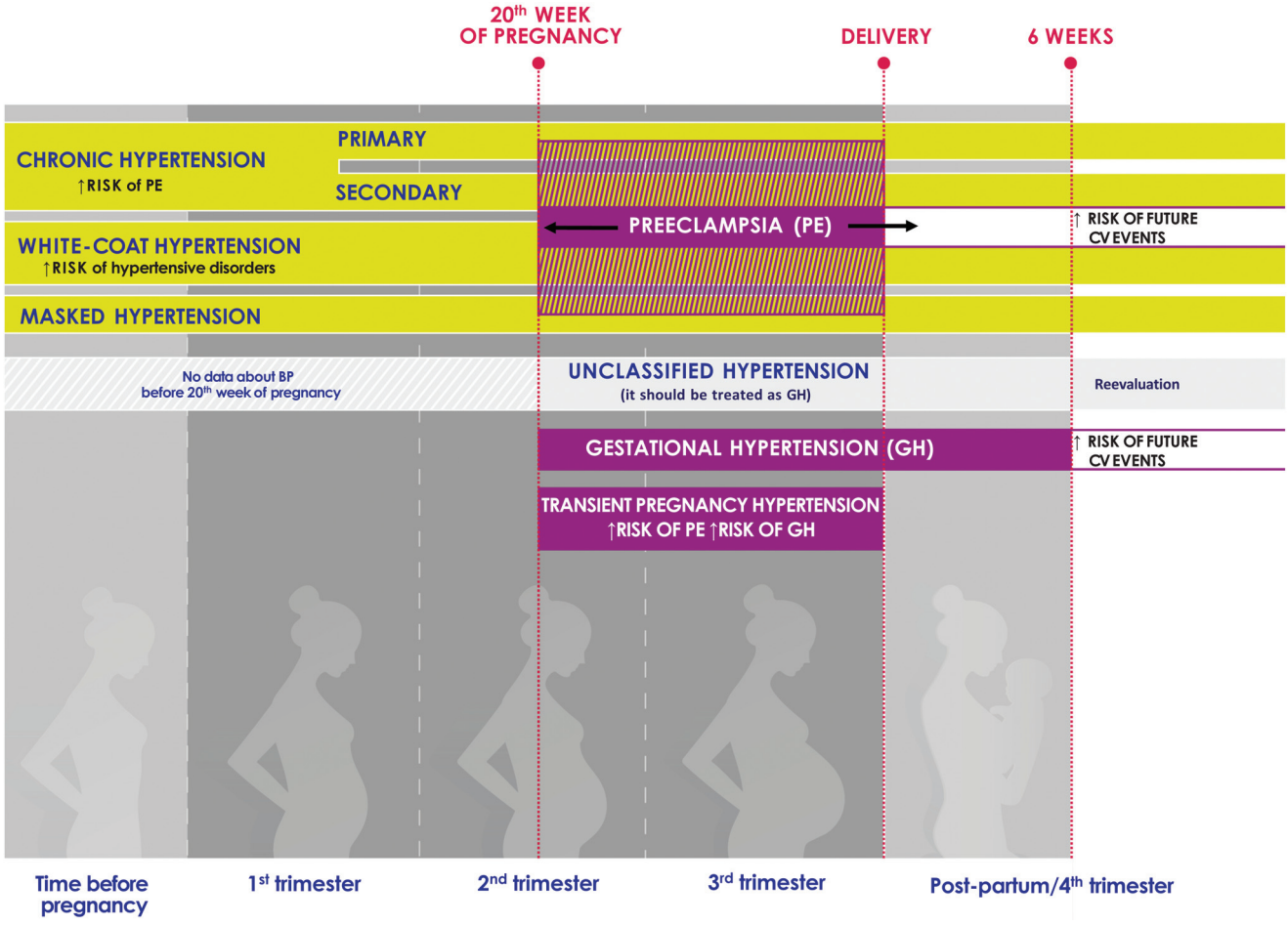

FIGURE 1 Overview of hypertensive disorders in pregnancy. BP, blood pressure; CV, cardiovascular; GH, gestational hypertension; PE, preeclampsia. Horizontal black arrows indicate that preeclampsia may develop from approximately the 20th week of pregnancy or may develop de novo, usually, during the first days postpartum in a previously normotensive pregnancy.

all forms of HDP and their offspring years and even decades after delivery [5].

Preeclampsia: pathogenetic considerations

Inadequate placentation, with a lack of spiral artery remodeling and poor villous development, represents the pathogenetic basis mostly observed in preterm preeclampsia and determines a reduced uteroplacental blood supply pattern leading to IUGR [20]. A normal placentation accompanied by either a multiple pregnancy, fetal macrosomia, or crowding of intervillous space is more frequently observed in cases of at-term or postterm preeclampsia. It produces a condition of increased fetoplacental demands. However, a variable cause of intervillous crowding can also be associated with a compromising uteroplacental blood flow. Reduced uteroplacental blood supply, increased fetoplacental demands, or their combination result in a uteroplacental mismatch that, in turn, increases placental stress-derived factors (e.g. pro-inflammatory cytokines) and promotes the imbalance of angiogenic placental factors [e.g. proangiogenic placental growth factor (PLGF) and antiangiogenic soluble fms-like tyrosine kinase 1 (sFlt-1)]. Placenta-derived mediators alone or combined with factors conferring a maternal predisposition (e.g. obesity, diabetes mellitus, immune system morbidities, preexisting hypertension, social determinants of poor health) determine endothelial damage in the mother with preeclampsia development. The same pathophysiological substrate may adversely impact fetoplacental health with emerging features such as fetal growth restriction, preterm birth (<37 weeks), low birth weight, small-for-gestational age (<10th percentile by sex), stillbirth, and placental abruption [20].

Endothelial damage associated with placental dysfunction and a maternal high-risk factor profile contributes to BP elevation, perpetuation of widespread vascular damage, and increased peripheral resistance. In the United Kingdom cohort of the ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial, women underwent hemodynamic evaluation by a bioreactance system, and the cardiac output, stroke volume, and peripheral resistance were registered during different pregnancy stages [23]. Women at low risk of hypertensive complications ineligible for consequent randomization to aspirin or placebo participated in hemodynamic measures evaluation. Low-risk women had normal hemodynamic adaptations throughout pregnancy, at variance with high-risk women who presented decreased cardiac output and stroke volume and

increased peripheral resistance. Moreover, the extent of hemodynamic derangement was similar between women randomized to aspirin or placebo, suggesting that the beneficial effects of aspirin on preeclampsia prevention might be independent of hemodynamics [23,24]. Inadequate cardiovascular adaptations during pregnancy, including increased arterial stiffness [25], maybe a marker of preeclampsia and should be further evaluated.

During pregnancy, the physiological increase in cardiac output is associated with a 50–70% increase in renal blood flow [26]. Also, in an uncomplicated pregnancy, there is an increase in glomerular filtration rate because of increased renal flow and expanded plasma volume, with a subsequent decrease in serum creatinine levels by an average of 0.4 mg/dl (35 mmol/l) compared with prepregnancy. A serum creatinine of 1.0 mg/dl (88 mmol/l), deemed normal out-of-pregnancy, indicates kidney dysfunction in a pregnant woman. In women with preeclampsia without preexisting renal disease, the glomerular filtration rate is generally greater than 60 ml/min despite a 20% reduction in renal blood flow compared with pregnant women without preeclampsia [26]. In preeclampsia, glomerular endotheliosis and loss of podocyte integrity contribute to proteinuria development, with nephrotic levels reserved for severe cases [20].

Preeclampsia: maternal complications

Women with HDP, especially preeclampsia, are prone to develop cardiovascular complications [26]. The pivotal three complications of cardiovascular interest are stroke, pulmonary edema, and pulmonary embolism. Stroke during pregnancy is a result of the development of severe hypertension, typically established acutely during the third trimester [27,28]. Pulmonary edema in women without a history of underlying cardiac disease before pregnancy may develop in late pregnancy, during delivery or the first days postpartum [29]. It may occur under two conditions: new-onset systolic heart failure in the context of peripartum cardiomyopathy, or heart failure with preserved ejection fraction. Although peripartum cardiomyopathy may have a sporadic epidemiological appearance in Western countries, it is more frequently, by almost four times, associated with preeclampsia compared with normotensive pregnancies [30]. In contrast, heart failure with preserved ejection fraction can result from acute left ventricle decompensation because of increased afterload in the context of pregnancy-mediated hypertensive disorders [29]. The mechanistic aspects of acute left ventricle decompensation are not different from those observed in nonpregnant women presenting with hypertension-mediated heart damage and long-standing uncontrolled hypertension. The combination of the following five conditions forces intravascular fluids to leak outside toward the alveoli: mobilization of interstitial fluids into vessels, including uterus autotransfusion effect during the first hours postpartum, fluid administration during postpartum to accompany tocolytic or other intravenous treatments, drop of almost 30% in colloid osmotic pressure in early postpartum because of volume expansion; in preeclampsia with clinically important proteinuria, the reduction of colloid osmotic pressure is higher because of the critically reduced plasma albumin levels, widespread endothelial damage associated with preeclampsia is extended to pulmonary microcirculation, and peripheral vascular resistance remains high despite antihypertensive treatment [26]. Preeclampsia is associated with activation of the coagulation system in a higher degree than in a normal pregnancy. Thus, the risk of venous thromboembolism increases by two to three times in the peripartum period in women with preeclampsia compared with those without preeclampsia [28]. Finally, in preeclampsia, increased blood loss in combination with coagulation derangement may promote disseminated intravascular coagulation with a high mortality rate, though the exact mechanism remains rather unclear [31].

Eclampsia

Eclampsia is the most severe complication of preeclampsia and, based on postmortem findings, is driven by microscopic bleedings associated with increased perfusion pressures that may exceed the cerebral circulation autoregulatory capacity [27]. An eclamptic convulsion is life-threatening. Fortunately, the incidence of eclampsia has been reduced with the advent of prompt management of preeclampsia. However, eclampsia may occur without premonitory signs or symptoms of underlying preeclampsia during partum, delivery, or first days postpartum. In selected cases, convulsions are preceded by imminent signs, including headache, visual disturbances, altered mental state, and angina-like or epigastric pain [32].

BLOOD PRESSURE MEASUREMENTS DURING PREGNANCY

Precise measurement of BP during pregnancy is of major importance to provide the best obstetrical management, allowing for the application of prevention and pharmacological intervention. However, BP evaluation may be difficult in pregnant women because of physiological hemodynamic adaptations and most devices for BP measurement are inaccurate and lack validation by an established and recognized protocol adapted for pregnancy [33].

