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HYPERTENSION IN PREGNANCY 55

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INTRODUCTION

Hypertensive disorders in pregnancy remain a major cause of maternal, fetal and neonatal morbidity and mortality not only in developing but also in developed countries. Pregnant women with hypertension are at higher risk for severe complications such as abruptio placentae, cerebrovascular accident, organ failure and disseminated intravascular coagulation. The fetus is at risk for intrauterine growth retardation, prematurity and intrauterine death. Hypertension is the most common medical problem in pregnancy; it may complicate 5–10% of pregnancies and accounts for approximately a quarter of all antenatal admissions. As women in developed countries currently delay childbirth, the impact of pre-existing hypertension will increase because the prevalence of hypertension increases with age. In 70% of cases, hypertension develops after 20 weeks' gestation, and only 30% of cases with hypertension are women with pre-existing hypertension.

PHYSIOLOGICAL CHANGES IN BLOOD PRESSURE DURING PREGNANCY

Early in the first trimester, there is a fall in blood pressure (BP), caused by active vasodilatation due to the action of local mediators, such as prostacyclin and nitric oxide. This reduction in BP primarily affects diastolic BP (DBP), and a drop of 10 mmHg is usual by 13–20 weeks' gestation. BP continues to fall until 20–24 weeks when a nadir is reached. After this, there is a gradual increase in BP until term, when pre-pregnancy levels are achieved. This BP fluctuation occurs in both normotensive and hypertensive women.

Women with pre-existing hypertension tend to have even greater decreases in their BP in early pregnancy, and their 'normal' rise in the third trimester may be misdiagnosed as gestational hypertension Women with DBP of 75 mmHg or systolic BP (SBP) of 120 mmHg in mid-pregnancy, or 85 mmHg DBP or 130 mmHg SBP in later pregnancy, should be monitored closely (1).

Immediately after delivery, BP usually falls, then increases over the first 5 postnatal days. Even women whose BP was normal throughout pregnancy may experience transient hypertension in the early postpartum period, perhaps reflecting a degree of vasomotor instability. A summary of changes in major hemodynamic parameters is given in Table 55.1.

BP MEASUREMENT

It is essential to confirm high BP readings, preferably on two occasions (2), at least 15 minutes apart in severe hypertension (i.e. ≥160/110 mmHg in the obstetric literature).

Blood pressure in pregnancy should be measured in the sitting position (or the left lateral recumbent during labour) with an appropriately sized arm cuff at heart level. Supine positioning is usually associated with lower BP values and left lateral positioning may provide the lowest values because the right arm is frequently elevated above heart level during BP measurement (3).

Mercury sphygmomanometers are still the gold standard for BP measurement in pregnancy. Automated devices tend to under-record the true BP values and are unreliable in severe pre-eclampsia. Mean reported differences have been as great as 15 mmHg when compared with mercury sphygmomanometry, and 25 mmHg when compared with intra-arterial measurements, with wide variation (4).

As mercury sphygmomanometers have been eliminated from many institutions, BP can be measured using automated (usually oscillometric) BP devices, which have been validated according to standardized protocols, specifically in pregnancy and pre-eclampsia (see: http://www.dableducational.org) (5).

Korotkoff phase V is now recommended for the measurement of DBP in pregnancy (6–8). If Korotkoff sounds persist as the level approaches 0 mmHg, then the point of muffling of the sound is used (phase IV) to indicate the DBP.