Auscultatory devices

Noninvasive devices comprise auscultatory and oscillometric methods. Korotkov sound V is preferred over sound IV for the auscultatory method, as it is closer to intra-arterial pressure and more reliably detected [34]. The auscultatory method is the initial gold standard for evaluating BP in pregnancy. However, mercury sphygmomanometers have been proscribed because of mercury toxicity and are now only recommended for the validation of devices. Auscultatory devices were replaced by aneroid devices that necessitate frequent recalibration and are subjected to error greater than 3 mmHg compared with mercury and automatic devices. An evaluation of the effect of systematic imprecisions by 3 and 5 mmHg in measurements of SBP would misjudge 24 and 43% of individuals with hypertension. It would wrongly comfort 19 and 30%, respectively, being falsely normotensive [35]. Automated oscillometric devices are now mainly used during pregnancy to estimate the mean arterial BP; then, an algorithm

extrapolates SBP by studying the shape of the arterial wall vibration and, finally, DBP can be easily calculated from mean BP and SBP [33].

Validation of devices

Because of hemodynamic changes during pregnancy, devices should be validated in pregnant women with or without HDP, including preeclampsia. Compared with a normotensive pregnancy, hemodynamic adaptations in preeclampsia (i.e. increased peripheral resistance, decreased stroke ejection volume, reduced vascular compliance, and reduced effective intravascular volume) may change the oscillometric shape of the pulse wave, and validation against mercury sphygmomanometers is necessary. STRIDE-BP (Science and Technology for Regional Innovation and Development in Europe – Blood Pressure), an international nonprofit organization aiming to improve the accuracy of BP measurements, provides a list of validated devices for pregnant women with different types of hypertensive disorders [36].

Technique of blood pressure measurement

Properly assessing BP during pregnancy implies quiet sitting for 5 min with feet flat on the ground, the arm supported at the level of the heart, and the back supported before measurement. The left lateral lying position to avoid abdominal venous compression by the gravid uterus is an alternative acceptable position in the third trimester or during the peripartum period. Using a cuff of an appropriate size is mandatory [37]. With the auscultatory method, ignoring the first measurement and considering the mean of the next two readings after 5 min of rest is advised. With oscillometric devices, an average of two readings is considered reliable. Devices automatically measure three BP values and provide the average BP, which can also be used.

Blood pressure trajectory during pregnancy

In normotensive pregnancy, SBP and DBP decrease compared with prepregnancy BP, attaining their maximum reduction of about 4 mmHg in the early second trimester with a gradual increase towards nonpregnant BP values in the last trimester. Healthy pregnancies seem to have lower SBP and DBP than previously assumed, namely less than 130/80 mmHg during the entire gestation, challenging the traditional, broader threshold for diagnosing gestational hypertension [38]. In a hypertensive pregnancy, SBP values may not be remarkably higher in the first part of gestation and may only lack the physiological decrease observed in normotensive pregnancy, and DBP may drop by 6 mmHg during the second trimester. However, in the third trimester, SBP and DBP may be increased by almost 30 mmHg compared with BP values of the first trimester [38]. One study demonstrated that BP categories with lower BP thresholds than those traditionally used to identify individuals as hypertensive may inevitably result in the identification of more women at risk of preeclampsia and gestational hypertension [39]. Whether a lower BP threshold to define hypertension in pregnancy should be applied remains unclear. Data confirming that intervention with pharmacological treatment introduced at a lower threshold (than $\geq$140/90 mm Hg) might be well tolerated are lacking [40].

Home blood pressure self-monitoring during pregnancy

A properly validated device for home BP measurements in pregnancy must be used, and appropriate instructions should be given on when and how to use the device. A Japanese study provided provisional criteria for diagnosing hypertension in pregnancy using home BP monitoring (HBPM). Based on population distribution and regression with office BP values, home BP values corresponding to a clinical BP of 140/90 mmHg were 120.8/83.5, 126.0/85.2, and 136.3/89.3 mmHg in the first, second, and third trimesters, respectively [41]. During pregnancy, home BP measurements define normal values at less than 135/85 mmHg, corresponding to a mean ambulatory BP of 126/76 mmHg [42].

The advantages of HBPM are that it allows evaluation of BP during different stages of pregnancy and offers a better longitudinal follow-up based on a greater number of readings than office BP measurements. It can also detect white-coat or masked hypertension [43]. According to the BUMP-1 (Blood Pressure Monitoring in High-Risk Pregnancy to Improve the Detection and Monitoring of Hypertension-1) trial [44], HBPM did not lead to earlier clinic-based detection of hypertension among pregnant women at higher risk of preeclampsia. However, the BUMP-1 trial also suggested that HBPM and office BP measurements may be used alternatively or in complement to diagnose HDP in women at risk of preeclampsia. In the BUMP-2 trial [45], HBPM was not associated with better BP control among pregnant women with preexisting or gestational hypertension compared with scheduled office BP measurements. Again, the BUMP-2 trial suggested that BP control, according to HBPM, can be used alternatively or complementarily to office BP measurements because both methods achieved similar rates of BP control. It has been shown that HBPM is feasible and acceptable for women of different ethnicities or socioeconomic backgrounds [46].

Ambulatory blood pressure monitoring during pregnancy

Ambulatory BP monitoring (ABPM) seems to predict better preeclampsia, IUGR, and adverse neonatal outcomes than conventional BP measurements, partly because nocturnal hypertension is associated with the future development of gestational hypertension and preeclampsia [47,48]. The indications of ABPM are confirming hypertension necessitating medical treatment or diagnosing white coat hypertension and thus mandating a close follow-up. In the presence of hypertension-mediated organ damage, including microalbuminuria, ABPM may reveal masked hypertension. ABPM may increase the sensitivity of prediction tools for preeclampsia, such as the Fetal Medicine Foundation algorithm [49], which currently includes the mean office arterial pressure. However, including ABPM in the scores to predict preeclampsia deserves future studies. An earlier cross-sectional study that included 276 ambulatory BP measurements defined the normal awake BP values for pregnancy at different pregnancy stages [50]. A gradual rise in the awake SBP and DBP was observed from early pregnancy into the third trimester. Moreover, awake BP

was slightly higher than resting BP measured by a mercury sphygmomanometer [50]. When a valid device for pregnancy has been used, normal values for 24 h ABPM in pregnancy are fairly similar to those described in other populations (i.e. below 130/80 mmHg). However, before 22 weeks, 24 h BP values should be below 126/76 mmHg, a threshold slightly below that for diagnosing hypertension in nonpregnant women [50].

LABORATORY EXAMS DURING PREGNANCY

Basic laboratory investigations for monitoring pregnant hypertensive women include urine analysis, blood count, hematocrit, liver enzymes, serum creatinine, and serum uric acid. Although uric acid is generally elevated in clinically evident preeclampsia and identifies women at increased risk of adverse maternal and fetal outcomes [6,51], it should not be used as a diagnostic criterion for preeclampsia or to determine the timing of delivery. Determination of proteinuria in early pregnancy is recommended to detect preexisting renal disease and, in the second half of pregnancy, to screen for preeclampsia. However, proteinuria is no longer a 'sine qua non' criterion for diagnosing preeclampsia [5,6]. Occasionally, proteinuria may anticipate a subsequent rise of BP in the natural course of preeclampsia. A dipstick test of at least 1+ should prompt evaluation of ACR in a single spot urine sample, and a value of less than 30 mg/mmol can reliably rule out proteinuria [52,53]. Other investigations to be considered are: renal ultrasound if serum creatinine or any of the urine testing is abnormal, Doppler ultrasound of uterine and umbilical arteries (performed after 20 weeks of gestation), and 24 h urine analysis to detect those at a higher risk of gestational hypertension, preeclampsia, and IUGR [5,6]. Laboratory exams that might be used to predict at-term preeclampsia are reported in the following section.

PREDICTION AND PREVENTION OF PREECLAMPSIA

High risk and moderate risk of preeclampsia

Available evidence allows us to distinguish women at high and moderate risk of developing preeclampsia. Clinical risk assessment for preeclampsia includes only risk factors that can be obtained from the medical history of pregnant women (Fig. 2) [5].

In a systematic review and meta-analysis of large cohort studies that evaluated the risk of preeclampsia using a common and generally accepted clinical risk factors assessed at 16 weeks or less of gestation, antiphospholipid antibody syndrome, prior preeclampsia, chronic hypertension, pregestational diabetes, assisted reproductive technology (ART), and BMI greater than 30 kg/m^2 were most strongly associated with a high rate of preeclampsia [54]. High-risk factors increased the risk of preeclampsia by at least 2.5-fold. In addition to established risk factors for preeclampsia, there is an emerging number of factors that may increase the risk, including high-normal prepregnancy BP, white-coat hypertension, insulin resistance, primary aldosteronism, overweight ($25 \leq$ BMI <30 kg/m^2), gestational diabetes, hyperthyroidism, and pregnancy with trisomy 13 fetus. Other possible genetic risk factors for preeclampsia include a paternal family history of preeclampsia and oocyte donation [55]. A prediction model