Several ambulatory BP monitoring (ABPM) devices have been successfully validated specifically for use in pregnancy and used to generate normal ranges for ABPM

Table 55.1	Cardiovascular changes in pregnancy	
Parameter	**Change**	**Timing**
Systolic blood pressure	↓4–6 mmHg	All bottom at 20–24 weeks, then rise gradually to pre-pregnancy values at term
Diastolic blood pressure	↓8–15 mmHg	
Mean arterial pressure	↓6–10 mmHg	
Heart rate	↑12–18 beats/min	Early 2nd trimester, then stable
Stroke volume	↑10–30%	Early 2nd trimester, then stable
Cardiac output	↑33–45%	Peaks in early 2nd trimester, then until term

throughout gestation. Clinical application of ABPM has been assessed in three main areas: white-coat hypertension, early prediction of pre-eclampsia, and prognostic assessment of hypertension in later pregnancy. As white-coat hypertension is a common phenomenon in pregnant women who appear to be hypertensive according to routine BP measurement early in pregnancy, ABPM might be useful in the initial assessment to avoid unnecessary antihypertensive treatment (9). On the other hand, hypertension in pregnancy, as diagnosed by ABPM, has been shown to be associated with lower birth weights (10,11), and is superior to the office measurement of BP in predicting the outcome of pregnancy (12–14). Ambulatory BP monitoring is a better predictor of proteinuria, preterm delivery, and low birth weight (13,14). It is therefore clinically useful in high-risk pregnant women with hypertension, or in those with diabetic or hypertensive nephropathy (15).

DEFINITION OF HYPERTENSION IN PREGNANCY

The definition of hypertension in pregnancy was not uniform for a long time (2,16,17). It used to include an elevation in BP during the second trimester from a baseline reading in the first trimester, or to pre-pregnancy levels, but a definition based on absolute BP values (SBP ≥140 mmHg or DBP ≥90 mmHg) is now preferred (2,17).

Most of the obstetric literature distinguishes mild and severe hypertension rather than grades used by the European Society of Hypertension and the European Society of Cardiology (ESH-ESC; 2,8).

CLASSIFICATION OF HYPERTENSION IN PREGNANCY

Hypertension in pregnancy is not a single entity but comprises (2,8,18):

- Pre-existing hypertension
- Gestational hypertension
- Pre-existing hypertension plus superimposed gestational hypertension with proteinuria
- Antenatally unclassifiable hypertension

PRE-EXISTING HYPERTENSION

Pre-existing hypertension complicates 1–5% of pregnancies and is defined as BP ≥140/90 mmHg that either pre-dates pregnancy or develops before 20 weeks of gestation. Hypertension usually persists more than 42 days postpartum. It may be associated with proteinuria.

However, there are several caveats to the diagnosis of pre-existing hypertension. Women with undiagnosed mild hypertension may appear normotensive in early pregnancy because of the normal fall of BP commencing in the first trimester. This may mask the pre-existing hypertension, and when hypertension is recorded later in pregnancy it may be interpreted as gestational. Sometimes the diagnosis is only made several months postpartum when the BP fails to normalize as would be expected with gestational hypertension.

GESTATIONAL HYPERTENSION

Gestational hypertension is pregnancy-induced hypertension, with or without proteinuria, complicating 6–7% of pregnancies and developing only after 20 weeks of gestation; it is characterized by poor organ perfusion and usually resolves within 42 days postpartum. Gestational hypertension associated with significant proteinuria (>0.3 g/24 h in a 24-h urine collection or ≥30 mg/mmol urinary creatinine in a spot random urine sample) is known as pre-eclampsia.

Pre-eclampsia is a pregnancy-specific syndrome that occurs after mid-gestation, defined by de novo appearance of hypertension, accompanied by new-onset proteinuria. It is a systemic disorder with both maternal and fetal manifestations. Pre-eclampsia was classically defined as a triad of hypertension, oedema and proteinuria, but oedema is no longer considered part of the diagnostic criteria, as it occurs in up to 60% of normal pregnancies and is no longer included because of the lack of specificity. Overall, pre-eclampsia complicates 5–6% of pregnancies, but this figure increases to up to 25% in women with pre-existing hypertension. Risk factors for developing pre-eclampsia are given in Table 55.2.