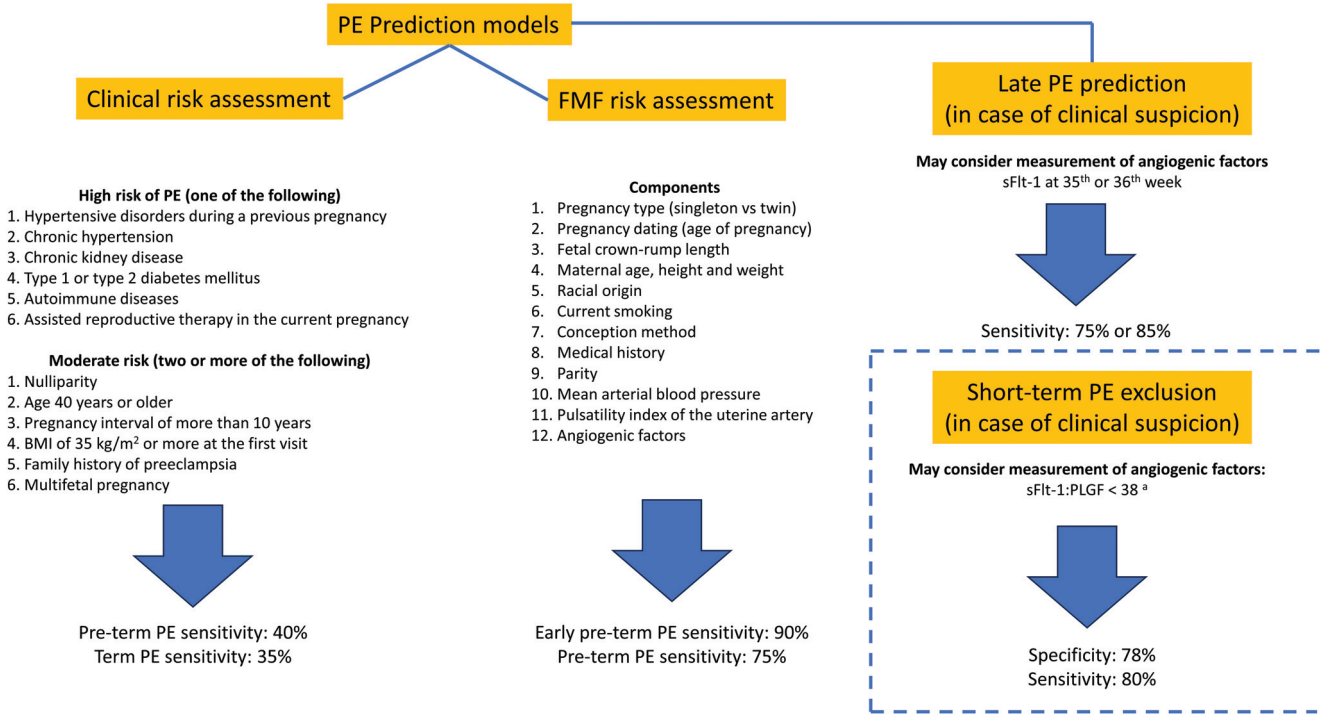

FIGURE 2 Risk assessment for preeclampsia prediction based on clinical risk factors, Fetal Medicine Foundation risk model, and biomarkers. a, depending on the manufacturer. FMF, Fetal Medicine Foundation; PE, preeclampsia; PLGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

based on high or intermediate clinical risk factors is sensitive to preterm preeclampsia or term preeclampsia of 40 or 35%, respectively.

Multivariable prediction models

Alterations in angiogenic factors are recognized as a likely consequence of abnormal placentation occurring in early pregnancy. Increased sFlt-1, an antiangiogenic factor of placental origin, counteracts proangiogenic factors such as PLGF and vascular endothelial growth factor, and this imbalance between antiangiogenic and proangiogenic factors contributes to BP increase and widespread vascular damage [56]. An increased sFlt-1/PLGF ratio may be particularly pronounced in women with early (<34 gestational weeks) preeclampsia. Measurements of angiogenic biomarkers have been incorporated into risk stratification in several contemporaneous trials for preeclampsia prevention [57,58] but are not routinely used to guide clinical care in most countries.

Multivariable models have high detection rates when used at 11–13 weeks of gestation for preterm preeclampsia and at 35–36 weeks for term preeclampsia. The internationally validated FMF (Fetal Medicine Foundation) model of maternal risk factors and biomarkers (i.e. BP, uterine–artery pulsatility index as measured by Doppler ultrasonography, and serum PLGF) identifies approximately 90% of women at 11–13 weeks of gestation in whom early preterm preeclampsia (at <34 weeks) will develop and approximately 75% of those in whom preterm preeclampsia (between 34 and 37 weeks) will develop (Fig. 2) [59]. For the 90% of women identified as being at low risk for preterm preeclampsia at 11–13 weeks of gestation, rescreening during the second and third trimesters can refine the risk stratification and identify women who require closer monitoring. In a high-income setting, randomization to the repeated measurement of PLGF and PLGF/sFlt-1 ratio in women with suspected preterm preeclampsia (between 22 weeks and 0 days' gestation and 35 weeks and 6 days' gestation at the time of the initial PLGF-based test) or usual care with concealed repeat PLGF-based testing, was not associated with improved perinatal outcomes [60]. Thus, universal, routine repeat PLGF-based testing of all individuals with suspected preeclampsia may not be recommended, and further studies are desirable. A single test in women with suspected preterm preeclampsia is still beneficial. However, the prediction of term preeclampsia is possible only at 35–36 weeks of gestation, with sFlt-1 making an independent contribution [61]; this screening approach at 35–36 weeks of gestation identifies 75–85% of women in whom term preeclampsia will develop (Fig. 2).

Prediction of preeclampsia complications

Although the diagnosis of term preeclampsia mandates labor induction [5,6], in women with a diagnosis of preterm preeclampsia, early delivery should be balanced against fetal prematurity and adverse maternal outcomes related to underlying preeclampsia. Adverse maternal outcomes may be predicted by using the full-PIERS (Preeclampsia Integrated Estimate of Risk; components: gestational age, chest pain or dyspnea, platelet count, serum creatinine, aspartate or alanine aminotransferase, and oxygen saturation) model twice weekly, and an online calculator is available: https://preempt.obgyn.ubc.ca/home-page/past-projects/fullpiers/. [62–64]. Fetal health should also be assessed during any expectant strategy in women with preeclampsia to make sure that delivery is safely postponed.

Prevention: the role of aspirin

Identification of a group at increased risk of developing preterm preeclampsia already at the beginning of pregnancy, many more weeks before the appearance of clinical symptoms, allows for the implementation of prevention. Meta-analyses of randomized controlled trials showed that taking aspirin starting before the 16th week of pregnancy, that is, before the end of the uterine spiral arteries remodeling, significantly reduces the risk of preeclampsia [65]. The results of the ASPRE multicenter trial confirmed the effectiveness of aspirin in reducing the number of women with preeclampsia before 34 weeks of gestation by 80% and less than 37 weeks of gestation by 63% [57]. The postulated mechanisms of aspirin's effect include the direct effect on apoptosis proliferation of trophoblast cells and antiplatelet prevention of placental infarctions [5]. As almost all the trials recruited women after 12 weeks of gestation, it is unclear whether starting treatment before 12 weeks of gestation would have additional benefits without any increase in adverse effects. The dose of aspirin used in most trials was 81–150 mg daily [6]. However, the higher dosages (i.e. 100–150 mg) of aspirin were associated with a greater reduction in the onset of preeclampsia [23,66]. Moreover, up to one-third of pregnant women proved to be aspirin-resistant (lack of platelet function response) at a dose of aspirin 81 mg [67]. To summarize, 100–150 mg of aspirin once daily, preferentially at bedtime, should be recommended as the preventive measure in women at high or moderate risk of preeclampsia, starting between 12 and 16 weeks of gestation until 36 weeks of gestation. Aspirin therapy is indicated when at least one high or at least two moderate risk factors are present (Table 2) [5,6,55]. Whether treatment with low-dose aspirin can reduce the incidence of superimposed preeclampsia in women with chronic hypertension remains a subject of debate [68].

Prevention: the role of calcium supplementation

A recent meta-analysis including 13 randomized controlled trials showed significant reductions in the risk of gestational hypertension and preeclampsia with high-dose calcium

TABLE 2. Indications for aspirin treatment based on clinical risk assessment

High risk of preeclampsia includes any of the following:
1. Hypertensive disorders during a previous pregnancy
2. Chronic hypertension
3. Chronic kidney disease
4. Type 1 or type 2 diabetes mellitus
5. Autoimmune diseases such as systemic lupus erythematosus or antiphospholipid syndrome
6. Assisted reproductive therapy in the current pregnancy
Moderate risk of preeclampsia includes two or more of the following:
1. Nulliparity
2. Age 40 years or older
3. Pregnancy interval of more than 10 years
4. BMI of 35 kg/m^2 or more at the first visit
5. Family history of preeclampsia
6. Multifetal pregnancy

supplementation (≥1 g/day) versus placebo [69]. However, this effect was clear only for women with low baseline calcium intake and greater for women at higher risk of preeclampsia. No differences in severe preeclampsia were observed [69,70]. Another meta-analysis, including 30 randomized controlled trials, confirmed that calcium supplementation decreases the incidence of preeclampsia by almost 50% [71]. The benefit exists regardless of the calcium dose (low dose, 500 mg/day versus higher dose >1 g/day), the baseline preeclampsia risk, vitamin D co-administration, or the timing of calcium initiation. Importantly, calcium was ineffective among women with adequate baseline calcium intake [71]. Of note, no clear evidence on the timing of initiation of supplementation has been provided, with a suggestion to start at the first antenatal care contact to improve compliance with the regimen. However, initiating calcium supplementation during the second trimester of pregnancy seems reasonable. Another issue is a lack of consensus definition for 'low calcium intake', which is usually considered at levels of less than 600–900 mg/day [5,20,72]. Overall, calcium supplementation with at least 500 mg/day is recommended in pregnant women whose calcium intake is less than 900 mg/day to reduce the risk of preeclampsia; a greater supplementation dose of 1–1.5 g/day seems harmless.

Prevention: the role of exercise

Epidemiological data from case–control studies have systematically demonstrated that women who participate in regular physical activity in the prepregnancy period and during pregnancy have a significantly reduced risk of developing pregnancy-related hypertensive disorders, particularly preeclampsia [73]. However, a recent pooled meta-analysis including 17 randomized controlled trials found that women practicing aerobic exercise for about 30–60 min, two to seven times per week, during early pregnancy had a significantly lower incidence of gestational hypertension but not preeclampsia [74]. Similar results favoring the impact of physical activity in reducing the incidence of gestational hypertension by 47%, but not preeclampsia, were shown in the most recent analysis derived from 23 systematic reviews, including 63 randomized trials [75]. Interestingly, the most favorable impact was observed in pregnant women who started light to moderate or moderate intensity exercise, with each session longer than 45 min, in the first and second trimester of pregnancy [75]. At the same time, the evidence regarding the benefit of physical exercise in overweight and obese pregnant women remains controversial [75–77]. The most recent meta-analysis involving 12 randomized controlled trials showed that regular exercise (the duration and intensity of which were different across the included studies) was associated with a decrease in the risk of developing gestational hypertension among overweight and obese pregnant women [78]. Additional studies are needed to clarify the potential impact of certain types of exercise, the initiation time and duration of exercise, and the level of intensity on pregnancy-related hypertensive disorders. Until then, assuming the absence of obstetric or medical complications or contraindications, physical activity in pregnancy is considered generally well tolerated and desirable with some modification when needed. Pregnant women are encouraged to continue or engage in physical activities because it controls weight gain and may reduce the likelihood of hypertension-related disorders [79]. Overall, in women where no contraindication exists, physical activity is recommended throughout pregnancy to prevent excessive weight gain and hypertension-related disorders. Reasonable advice would be to moderately exercise three to four times weekly in sessions of an average of 45 min.

Prevention: additional measures

Higher gestational weight gain has been considered a potential risk factor for HDP, but data so far are limited and inconclusive. In a meta-analysis including 23 randomized controlled trials, increased gestational weight gain was associated with a nonsignificant increase in the incidence of preeclampsia and gestational hypertension [80]. In a subsequent meta-analysis including 13 observational studies, it was found that excessive gestational weight gain was associated with an increased incidence of preeclampsia [81]. Finally, a meta-analysis of individual participant data, including 39 European, North American, and Australian cohorts, showed that a higher increase in gestational weight gain was associated with a significantly higher risk of gestational hypertension and preeclampsia. Interestingly, prepregnancy obese mothers with high gestational weight gain had the highest risks of gestational hypertension and preeclampsia [82]. Although weight reduction during pregnancy is not recommended to prevent HDP, antenatal counseling should include advice for achieving an ideal body weight before pregnancy.

The effect of sodium intake on BP response and hypertension-associated complications in pregnant women remains a subject of investigation. Although there are a few studies that have shown a positive association between increased salt intake and a higher risk of gestational hypertension and preeclampsia [83–85], no convincing data exist demonstrating a relation between a low salt diet and a lower incidence of hypertension-related pregnancy disorders. The first multicenter randomized, controlled trial of a sodium-restricted diet during pregnancy evaluated 184 pregnant women given a low sodium diet (<50 mmol sodium/day) and a control group of 177 women given a normal diet. No differences were found in the DBP between groups, nor were there differences in the percentage of referrals and admissions to the hospital for hypertension or incidence of preeclampsia [86]. Overall, no evidence exists for a favorable effect of reduced salt intake during pregnancy in preventing or treating preeclampsia, and salt consumption should remain a matter of personal preference [87]. However, it is reasonable that women with preexisting hypertension should continue pursuing a limited salt intake diet [88].

Regarding timed birth, a trial involving greater than 6000 low-risk nulliparous women showed that labor induction at 39 weeks 0 days to 39 weeks 4 days of gestation, as compared with expectant care, reduced, though marginally, the risks of the primary perinatal adverse outcome, lowered the frequency of cesarean delivery and also reduced the rate of

HDP [89]. Postterm preeclampsia ($\geq$ 39 weeks) may be prevented by prompt labor induction in low-risk nulliparous women, but whether the results of the trial [89] can be generalized to a different parity category or women at higher risk is unknown.

The role of candidate pharmacological agents with an acceptable safety profile, such as pravastatin or metformin, in preventing HDP is currently being evaluated [20]. In a German multicenter, double-blinded study of 1120 high-risk women for term preeclampsia randomized to pravastatin 20 mg or placebo at 35 or 36 weeks of gestation, the rates of term preeclampsia were not different between the groups [90]. The short interval between the intervention and outcome might be responsible for the neutral trial results.

Prevention: the role of a multidisciplinary team

Recognized guidelines on the management of HDP advocate the referral of women identified as high-risk for developing preeclampsia to specialized multidisciplinary teams, from preconception to postpartum follow-up. These teams should encompass obstetricians, cardiologists, and specialists in hypertension and obstetric medicine [55]. Although preliminary, results from observational studies have shown a reduction in adverse pregnancy outcomes in women undergoing multidisciplinary team follow-up during pregnancy compared with standard care [91,92]. Adverse pregnancy outcomes in women diagnosed with HDP may be mitigated through risk stratification and a personalized treatment approach elaborated by a multidisciplinary team. Future controlled studies are warranted to obtain enough evidence to implement this strategy in usual clinical practice.

CLINICAL MANAGEMENT: MILD PREEXISTING ESSENTIAL HYPERTENSION

The clinical history of women entering pregnancy with a previous diagnosis of essential hypertension is important for decision-making during pregnancy. The grade of hypertension at the time of diagnosis (without on-treatment drugs) and the estimated cardiovascular risk, including assessment of hypertension-mediated organ damage, are important and should be registered [5]. Another crucial set of relevant clinical factors in women with preexisting essential hypertension is the type and dose of drugs used before pregnancy and whether on-treatment SBP/DBP is controlled within the optimal BP target (i.e., usually <130/80 mmHg). Although women are usually not at high risk before pregnancy, there is a subset of women with a history of cardiovascular disease or proteinuria under treatment with renin–angiotensin system blockers. It is recommended that hypertensive women at reproductive age, in primary prevention, and without proteinuria, should not be treated with renin–angiotensin system blockers unless they use reliable contraception [5]. Other drug classes (i.e. calcium channel blockers, beta-blockers, diuretics) can and should be used in monotherapy or combinations (based on individual cardiovascular risk) to control hypertension [5].

In secondary prevention or the presence of proteinuria, renin–angiotensin system blockers are used before pregnancy. However, withdrawal of these drugs is mandatory in case of a suspected pregnancy (e.g. menses delay) because these drugs are associated with teratogenesis and renal failure of the fetus [5]. Thus, renin–angiotensin system blockers are contraindicated in the second and third trimester, especially after week 20 of pregnancy. However, if possible, they should also not be used in the first trimester. If inadvertent treatment with these drugs early in pregnancy, the pregnant woman should be switched to a lower risk antihypertensive agent [93–95]. A further obstetric examination by fetal ultrasounds may be offered to ensure fetal well being. In the event of exposure till after week 20, treatment must be stopped immediately and switched, and oligohydramnios should be ruled out during the rest of pregnancy. The kidney function of the newborn should be checked, an ultrasound examination of the kidneys should be carried out, and attention should be paid to possible hypotonia. Kidney structure, function, and BP levels should also be monitored again in later childhood [96]. Overall, throughout all trimesters of pregnancy, renin–angiotensin system blockers are contraindicated.

In women receiving drug classes other than renin–angiotensin system blockers, drug discontinuation or treatment replacement should also be decided on an individual basis. The decision of treatment discontinuation or replacement should take into consideration the balance between the risks of drug treatment during fetal organogenesis and the risks of inappropriate hemodynamic adaptations in early pregnancy because of uncontrolled hypertension. The selection of alpha-methyl-DOPA as a first-line agent in early pregnancy seems reasonable [97].

Which women with preexisting essential hypertension are eligible to discontinue antihypertensive treatment without drug replacement? Although a definite answer is not available because of different BP responses to treatment withdrawal, some women may be selected for complete first-trimester and early second-trimester drug discontinuation [5]. The decision to discontinue antihypertensive treatment during this period should be individualized based on mild prepregnancy untreated BP levels (preexisting grade 1 hypertension), controlled on-treatment early first trimester BP values, the absence of hypertension-mediated organ damage, and the perpetuation of well controlled BP levels after a short-term trial of antihypertensive treatment withdrawal. Whenever complete drug discontinuation is decided, BP should be carefully monitored by office BP measurements at least every 2 weeks and ideally complemented by home BP measurements. In women with moderate or severe prepregnancy untreated BP levels (preexisting grade 2 or 3 hypertension); uncontrolled early on-treatment first trimester BP values; presence of hypertension-mediated organ damage; and sustained BP elevation after a short-term trial of antihypertensive treatment withdrawal, drug replacement should be established. In this case, the potency of the initial antihypertensive treatment monotherapy should be mild, and careful dose escalation should be attempted to control hypertension. In case of uncontrolled hypertension with monotherapy at the maximum tolerated dose, a second antihypertensive agent may

be used. In preexisting hypertension, the presence of intense antihypertensive treatment during the early second trimester may promote a profuse DBP drop, potentially accompanied by miscarriage due to a synergistic effect with the physiological second-trimester BP reduction. To summarize the above, a wise clinical attitude for women with preexisting hypertension might be 'go slow and avoid going too low'.

The optimal BP targets during pregnancy in women with preexisting hypertension largely remain unsettled. In 2015, a relatively small study, the Control of Hypertension in Pregnancy Study (CHIPS) [98], evaluated whether less or more tight control of hypertension (i.e. achieved DBP values less than 100 or 85 mmHg, respectively) was associated with different perinatal and maternal outcomes. In CHIPS, 987 pregnant women with nonsevere and nonproteinuric preexisting hypertension (75%) or gestational hypertension were enrolled at 14–33 weeks. The primary outcome was a composite of pregnancy loss or substantial long-standing intensive neonatal care, with serious maternal complications as a secondary outcome. Both outcomes were not different for an average DBP reduction difference of 4.6 mmHg between groups during follow-up. However, as expected from previous evidence [99], the development of severe hypertension, a nonprespecified secondary outcome, was 1.8-fold more frequent in the less tight compared with the tight DBP control group. Finally, in the subgroup of women with chronic hypertension, less tight BP control was associated with lower rates of small-for-gestational-age newborns than tight BP control.

In 2022, an open-label multicenter randomized trial, the Chronic Hypertension and Pregnancy (CHAP), was published [100]. The CHAP trial addressed the outcomes and safety of antihypertensive drug treatment in singleton-pregnancy women with mild preexisting hypertension. Antihypertensive drug treatment with a target below 140/90 mmHg (active-treatment group) was compared with a conservative strategy of withholding or stopping such treatment unless severe hypertension developed (control group). The CHAP trial outcomes were preeclampsia with severe features or preterm delivery or placental abruption or fetal/neonatal death (primary outcome); small-for-gestational-age newborn (safety outcome); and serious neonatal or maternal complications or preeclampsia or preterm birth (secondary outcomes). The participants were enrolled before the 23rd week of gestation, and those at higher risk for severe hypertension development (i.e. treated with more than one antihypertensive agent at baseline) were excluded. The preferred drugs were labetalol or extended-release nifedipine, either used in 97% of participants. A combination drug treatment was only used after monotherapy dose escalation. During follow-up, the achieved SBP/DBP difference was 3.1/2.3 mmHg lower in the active treatment than in the control group. The composite primary outcome occurred 18% less frequently in the active-treatment group than in controls [95% confidence interval (CI) 8–27%]. In subgroup analyses, placental abruption and fetal/neonatal deaths were not different between groups. However, both of the following primary outcome components were reduced in the active treatment compared with the control group: preeclampsia with severe features by 20% (95% CI 8–30%) and preterm birth for medical reasons by 27% (95% CI 11–40%). The prespecified composite maternal or neonatal secondary outcomes were not different between groups, including small-for-gestational-age newborns. Severe hypertension developed 18% less frequently in the active treatment group compared to the control group (95% CI 0.74–0.90); however, no stroke event occurred in either study group during the trial. In light of the on-treatment BP values observed in CHIPS and CHAP trials (133/85 and 129/79 mmHg, respectively) [98,100], we suggest antihypertensive treatment should be restarted or potentiated in case of BP increase to at least 140/90 mmHg at any gestational age. Intensified BP-lowering should be avoided because of the potential risk of fetal hypoperfusion. Thus, a conservative target of less than 140/90 mmHg seems reasonable. Labetalol and alpha-methyldopa remain the first-choice drugs for BP control in women with preexisting hypertension [5,55,98,100]. An alternative agent is extended-release nifedipine [5,55,98,100]. However, it should also be noted that the use of labetalol is not a choice in several countries in which it was removed from the market 30 years ago, mainly because of hepatotoxicity, which may also occur when used in pregnancy [101]. Atenolol should be avoided during pregnancy because of the increased risk of low birth weight [102]. Bisoprolol may be well tolerated during the first trimester of pregnancy, whereas a potential adverse effect of prolonged bisoprolol exposure on fetal growth cannot be ruled out [103]. Indeed, long-term intrauterine exposure to metoprolol or bisoprolol (during the second and third trimesters) may increase the risk of being born small for gestational age, though without serious neonatal complications. It is still a matter of debate to which extent maternal hypertension contributes to lower birth weight. Treatments with metoprolol or bisoprolol are well tolerated treatment options, but a case-by-case decision on close neonatal monitoring is recommended [104].