Pre-eclampsia remains one of the three most frequently cited causes of maternal death and is responsible for an estimated 64,000 deaths a year worldwide (19). Developing countries have had persistently higher rates of

Table 55.2   Risk factors for developing pre-eclampsia
Nulliparity
Multiple pregnancy Family history of pre-eclampsia Chronic hypertension
Diabetes Increased insulin resistance Increased body mass index Hypercoagulability (inherited thrombophilia)
Renal disease even without significant impairment Low socioeconomic status Antiphospholipid syndrome (acquired thrombophilia)
Previous pre-eclampsia Hydatidiform mole Black ethnicity

maternal and child mortality due to pre-eclampsia compared with developed countries. While the immunological and genetic alterations are relevant in the development of pre-eclampsia in developed countries, nutritional, metabolic and infectious factors are largely responsible for the high incidence of pre-eclampsia in developing countries. In the United States, the rate of pre-eclampsia increased by 40% between 1990 and 1994, probably as a consequence of increasing maternal age and multiple births, factors predisposing to pre-eclampsia (20).

The risks to the fetus from pre-eclampsia include growth restriction secondary to placental insufficiency and premature delivery. Pre-eclampsia is one of the most common causes of prematurity, accounting for 25% of all infants with very low birth weight, <1500 g; it is also associated with an increased incidence of cardiovascular disease in later life in mothers and babies (21,22). A paternal, but not maternal, history of essential hypertension is associated with increased risk of hypertension in children, the risk being greater in daughters than sons. Pregnancy may thus unveil or exacerbate this effect, possibly reflecting underlying endothelial vulnerability (23).

The main feature of pre-eclampsia is impaired perfusion to virtually every organ of the body. There is vasospasm and activation of platelets and the coagulation system resulting in the formation of microthrombi. The link between the placenta and the systemic disorder appears to involve endothelial dysfunction and oxidative stress. Symptoms and signs of severe pre-eclampsia include right upper quadrant/epigastric pain due to liver oedema ± hepatic haemorrhage; headache ± visual disturbance (cerebral oedema); occipital lobe blindness; hyperreflexia ± clonus; and convulsions (cerebral oedema). Management of pre-eclampsia essentially focuses on recognition of the condition and ultimately delivery of the placenta, which is curative.

As proteinuria may be a late manifestation of pre-eclampsia, it is advised to be suspicious when de novo hypertension is accompanied by headache, abdominal pain, or abnormal laboratory tests, specifically low platelet count and abnormal liver enzymes, and it is recommended to treat such patients as pre-eclamptic.

The pathophysiology of pre-eclampsia can be divided into two stages: alterations in placental perfusion (stage 1) and maternal syndrome (stage 2). The placenta is the key component of pregnancy that leads to pre-eclampsia. The reduced placental perfusion is primarily due to abnormalities in implantation and vascular remodelling (24). In normal pregnancy, the spiral arteries that perfuse the placenta undergo remarkable remodelling from small muscular arteries in the pregnant state to significantly distended vessels that have lost both their smooth muscle and inner elastic lamina layers. This extensive remodelling does not occur in pre-eclampsia. There may be some superficial remodelling, but it never extends beyond the decidual lining, whereas in normal pregnancy, the modified vessels extend into the inner third of the myometrium (25). Many vessels in pre-eclamptic women undergo no remodelling, and this results in reduced placental perfusion. It is now evident that these interactions include precisely regulated expression molecules involved in attachment and invasion in response to environmental and maternal signals, and that this process is impaired in pre-eclampsia (26). Several conditions associated with macrovascular disease such as hypertension, diabetes and collagen vascular diseases also increase the risk of pre-eclampsia, leading to speculation that impaired placental perfusion may be the common denominator. Obstetric conditions associated with large placentas (hydatidiform mole, hydropic placentas, and placentas with multiple gestations) all increase the risk of pre-eclampsia (27). It is proposed that, in these large placentas, there is a relative reduction in placental perfusion. Another alteration of the spiral arteries in pre-eclampsia, atherosis, results in occlusion of the decidual vessels reminiscent of the vascular findings of allograft rejection supporting an immunological component of pre-eclampsia (28).