CLINICAL MANAGEMENT: MILD GESTATIONAL HYPERTENSION

In women with mild gestational hypertension, the prepregnancy or until early second-trimester BP values are well below 140/90 mmHg and many times below 120/70 mmHg. Often, these otherwise healthy women are at low cardiovascular risk and without comorbidities. The physiological drop in BP in the second trimester produces a further BP reduction [5]. However, a small amount of these women will indeed develop, for the first time, hypertension after the 20th week of pregnancy with BP levels greater than 140/90 mmHg. Earlier hypertension guidelines [105–107] have considered the difference in BP between the first trimester and after the 20th week to draft recommendations about antihypertensive treatment initiation in mild gestational hypertension. In the 1999 World Health Association/International Society of Hypertension guidelines [108,109], a rise in BP from preconception or first trimester levels (e.g. SBP rise $\geq$25 mmHg and/or DBP rise $\geq$15 mmHg) defined gestational hypertension alternatively to BP greater than 140/90 mmHg. For example, a woman with an early pregnancy BP of 100/60 mmHg and a BP at the 22nd week of 135/85 mmHg may have a significant hemodynamic deterioration that may produce complications

for the mother and fetus. A less pronounced BP difference during the same gestational timeframe may not be associated with adverse hemodynamic adaptations [108,109].

Previous, though more recent, hypertension guidelines [8] suggested that treatment of mild gestational hypertension might be initiated from thresholds well above 140/90 mmHg (e.g. >150/95 mmHg). This expert opinion-based recommendation mainly stems from the notion that a mild-to-moderate BP elevation in pregnancy may be seen as a counterbalancing mechanism to support inadequate hemodynamic adaptations or fetal perfusion such as a relatively decreased cardiac output or increased peripheral resistance, respectively, always related to the gestational age [23]. Although the CHIPS trial [98] included a limited number of women with gestational hypertension, secondary analyses did not indicate a differential outcome effect between women with gestational and preexisting hypertension, both for primary and secondary outcomes. To synthesize the pathophysiological considerations and the limited available evidence from the CHIPS trial [98] related to women with mild gestational hypertension, treatment initiation at values at least 140/90 mmHg appears to be reasonable. At the same time, a DBP reduction to less than 80 mmHg is not recommended. The same drugs recommended for preexisting hypertension (see above) can be used in women with gestational hypertension.

CLINICAL MANAGEMENT: MATERNAL HEMODYNAMICS-GUIDED THERAPY

Recent studies have explored the impact of the hemodynamic profile of women with gestational hypertension in the choice of the first-line antihypertensive agent. Before the clinical presentation of hypertension, around 24 gestational weeks, women who will develop preterm preeclampsia demonstrated significantly higher systemic vascular resistance and lower cardiac output compared with normotensive pregnant women. On the contrary, women who later developed term preeclampsia had lower systemic vascular resistance and higher cardiac output compared to normotensive pregnant women [110]. Based on current evidence, the Italian Association of Preeclampsia (AIPE) recently proposed a classification into three maternal hemodynamic profiles: hypodynamic (>1300 dynes s/cm^5), normodynamic, and hyperdynamic (<800 dynes s/cm^5) [111].

Administering antihypertensive treatment to hypertensive pregnant women based on their hemodynamic profile substantially decreased the occurrence of severe maternal hypertension from 18 to 3.8% [112]. Furthermore, the recurrence of preeclampsia was lower with treatment tailored to the hemodynamic profile compared with the standard of care [113]. Nifedipine and alpha-methyldopa may be more effective in treating women with a 'hypodynamic' profile, namely those with high peripheral resistance and low cardiac output. Beta-blockers may be more effective for women with a 'hyperdynamic' profile characterized by high cardiac output and low resistance [113]. Future randomized studies may clarify the best strategy and therapeutic option for all subtypes of HDP. At present, we do not recommend treatment decisions based on hemodynamic data.

CLINICAL MANAGEMENT: SEVERE HYPERTENSION

Severe hypertension in pregnancy is defined as sustained SBP at least 160 mmHg and/or DBP at least 110 mmHg. Despite having no evidence from large clinical trials, there is a consensus that severe hypertension in pregnancy should be treated. Timely treatment (within 60 min of diagnosis) is associated with a 72% reduction in the relative risk of severe maternal morbidity [114]. The expected delivery time determines the selection of antihypertensive drugs and the route of administration.

Severe hypertension before 20 weeks of gestation

Preexisting (chronic) hypertension in pregnancy is rarely severe. However, in severe cases, secondary hypertension should be ruled out, particularly in the absence of a family history of hypertension, obesity, or Black ethnicity, and if hypertension seems to be treatment-resistant. The patient should be assessed in a specialized center. In addition to basic laboratory tests, a hypertension-mediated organ damage assessment should be performed. It includes urinalysis, preferably albumin to creatinine ratio in a single spot urine sample, electrocardiogram, echocardiography, and fundoscopy. In the absence of preeclampsia, treatment of severe hypertension can be initiated with oral drugs: labetalol, methyldopa, or nifedipine extended-release [55]. BP control can usually be achieved within several days.

Severe hypertension after 20 weeks of gestation

Severe hypertension after 20 weeks can be due to gestational hypertension, preeclampsia, or superimposed gestational hypertension in women with preexisting hypertension or poorly controlled preexisting hypertension. For oral treatment, the same drugs (labetalol, methyldopa, or nifedipine extended-release) can be used. If intravenous treatment is necessary, intravenous labetalol is the drug of choice. Due to the number of adverse effects mostly related to maternal hypotension, hydralazine intravenous should be used only when other drugs are ineffective or when labetalol is contraindicated [115]. However, intravenous hydralazine is still widely used in North America. Recent systematic reviews and meta-analyses found hydralazine comparable to labetalol and nifedipine in safety and efficacy [116,117]. Urapidil intravenous can also be considered, whereas sodium nitroprusside should be used as the last option because of an increased risk of fetal cyanide poisoning with prolonged use. Intravenous nitroglycerine is the drug of choice if preeclampsia is associated with pulmonary edema (starting with an infusion of 5 μg/min with a subsequent gradual increase every 3–5 min to a maximum dose of 100 up to 200 μg/min) [118]. Occasionally, short-acting nifedipine can be given orally to pregnant women if intravenous access is not available, with the second dose given only after 30–60 min if severe hypertension persists. However, sublingual short-acting nifedipine is contraindicated.

TABLE 3. Risk factors for hypertensive emergency during pregnancy

Preeclampsia
Cardiac disease
Chronic renal disease
Concomitant use of recreational drugs or other BP-raising medication (e.g. erythropoietin, anabolic steroids, and some herbal remedies)
Noncompliance with antihypertensive drugs
Use of utero-contractive drugs (e.g. ergonovine maleate, methyl-ergonovine maleate) for the prevention and treatment of postpartum hemorrhage caused by uterine atony
Non-Hispanic Black population
Low socioeconomic status

Modified from reference [118], with permission from Oxford University Press. BP, blood pressure.

Hypertensive emergency during pregnancy

Hypertensive emergency in pregnancy is defined as preeclampsia/eclampsia and SBP at least 160 mmHg and DBP at least 110 mmHg or markedly elevated BP (DBP >120 mmHg) and progressive acute end-organ damage (aortic dissection, acute myocardial infarction, pulmonary edema, and respiratory failure). Several risk factors for hypertensive emergency in pregnancy have been identified (Table 3). Patient history should include questions about compliance/noncompliance with antihypertensive drugs, use of recreational drugs, and other drugs potentially increasing BP (e.g. nonsteroid anti-inflammatory drugs, steroids, sympathomimetics, utero-contractive drugs). Physicians should pay attention to emergency symptoms such as headache, particularly when accompanied by visual disturbances, chest pain, dyspnea, neurological symptoms, nausea, or abdominal pain. Primary diagnostic workups and specific tests in a suspected hypertensive emergency during pregnancy are shown in Table 4. In women in whom at-term preeclampsia is suspected, an sFlt-1:PLGF ratio less than 38 may be used (Fig. 2) [60,119,120]. Assessment of fetal well being should be an integral part of the diagnostic workup, particularly in the later phase of pregnancy and peripartum. Table 5 lists maternal abnormal parameters needing immediate bedside evaluation [121]. The immediate goal is to decrease mean BP by 15–25% to achieve SBP 140–150 mmHg and DBP 90–100 mmHg. Table 6 provides the list of the most frequently used drugs for the treatment of hypertensive emergencies in pregnancy. Intravenous administration of magnesium sulfate is recommended for the prevention of eclampsia and treatment of seizures [122,123]. Concomitant use of calcium channel blockers may induce hypotension because of potential synergism [32]. Primary prevention of eclampsia is recommended by most guidelines in patients with severe preeclampsia and persistent neurological symptoms such as severe headache, visual disturbances, and hyperactive deep-tendon reflexes during pregnancy and the postpartum period (4 g magnesium sulfate intravenous loading dose followed by continuous infusion of 1 g/h until delivery for 24 h max, under close monitoring of the mother) [5,124].