Stage 2, the maternal syndrome, begins when the plasma volume is reduced, with decreased blood flow to organs other than placenta, resulting in hemoconcentration, hemorrhage and necrosis (29). In the liver, evidence can be found of reduced perfusion with secondary necrosis and hemorrhage. In the heart, subendocardial necrosis similar to that seen in hypovolemic shock can occur. The explanation for systematically reduced perfusion includes vasoconstriction, microthrombi and reduced plasma volume secondary to loss of fluid from the vascular compartment. The vasoconstriction is not attributable to increased endogenous pressors, but rather to an increased sensitivity to virtually all circulating pressor agents. Pre-eclampsia is also characterized by activation of the coagulation cascade. Renal biopsy specimens from women with pre-eclampsia reveal a change seen in no other form of hypertension. Termed glomeruloendotheliosis, the lesion consists primarily of enlargement of the glomerulus caused by hypertrophy of endothelial cells. Numerous markers of endothelial activation are present in the circulation of pre-eclamptic women weeks to months before clinically evident disease (30). Vessels from women with pre-eclampsia manifest reduced endothelium-mediated relaxation and plasma or serum from pre-eclamptic women can adversely alter endothelial function in vitro either with cells in culture or intact vessels.

There is a considerable amount of evidence supporting the role of angiogenic factors in triggering pre-eclampsia (tyrosine-like soluble factor, and soluble endoglin) (31). These molecules bind to angiogenic proteins such as VEGF and prevent them from joining their membrane receptors on endothelial cells leading to endothelial dysfunction.

These factors are elevated about 6–8 weeks before the clinical manifestation of pre-eclampsia and their plasma concentrations are related to the severity of disease (32).

Women destined to develop pre-eclampsia have lower placental growth factor (PlGF) levels and higher soluble fms-like tyrosine kinase-1 (sFlt-1) than women with normal pregnancies (33). Changes in the circulating concentrations of these parameters precede the onset of pre-eclampsia. A ratio of sFlt-1/PlGF ≤38 can be used to exclude the development of pre-eclampsia in the next week when suspected clinically (34).

PRE-EXISTING HYPERTENSION PLUS SUPERIMPOSED GESTATIONAL HYPERTENSION WITH PROTEINURIA

Pre-existing hypertension is associated with further worsening of BP and protein excretion ≥3 g/day in 24-h urine collection after 20 weeks' gestation; it corresponds to the previous terminology 'chronic hypertension with superimposed pre-eclampsia'.

ANTENATALLY UNCLASSIFIABLE HYPERTENSION

This is hypertension with or without systemic manifestation, if BP was first recorded after 20 weeks' gestation. Reassessment is necessary at or after 42 days postpartum. If hypertension is resolved by then, the condition should be reclassified as gestational hypertension with or without proteinuria. If the hypertension is not resolved by then, the condition should be reclassified as pre-existing hypertension.

RECOMMENDED LABORATORY INVESTIGATIONS

Hypertensive disorders in pregnancy, particularly gestational hypertension with or without proteinuria, may produce changes in the hematologic, renal and hepatic profiles that may adversely affect prognosis and both neonatal and maternal outcomes.

Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy are presented in Table 55.3. All pregnant women should be assessed for proteinuria and early pregnancy to rule out pre-existing renal disease and, in the second half of pregnancy, to screen for pre-eclampsia. A positive dipstick test (≥ +) should prompt further investigations, including an albumin-to-creatinine ratio (ACR), which can be quickly determined in a single spot urine sample.

Some authors (35) recommend ultrasound investigation of the adrenals and urine metanephrine and normetanephrine assays in all pregnant women with hypertension, as pheochromocytoma may be completely asymptomatic, and if not diagnosed before labour, fatal.

Determination of the sFlt-1-to-PlGF ratio is now widely available to rule out the development of pre-eclampsia in the next week when suspected clinically (33,34).

PHEOCHROMOCYTOMA IN PREGNANCY

A pheochromocytoma in pregnancy is one of the most life-threatening conditions for the mother and fetus. Although extraordinarily rare, with a frequency of 0.002% of all pregnancies, this tumour is notorious for its devastating consequences (36). As in nonpregnant patients, the signs

Table 55.3 Basic laboratory investigations recommended for monitoring patients with hypertension in pregnancy	
Hemoglobulin and hematocrit	Hemoconcentration supports diagnosis of gestational hypertension with or without proteinuria. It indicates severity. Levels may be low in very severe cases because of hemolysis.
Platelet count	Low levels <100,000 × 10⁹/L may suggest consumption in the microvasculature. Levels correspond to severity and are predictive of recovery rate in postpartum period, especially for women with HELLP syndrome.
Serum AST, ALT	Elevated levels suggest hepatic involvement. Increasing levels suggest worsening severity.
Serum LDH	Elevated levels are associated with haemolysis and hepatic involvement. May reflect severity and may predict potential for recovery post partum, especially for women with HELLP syndrome.
Urinalysis	Dipstick test for proteinuria has significant false-positive and false-negative rates. Positive dipstick results (≥1) should prompt further investigations including albumin/creatinine ratio. Negative dipstick results do not rule out proteinuria, especially if DBP ≥90 mmHg.
Urinary albumin/creatinine (ACR)	Can be quickly determined in a single-spot urine sample; a value <30 mg/mmol can reliably rule out proteinuria in pregnancy. Values ≥30 mg/mmol identify significant proteinuria.
Proteinuria (24-hour urine collection)	Standard to quantify proteinuria, but often inaccurate. If in excess of 2 g/day, very close monitoring is warranted. If in excess of 3 g/day, delivery should be considered.
Serum uric acid	Elevated levels aid in differential diagnosis of gestational hypertension and may reflect severity.
Serum creatinine	Levels drop in pregnancy. Elevated levels suggest increasing severity of hypertension; assessment of 24-hour creatinine clearance may be necessary.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HELLP, Hemolysis, Elevated Liver enzyme levels, and Low Platelet count; LDH, lactate dehydrogenase.

and symptoms are quite variable but not specific, with hypertension being of one of the most prominent signs. If undiagnosed, maternal and fetal mortality is around 50%; on the other hand, early detection and proper treatment during pregnancy decrease the maternal and fetal mortality to <5 and <15%, respectively. For the biochemical diagnosis, plasma or urinary metanephrines are the test of choice since they have the highest sensitivity and the highest negative predictive value. For reliable localization, magnetic resonance imaging is the most suitable technique, with a sensitivity of more than 90%. When a pheochromocytoma is diagnosed, it should be removed by laparoscopic adrenalectomy after 10–14 days of drug pretreatment as in nonpregnant patients (alpha-adrenoreceptor blockade combined with beta-adrenergic blockade started some days later). If the pheochromocytoma is diagnosed in the third trimester, the patient should be managed until the fetus is viable using the same drug regimen as for regular surgical preparation. Cesarean section with tumor removal in the same session or at later stage is than preferred, since vaginal delivery is possibly associated with higher mortality.

MANAGEMENT OF HYPERTENSION IN PREGNANCY

The majority of women with pre-existing hypertension in pregnancy have mild to moderate hypertension (140–179/90–109 mmHg) and are at low risk for cardiovascular complications within the short timeframe of pregnancy. Women with essential hypertension and normal renal function have good maternal and neonatal outcomes; they are candidates for non-drug therapy because there is no evidence that pharmacological treatment results in improved neonatal outcome. Some women with treated pre-existing hypertension are able to stop their medication in the first half of pregnancy because of the physiological fall in BP during this period. However, close monitoring and if necessary, resumption of treatment, are essential.