TABLE 4. Diagnostic workups and specific tests in a suspected hypertensive emergency during pregnancy

Primary work-up
Fundoscopy
EKG
Hemoglobin, platelet count, fibrinogen
Serum creatinine, eGFR, electrolytes, LDH, haptoglobin
Urine: ACR
Urine microscopy: red cells, leukocytes, casts
Specific tests
Troponin (acute chest pain)
NT-proBNP (heart failure)
Plasma or urinary fractionated metanephrines (to rule out pheochromocytoma)
sFlt-1/PLGF (preeclampsia)
Echocardiography (aortic dissection, heart failure, or ischemia)
Brain CT or MRI
Renal ultrasound (renal parenchymal disease) and duplex renal artery Doppler (renovascular disease)
Urine drug screen (suspected methamphetamine or cocaine use)
Assessment of fetal wellbeing
Electronic fetal heart monitoring
Ultrasound examination for fetal growth
Amniotic fluid assessment
Uterine artery Doppler velocimetry (mean pulsatility index >95th percentile in the second trimester and/or bilateral notching)

Modified from reference [118], with permission from Oxford University Press. ACR, albumin to creatinine ratio; CT, computed tomography; eGFR, estimated glomerular filtration rate; EKG, electrocardiogram; sFlt-1, soluble fms-like tyrosine kinase-1; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-brain natriuretic peptide; PLGF, placental growth factor.

TABLE 5. Maternal early warning criteria needing immediate bedside evaluation

SBP <90 or >160 mmHg
DBP >100 mmHg
Heart rate <50 or >130 beats per minute
Oxygen saturation on room air, at sea level, <95%
Oliguria (<35 ml/h for 2 h or more)
Maternal agitation, confusion, or unresponsiveness (changed mental status)
Nonremitting headache in patients with hypertensive disease of pregnancy
Shortness of breath

Modified from reference [118], with permission from Oxford University Press.

CLINICAL MANAGEMENT OF PREEXISTING SECONDARY HYPERTENSION

In women of childbearing age, preexisting secondary hypertension remains a rare and heterogeneous group of diseases with unclear prevalence. According to the 2023 ESH guidelines for the management of hypertension [5], abdominal ultrasound investigation may be considered in addition to basic laboratory tests in pregnant women with a history suggestive of phaeochromocytoma/paraganglioma (PPGL) and women at high risk of gestational hypertension, preeclampsia, or IUGR.

In young women with unexplained preexisting hypertension, particularly in the absence of family history, overweight, older age, or Black ethnicity, it is recommended to rule out a secondary cause of hypertension before pregnancy. This strategy allows us to implement an interventional treatment before pregnancy when required, to evaluate the risk of subsequent fetomaternal complications, and to avoid workups involving irradiation during pregnancy [9]. During pregnancy, secondary hypertension should be strongly considered in women with severe hypertension (including hypertensive emergencies) or underlying renal disease with persistent proteinuria (<20 weeks of amenorrhea) [118].

TABLE 6. Most used drugs for the treatment of hypertensive emergencies in pregnancy

Drug	Route	Onset of action	Duration of action	Starting dose	Titration dose	Maximum dose	Perinatal concerns	Contra-indications	Possible adverse effects
Labetalol	i.v. (intermittent) i.v. (infusion)	5–10 min	2–6 h	10–20 mg i.v. (over 2 min) 1–2 mg/min	20–80 mg i.v. every 20–30 min Increase by 1 mg/min every 10 min	300 mg	Fetal distress secondary to abrupt maternal hypotension; neonatal bradycardia and hypoglycemia	II or III degree AV block; systolic heart failure; asthma; bradycardia	Bronchoconstriction (CAUTION in women with asthma); fetal bradycardia; postural hypotension; sleep disturbances; rebound hypertension; masking hypoglycemia
Hydralazine	i.v. (intermittent)	10 min	12 h	5 mg/i.v. or i.m.	5–10 mg i.v. every 20–40 min	30 mg	Fetal distress secondary to abrupt maternal hypotension; caesarean section; abruption; APGAR score <7 more common; rarely neonatal thrombocytopenia and neonatal lupus		Headache; palpitations; tachycardia; nausea/vomiting; flushing; hypotension; lupus-like syndrome; CAUTION: side effects may mimic worsening preeclampsia
Nifedipine short-acting formulation	Oral	5–10 min	2–4 h	10–20 mg	Repeat in 30 min if needed	30 mg	Fetal distress secondary to abrupt maternal hypotension; increased liver clearance may require higher doses		Uncontrolled hypotension (high when combined with magnesium sulfate); stroke; maternal hypotension (particularly when given sublingually); headache; flushing; reflex tachycardia
Nitroglycerine	i.v. (infusion)	1–5 min	3–5 min	5 μg/min	Increase by 5 μg/min every 5 min	200 μg/min			headache; reflex tachycardia
Esmolol	i.v. (infusion)	<1 min	15–30 min	Bolus 500 μg/kg; maintenance 50 μg/kg/min	Increase by 50 μg/kg/min every 4 min	300 μg/kg/min	Fetal bradycardia; resistant fetal beta-blockade	II or III degree AV block; systolic heart failure; asthma; bradycardia	First-degree heart block; maternal bradycardia; CHF; bronchospasm
Nicardipine	i.v. (infusion)	1–5 min	4–6 h	5 mg/h	Increase by 2.5 mg/h every 5–15 min	15 mg/h		liver failure	Tachycardia; flushing; headache
Urapidil	i.v. (infusion)	3–5 min	4–6 h	Bolus 12.5–25 mg; maintenance 5–40 mg/h		40 mg/h			
Sodium nitroprusside	i.v. (infusion)	<1 min	2–3 min	0.25 μg/kg/min	Increase by 0.25–0.5 μg/kg/min every 2–3 min	5 μg/kg/min	Fetal cyanide and thiocyanide toxicity if used >4 h		Nausea; vomiting

Modified from reference [118], with permission from Oxford University Press. AV, atrioventricular; CHF, chronic heart failure; i.v., intravenous; i.m., intramuscular; NO, nitric oxide.

Fibromuscular dysplasia and renal artery stenosis

Fibromuscular dysplasia (FMD) is an idiopathic, segmental, nonatherosclerotic, and noninflammatory disease of the musculature of the arterial walls [125]. It is probably one of the main causes of secondary hypertension in women of childbearing age. Pregnancies in patients with known FMD are considered to be at increased risk, particularly in the case of previous cervical artery dissection, spontaneous coronary artery dissection, or poorly controlled hypertension. Accordingly, in patients with FMD, an intensive follow-up is required each trimester throughout pregnancy, as well as in the immediate postpartum. A delivery plan must be set up and adapted to the profile of the patient, especially in those women with a history of arterial dissection or aneurysms [125]. According to data collected from 534 pregnancies of 232 women subsequently diagnosed with FMD and enrolled in the European/International FMD Registry (FEIRI), the risk of gestational hypertension, preterm birth, and, to a lesser extent, preeclampsia was higher than in historical cohorts of normotensive or hypertensive women. In an overwhelming proportion of cases (96%), FMD was diagnosed only after pregnancy. It is reasonable to hypothesize that timely diagnosis of renal FMD leading to renal artery revascularization before pregnancy, wherever appropriate, would have significantly limited the risk of pregnancy-related complications [126]. The risk of pregnancy-related complications associated with FMD in this cohort – admittedly including mostly patients with renal FMD and a low prevalence of aneurysms and dissection – was much lower than in a genetic arteriopathy such as vascular Ehlers–Danlos [126]. Therefore, pregnancies in patients with FMD deserve a close follow-up but are not contraindicated.

Phaeochromocytoma/paraganglioma

Among secondary hypertension, PPGL remains a very rare tumor (0.002% of all pregnancies) but with devastating consequences (maternal and fetal mortality is around 50% if undiagnosed) [32,127]. The clinical presentation of PPGL during pregnancy is not essentially different from that in nonpregnant patients. Factors independently associated with an antenatal diagnosis of PPGL are hypertension at admission, sweating, and admission because of a history of PPGL/gene mutation/adrenal mass. Preeclampsia remains a factor independently associated with a postnatal diagnosis of PPGL. Three main factors associated with adverse maternal and fetal outcomes are PPGL discovered after pregnancy, catecholamine excess at least 10 times the normal levels, and no α-blockade during pregnancy [128]. Plasma-free metanephrines or urinary fractionated metanephrines are the first-choice screening tests for suspected PPGL. While it avoids radiation exposure, MRI allows reliable tumor localization (sensitivity >90%) [129]. If a PPGL is diagnosed in the first 24 amenorrhea weeks, laparoscopic adrenalectomy after 10–14 days of medical pretreatment with α-adrenergic blockade is recommended. Calcium channel blockers and magnesium sulfate may also be used. If the tumor is diagnosed near the third trimester, the same protocol is proposed as surgical preparation until the fetus is viable. Vaginal delivery with PPGL in-situ ablation is probably as well tolerated as delivery by cesarean section [117,127,130]. Finally, it has been shown in an international multicenter study and systematic review of 249 pregnancies that both maternal and fetal outcomes were excellent when catecholamine excess was treated. Alpha-adrenergic blockade therapy was associated with better outcomes. However, several severe and even fatal events occurred, mainly in patients with unrecognized PPGL [130]. Timely consideration and diagnosis of PPGL before or during pregnancy are key features for an optimal outcome.

Chronic kidney disease

Chronic kidney disease (CKD) is probably the most common cause of secondary hypertension in nonobese, nondiabetic young women and often remains undetected [131,132]. Preexisting CKD is present in 3% of pregnancies in high-income countries [55]. In pregnant women, a history of preeclampsia, advanced maternal age, assisted reproduction, multiple pregnancies, Black race, or clinical findings such as masked hypertension, chronic uncontrolled hypertension, or intra-uterine growth restriction is associated with an increased likelihood of CKD [10,54,55,133]. In women with renal insufficiency, the presence of either an estimated glomerular filtration rate (eGFR) less than 40 ml/min/1.73 m^2 (<0.67 ml/s/m^2) or proteinuria greater than 1 g/day before conception predicts poor maternal and fetal outcomes [134]. Angiogenic markers may be particularly useful in pregnant women with CKD [10,135,136]. Monitoring the sFlt-1/PLGF ratio, starting at the 20th week, may allow for anticipating placental ischemia syndromes [137]. Moreover, a small study [133] suggested that the sFlt-1 to PLGF ratio may help differentiate between the variable causes of increasing proteinuria, especially in CKD patients. Indeed, a low ratio (i.e. <30) was associated with CKD alone, whereas a ratio of greater than 150 was less likely compatible with CKD alone and deemed suggestive of preeclampsia [133]. Although several guidelines call for more aggressive treatment in pregnant women with CKD, the specific BP target to achieve remains unclear. Diuretics can be used safely in case of reduced eGFR but perhaps at lower doses [55]. Women at high risk of preeclampsia, including women with CKD, should be advised to take 100–150 mg of aspirin daily starting from weeks 12–16 until the end of week 35 [5,10].

Primary aldosteronism

Ten percent of hypertensive pregnancies are due to primary aldosteronism. There is very little data on primary aldosteronism and pregnancy. Given the changes in the renin–angiotensin system during pregnancy, the diagnosis of primary aldosteronism is difficult to establish during gestation. It may be suspected in hypertensive patients with hypokalemia. A comprehensive literature review identified reports covering 40 pregnancies in patients suffering from primary aldosteronism. Analysis of these cases shows them to be high-risk pregnancies leading to maternal and fetal complications [138]. A recent case–control study of 59 women compared the management and outcome of pregnancies in women with primary aldosteronism to a group of

high-risk pregnant women without primary aldosteronism and to a group of low-risk pregnant women. Women with primary aldosteronism during pregnancy delivered earlier but at term and required longer hospitalization and more antihypertensive drugs after delivery. There was no difference in the rates of maternal or neonatal adverse events, including neonatal death, compared with their high-risk nonprimary aldosteronism counterparts. Overall, this study showed that women with primary aldosteronism had better pregnancy outcomes than previously stated in the literature, including the risk of preeclampsia or preterm delivery [139].

In women with primary aldosteronism, pregnancy needs to be planned, and if the patient has a unilateral form of primary aldosteronism, an adrenalectomy should be performed before conception. It is customary to stop spironolactone before conception and to introduce antihypertensive drugs that present no risk of teratogenicity, but this recommendation could change with more data [140]. In small studies, drugs such as eplerenone or amiloride have shown no adverse effects during pregnancy, though because of the scarcity of data, they should better be avoided [55]. When conventional antihypertensive drugs used during pregnancy fail to control high blood pressure, diuretics, including potassium-sparing diuretics, may nevertheless be prescribed. Adrenalectomy may be considered during the second trimester of pregnancy, exclusively in cases of refractory hypertension [138].

POSTPARTUM HYPERTENSION (THE FOURTH TRIMESTER)

Postpartum BP elevation is common during the first week, and 10% of normotensive women demonstrate a DBP increase to levels greater than 100 mmHg after delivery [141]. Also, in women with a normotensive pregnancy, a BP elevation during the first day postpartum is usually associated with the use of vasoactive drugs to favor uterine contraction (oxytocin, methergine), blood transfusions, the physiological uterine 'auto-transfusion phenomenon' or an excessive intravenous fluid administration. In women with preeclampsia, a reduced diuresis during 12–36 h postpartum is observed because of a delayed fluid redistribution associated with a greater colloid osmotic pressure drop compared with a normal pregnancy [26]. In a small, randomized placebo-controlled trial in women with hypertension during pregnancy, administration of furosemide 20 mg daily during the first 5 days postpartum prevented 1 woman out of 13 from developing postpartum hypertension [142]. However, the wide use of furosemide postpartum needs confirmation from larger studies. Finally, it should be noted that 70% of women with preeclampsia maintain hypertensive BP levels, even under antihypertensive treatment, for the first week after delivery [143].

During puerperium, BP levels usually normalize within the first 6 weeks in women with gestational hypertension or preeclampsia, but this arbitrary rule is not without exceptions [5]. By contrast, women with preexisting hypertension or superimposed preeclampsia perpetuate elevated BP values beyond the 6 weeks of puerperium. A rare postpartum hypertension phenotype is the so-called 'late postpartum hypertension', which appears weeks to 6 months after delivery and usually resolves before the first year postpartum [32]. The pathogenesis of this condition is unknown, but one possibility is that the return of postpartum menses increases BP through a spillover of the excess of progesterone and activation of mineralocorticoid receptors. This mechanism seems similar to that documented in patients with Geller syndrome, who exhibit exacerbated hypertension in the third trimester of pregnancy [32,144]. In a relatively small single-center trial, the combined self-monitoring and physician-guided drug titration was associated with lower BP and improvement of cardiac remodeling measures during the first 9 months postpartum compared with usual postnatal outpatient care [145,146]. Hypertension specialists may play a pivotal role in the postpartum care of women with HDP, educating them about the importance of ongoing BP monitoring, suggesting appropriate lifestyle changes, and prescribing the appropriate and tailored medications to optimize BP control and overall cardiovascular health.

All antihypertensive agents used during pregnancy may be used during puerperium to achieve BP control. The use of angiotensin-converting enzyme inhibitors in the postpartum period should be reserved for women with cardiorenal comorbidities except in cases of premature birth or renal failure in newborns. Renin–angiotensin system blockers are not recommended in healthy women with hypertensive disorders during puerperium [5,109]. Methyl-dopa should be used with caution because of the risk of postpartum depression [5,147]. Different BP phenotypes during puerperium are summarized in Supplemental Figure S1, http://links.lww.com/HJH/C456 (online Data Supplement).

ANTIHYPERTENSIVE MEDICATIONS AND LACTATION

During the postpartum period, some drugs taken by the nursing mother may have a greater effect on the neonate compared with others [148]. It is especially evident for drugs with a low distribution volume, small protein binding, increased lipophilicity (because of the different pharmacokinetic drug properties between the mother and newborn), and electrical neutrality within normal pH levels [149]. The amount of milk, the bioavailability, and the clearance of the drug are additional factors that modulate drug effects on the neonate [148]. Although diuretics are not contraindicated, they may be associated with reduced milk production. Among beta-blockers, atenolol should be avoided, whereas labetalol, bisoprolol, and propranolol may be used. However, beta-blockers during breastfeeding may be accompanied by neonate low glucose levels. Verapamil and nifedipine are considered compatible with breastfeeding. Alpha-methyl-dopa is also compatible with breastfeeding. However, it should be remembered that it may induce depression in the mother. Finally, in women with a history of cardiovascular disease, angiotensin-converting enzyme inhibitors, especially captopril and enalapril, should be used because they have the most safety data available. Angiotensin receptor blockers are not currently recommended in lactating women because of limited safety evidence [5]. A summary of the relative safety of

antihypertensive agents during lactation is provided in Supplemental Table S1, http://links.lww.com/HJH/C456 (online Data Supplement) [7].

RISK OF HYPERTENSIVE DISORDER RECURRENCE IN A SUBSEQUENT PREGNANCY

Women who have experienced a pregnancy complicated by hypertensive disorders are concerned about the recurrence of the same disorder in a future pregnancy [150]. Studies that evaluated the recurrence rate of HDP showed divergent results not only due to an important heterogeneity in pathophysiology and clinical presentation but also because of different study designs [151]. A meta-analysis including 99 415 women showed that the recurrence rate of pregnancy-related hypertensive disorders was 20.7% [152]. Recurrence manifested as preeclampsia in 13.8%, gestational hypertension in 8.6%, and HELLP syndrome in 0.2%. However, in most cases, HDP recurred in a milder form [152]. Along the same lines, earlier studies reported a recurrence rate of preeclampsia ranging from 5.9 to 25%, with a weighted average rate of 14% [151]. One population-based study in Norway demonstrated that women with preterm preeclampsia in the first pregnancy had an early or late preterm preeclampsia recurrence rate of 39.4 and 30.4%, respectively [153]. Similar rates were found in another population-based study in Australia, with the reappearance of preeclampsia in 33.8% during the following pregnancy [150]. Risk factors of a recurrent pregnancy-related hypertensive disorder are early onset preeclampsia, HELLP syndrome or delivery of small-for-gestational age, prematurity, chronic hypertension, increased body weight, between-pregnancy interval longer than 5–10 years or short interbirth interval (<2 years), and thrombophilia [153–155]. In summary, the risk of recurrence of pregnancy-related hypertensive disorders is higher with a previous hypertensive pregnancy than with a previous normotensive pregnancy. Regarding counseling, maternal and perinatal outcomes in the subsequent pregnancy seem less severe than in the previous pregnancy. However, concomitant risk factors are important to future pregnancy outcomes [150].

INFERTILITY TREATMENTS

According to the WHO, infertility is a global health issue affecting almost 15% of reproductive-age couples. ART procedures are expanding rapidly, with concerns for maternal and fetal health. Large meta-analyses of more than eight million pregnancies have shown that any ART procedure is associated with an approximately 1.5–2 times higher risk of developing HDP compared with spontaneously achieved pregnancies [156,157]. However, distinctions do exist concerning the type of ART procedure. Intrauterine insemination (IUI) is considered a noninvasive or minimally invasive ART. In contrast, in-vitro fertilization (IVF) techniques, including Fertilization in Vitro and Embryo Transfer (FIVET) and Intra-Cytoplasmic Sperm Injection (ICSI), are considered invasive ART procedures. No adequately powered studies exist to compare the risk of pregnancy-related hypertensive disorders between invasive and minimally invasive ART procedures and between FIVET and ICSI techniques. By contrast, IUI with donor sperm was shown to be associated with an increased risk of preeclampsia or gestational hypertension compared with IUI with partner sperm [158]. The immune system hypothesis suggests that previous long enough exposure to the partner sperm induces an immune tolerance towards the partner, reducing the inflammatory response and thus the likelihood of preeclampsia development [159]. Regarding invasive procedures, heterologous IVF with oocyte donation seems to increase the risk of preeclampsia up to three times compared with IVF with autologous oocytes [160]. Finally, frozen–thawed embryo transfer (FET) is associated with an increased risk for preeclampsia compared with fresh embryo transfer, and programmed FET cycles are at higher risk compared with other endometrial preparation protocols [157,161].

Although women who resort to ART may have additional risk factors for preeclampsia, such as primiparity, preexisting hypertension, and advanced maternal age, the heterogeneity in preeclampsia risk for different ART techniques suggests that these preexisting maternal risk factors do not entirely explain the increased risk of developing hypertensive disorders in ART pregnancies (Fig. 3). Thus, other pathophysiological hypotheses have been proposed for the association between ART and hypertensive risk. The placental insufficiency hypothesis suggests that IVF-induced suboptimal endometrial preparation and generation of the trophoblast cells outside of the uterus lead to pathological placentation and placental insufficiency, which in turn causes systemic endothelial dysfunction [162]. Another hypothesis sees the absence of a corpus luteum as a key factor for cardiovascular and renal maladaptation during pregnancy, which ultimately leads to the development of hypertension. This hypothesis is corroborated by the results of several studies on women undergoing different IVF cycles that demonstrated a protective role of one or multiple corpora lutea compared to the absence of a corpus luteum [163]. Primary causes of infertility also play a role. For example, polycystic ovary syndrome has been associated with an increased risk for preeclampsia even after adjustment for age, race, obesity, recourse to ART, and other maternal factors [164].