There are not sufficient data regarding treatment of hypertension in pregnancy, as pharmaceutical companies have been reluctant to test drugs in this small market with a high potential of litigation. Childbearing potential without reliable contraception is an exclusion criterion in basically all clinical trials testing antihypertensive drugs. Pharmaceutical companies are not willing to take any, even a small risk, and as no data are available for most of the antihypertensive drugs marketed over the last 20 years, the vast majority of newer antihypertensive drugs is strictly contraindicated in pregnancy.

The only trial of treatment of hypertension in pregnancy with adequate infant follow-up (7.5 years) was performed more than 30 years ago with alpha-methyldopa, now rarely used in nonpregnant women (37,38). Past clinical trials also have not supported a beneficial effect on pregnancy outcome of treating mild hypertension. There has been no reduction in perinatal mortality, placental abruption, or superimposed pre-eclampsia (39,40). All these trials are subject to criticism, including small numbers, starting the drug too late in pregnancy, or flawed study design; however, no other data are available. These studies have led to recommendations to treat only on the basis of BP sufficiently elevated to pose a potential acute risk to the mother (41). Small and frequently poorly designed studies have recently suggested that therapy of mildly elevated BP may prevent progression to pre-eclampsia (42,43). Even for women with BP elevation sufficient to justify therapy for their own benefit, it is not clear whether it is beneficial for or detrimental to the fetus. In several studies, treatment of hypertensive women resulted in an increased risk of growth restriction in their infants (44). It is not known whether this is the inevitable consequence of lower BP during pregnancy or if it is due to excessive pressure decreases or too specific drugs.

NONPHARMACOLOGICAL MANAGEMENT AND PREVENTION OF HYPERTENSION IN PREGNANCY

Nonpharmacological management (45) of hypertension in pregnancy has a limited role because randomized studies of dietary and lifestyle interventions showed only minimal effects on pregnancy outcomes. A short-term hospital stay may be required for confirming the diagnosis of and ruling out severe gestational hypertension (pre-eclampsia), in which the only effective treatment is delivery. Management, depending on BP, gestational age and presence of associated maternal and fetal risk factors, includes close supervision, limitation of activities and some bed rest in the left lateral position.

A normal diet without salt restriction is advised, particularly close to delivery, as salt restriction may induce a low intravascular volume. Increased energy and protein intake are not beneficial in the prevention of gestational hypertension. Although weight reduction may be helpful in reducing BP in nonpregnant women, it is not recommended during pregnancy in obese women, as weight reduction can be associated with reduced neonatal weight and slower subsequent growth in infants of dieting obese mothers.

However, as maternal obesity can result in negative outcomes for both women and fetuses, guidelines for healthy ranges of weight gain in pregnancy have been established. In pregnant women with normal body mass index (BMI <25 kg/m^2), the recommended weight gain is 11.2–15.9 kg; for overweight pregnant women (BMI 25.0–29.9 kg/m^2) it is 6.8–11.2 kg; and for obese pregnant women (BMI ≥30 kg/m^2) the recommended weight gain is <6.8 kg (46).

Regular exercise might be continued with caution.

Calcium supplementation (1.5–2 g orally) is recommended for prevention of pre-eclampsia in women with low dietary calcium intake (<600 mg/d) (47) from the first antenatal clinic visit.

In a multicentre randomized clinical trial of effect of fish oil in a high-risk population of pregnant women with pregnancy complications, fish oil supplementation delayed the onset of delivery in low and middle, but not in high, fish consumers (48).

Fish oil supplementation as well as vitamin and nutrient supplements have no role in the prevention of hypertensive disorders. Some studies with vitamin C and vitamin E supplementation were associated with more frequent low birthweight (<2.5 kg) and adverse perinatal outcome (49–52).