In conclusion, the 2023 ESH guidelines for the management of hypertension [5] considered ART as an independent risk factor for preeclampsia. Thus, they recommended the initiation of low-dose aspirin in all women undergoing ART before 16 weeks of pregnancy [5,6]. Future controlled studies are warranted to identify additional preventive and therapeutic measures for women undergoing ART procedures.

PREGNANCY-RELATED HYPERTENSIVE DISORDERS AND FUTURE CARDIOVASCULAR OUTCOMES

Preeclampsia is associated with a poor future cardiovascular outcome, as has been constantly shown in different longitudinal studies with a prospective or retrospective design after adjustment for known confounders [5,55]. All types of cardiovascular outcomes were found to increase after preeclampsia compared with uneventful pregnancies

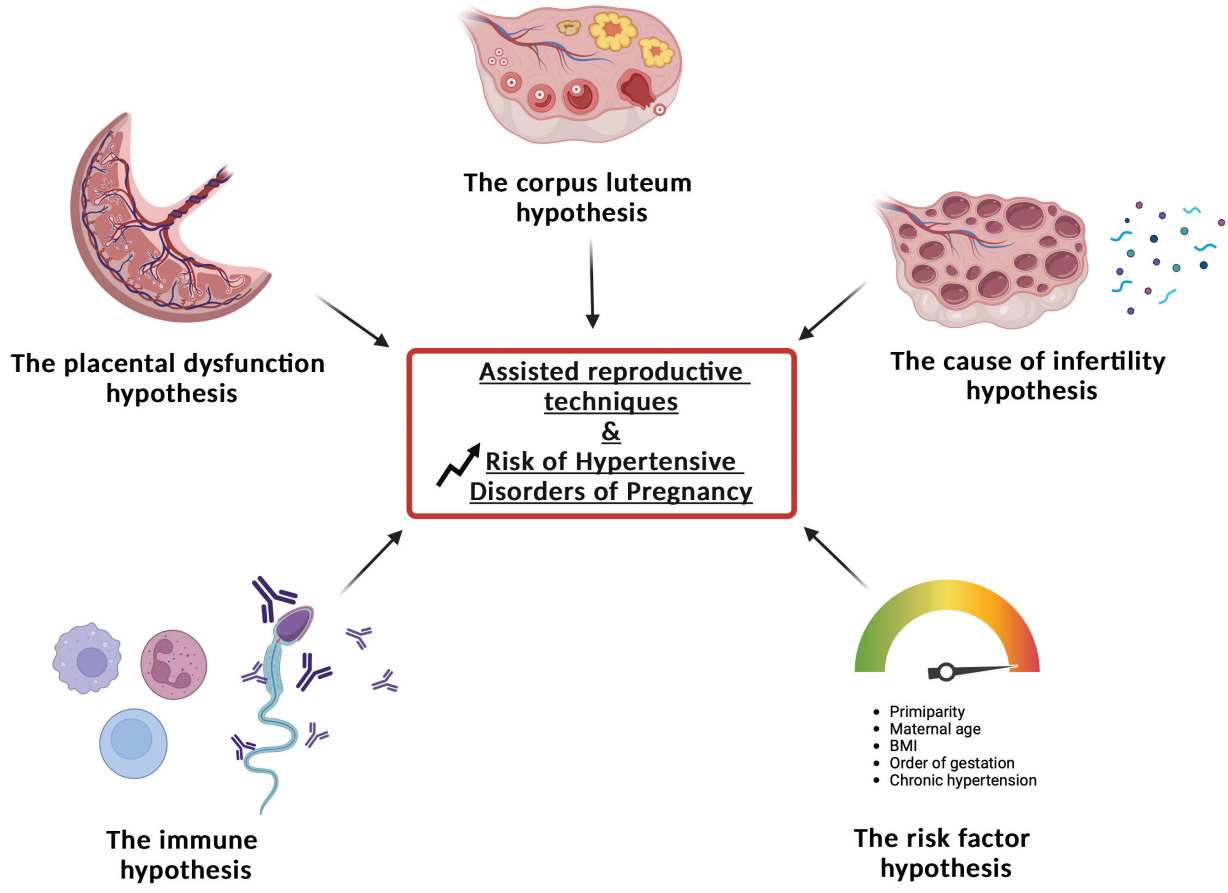

FIGURE 3 Why assisted techniques are related to an increased risk of hypertensive disorders? The mosaic of hypotheses. Order of gestation refers to the number of fetuses in each pregnancy.

(i.e. heart failure, acute coronary syndromes, stroke, pulmonary embolism, valvular heart disease) [165–168], as well as a five-fold increased risk of end-stage kidney disease compared with parous women with no preeclampsia [169]. A meta-analysis of cohort studies showed that preeclampsia with more severe features was associated with a higher incidence of future disease compared with preeclampsia with less severe features [170]. A genome-wide genetic association study using Mendelian randomization provided genetic evidence supporting an association between pregnancy-related hypertensive disorders and a higher risk of coronary heart disease or stroke, which is only partially mediated by cardiometabolic factors [171]. Although the association between preeclampsia and future cardiovascular events is consistently shown in most of the observations so far [165–168], we acknowledge that studies suffer from unmeasured confounding before or after the preeclamptic pregnancy, that in many studies, the term 'pregnancy-induced hypertension' was used instead of preeclampsia or gestational hypertension [172]. Finally, it remains unknown whether some cases of preeclampsia were complicated by subclinical myocardial injury, as in the case of overlapping peripartum cardiomyopathy [30]. Because preeclampsia is highly prevalent among women with high-risk profiles, it can be assumed that the development of preeclampsia may further re-stratify these women at very high cardiovascular risk. Also, it cannot be ignored that preeclampsia represents a vascular event of variable intensity centered on spiral arteries and the placenta [173]. Indeed, spiral arteries from preeclamptic decidual tissue demonstrate histopathological forms of acute atherosis, with lipid-laden foam cells in the vessel wall lining the subendothelial area and occasionally a lumen thrombus [174]. Whether vascular alterations were preexistent to pregnancy (as a consequence of a subclinical atherosclerotic process in the mother) or developed during pregnancy (as a consequence of preeclamptic systemic vascular dysfunction) remains unclear. By summarizing the above, in women who have experienced HDP, lifestyle modifications are indicated to reduce the risk of complications in subsequent pregnancies as well as to reduce cardiovascular risk in general [175,176]. Regular visits for cardiovascular risk assessment and frequent home BP measurements are recommended [176]. After delivery and hospital discharge, the role of telemonitoring in women with HDP should be investigated in future trials to confirm the already published promising evidence [145,146].

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Pregnancy-related hypertensive disorders continue to be a major cause of maternal, fetal, and neonatal morbidity and mortality worldwide. About 10% of pregnancies are complicated by hypertension, and these rates are likely to rise

because of the increasing age and prevalence of obesity in pregnant women. Moreover, ART procedures, regardless of the type of treatment, are associated with an increased risk of developing HDP, with the highest risk being documented in FET and OD pregnancies [157]. It is estimated that about 2–6% of children in high-income countries are conceived using assisted reproductive technology [177].

There is an alarming fact that maternal death in some developed countries, such as the United States of America, has been steadily increasing over the past 30 years. This phenomenon may be partly because of more sensitive and accurate reporting or to an increase in chronic comorbidities such as diabetes and obesity, renal disease, and systemic vascular disease in pregnant women. Each of these comorbidities increases the risk of developing preeclampsia. We are not predicting preeclampsia well, which is an important area for future research. Early detection of preeclampsia improves outcomes; however, no reliable screening test can predict its development during the second or early third trimester [178]. The lack of reliable testing in HDP opens prospects for investigating endothelial dysfunction by measuring blood and urine biomarkers (e.g. proteomics), not only for diagnostic purposes but also to target personalized therapy [179].

A low dose of aspirin, when initiated before 16 weeks of gestation, can substantially reduce the risk of preeclampsia. Despite the evidence for the protective effect of a low dose of aspirin, it is still not adequately used. The CHAP trial in chronic hypertension in pregnancy showed that only 44.6% of women were taking a low dose of aspirin [100], suggesting that preconception counseling is inadequate or that this issue was not discussed. Some promising data for statins shows that they might be beneficial in preventing preeclampsia; however, further studies are needed to draw definitive conclusions [180,181].

Based on the results of the CHIPS and CHAP trials [1,98,100], most guidelines have reduced the threshold for initiating drug treatment in pregnancy to at least 140/90 mmHg. However, the target DBP is still unclear, and the 2023 ESH guidelines suggest not reducing BP 80 mmHg or less [5]. Future clinical trials should address the optimal BP targets and their effects on maternal and fetal/neonatal outcomes. The role of maternal hemodynamics seems promising for the future management of HDP [111].

In general, for hypertension in pregnancy, there is still a lack of evidence from large clinical trials, which are quite difficult to organize for several reasons. Firstly, there might be ethical problems. Secondly, pregnant women are not interested in participating in clinical trials, at least partly because pregnant women are unaware of the association between pregnancy complications and cardiovascular disease [182]. Finally, there has been minimal effort from pharma companies for testing antihypertensive drugs in pregnancy. Therefore, the only substances that have been tested in large clinical outcome trials in pregnancy are methyldopa, labetalol, and long-acting nifedipine, and they are all recommended by the 2023 ESH guidelines [5]. Additional substances need to be tested in large clinical outcome trials, and till then, clinical experiences will guide the recommendations.

Women with a history of gestational hypertension, and preeclampsia in particular, have a higher risk of developing hypertension and stroke later in life [183]. Additionally, preeclampsia was found to be associated with an increase in heart failure, coronary heart disease, and cardiovascular death. Although the absolute risk of end-stage renal disease in women who have had preeclampsia is low, preeclampsia is a marker for an increased risk of subsequent kidney deterioration [184]. Women with a history of HDP may subsequently develop hypertension and premature cardiovascular disease. They are now recognized as high-risk individuals. However, recommendations on systematic checkups are still lacking, and doctors in their usual practice often forget to ask about that when taking history. BP monitoring in the early postpartum period is strongly advised, using BP self-measurement if feasible, with BP values directly reported to the attending doctors. In conclusion, several aspects of hypertension in pregnancy should be further tested to ensure their future inclusion in the guidelines.

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Figure 3 was created with BioRender.com with permission.

Conflicts of interest

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