There has been considerable controversy regarding the efficacy of low-dose aspirin for the prevention of pre-eclampsia. Despite a large meta-analysis reporting a small

benefit of aspirin in preventing pre-eclampsia (53), two other analyses came to opposing conclusions. Rossi and Mullin used pooled data from approximately 5000 women at high risk and 5000 at low risk for pre-eclampsia and reported no effect of low-dose aspirin in the prevention of the disease (54). Bujold et al., however, pooled data from over 11,000 women enrolled in RTCs of low-dose aspirin in pregnant women and concluded that women who initiated treatment at <16 weeks of gestation had a significant and marked reduction of the relative risk for developing pre-eclampsia (relative risk: 0.47) and severe pre-eclampsia (relative risk: 0.09) compared with control (55). The ASPRA (Aspirin for Evidence-based Pre-eclampsia Prevention) trial showed that 150 mg of aspirin compared with placebo resulted in a lower incidence of pre-eclampsia (56). Thus, women at high or moderate risk of pre-eclampsia should be advised to take 100–150 mg of aspirin daily form weeks 12–36.

High risk of pre-eclampsia includes any of the following:

- Hypertensive disease during a previous pregnancy
- Chronic kidney disease
- Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- Type 1 or type 2 diabetes
- Chronic hypertension.

Moderate risk of pre-eclampsia includes ≥1 of the following risk factors:

- First pregnancy
- Age 40 years or older
- Pregnancy interval of more than 10 years
- Body mass index (BMI) of 35 kg/m^2 or more at first visit
- Family history of pre-eclampsia
- Multiple pregnancy

PHARMACOLOGICAL MANAGEMENT OF HYPERTENSION IN PREGNANCY

The value of continued administration of antihypertensive drugs to pregnant women with chronic hypertension continues to be an area of debate. While there is a consensus that drug treatment of severe hypertension in pregnancy is required and beneficial (57), treatment of less severe hypertension is controversial. Although it might be beneficial for the mother with hypertension to reduce her BP, lower BP may impair uteroplacental perfusion and thereby jeopardize fetal development. Much uncertainty about the benefits of BP lowering in pregnant women with mild pre-existing hypertension stems from published trials too small to detect a modest reduction in obstetric complications.

All antihypertensive drugs have either been shown or are assumed to cross the placenta and reach the fetal circulation. However, none of the antihypertensive agents in routine use has been documented to be teratogenic, although angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, and aliskiren, a direct renin inhibitor, are fetotoxic.

While the goal of treating hypertension is to reduce maternal risk, the agents selected must be efficacious and safe for the fetus (6,58).

TREATMENT OF SEVERE HYPERTENSION

While there is no agreement on the definition of severe hypertension in pregnancy (with values ranging between 160–180 mmHg/>110 mmHg), there is a consensus that SBP ≥170 or DBP ≥110 mmHg in a pregnant woman should be considered an emergency, and hospitalization is absolutely essential (8). The selection of the antihypertensive drug and its route of administration depend of the expected time of delivery. Pharmacological treatment with intravenous labetalol, oral methyldopa or nifedipine is to be initiated. Intravenous hydralazine should no longer be thought of as the drug of choice as its use is associated with more perinatal adverse effects than other drugs (59). However, hydralazine is still commonly used when other treatment regimens have failed to achieve adequate BP control, as for most obstetricians, its side effect profile is acceptable. Prolonged treatment with sodium nitroprusside is associated with an increased risk of fetal cyanide poisoning, as nitroprusside is metabolized into thiocyanate excreted into urine (60). Therefore, sodium nitroprusside should be reserved for extreme emergencies and used for the shortest period of time possible.

The drug of choice in pre-eclampsia associated with pulmonary oedema is nitroglycerin (given as intravenous infusion of 5 μg/min, gradually increased every 3–5 min to a maximum dose of 100 μg/min).

TREATMENT OF MILD TO MODERATE HYPERTENSION

The benefits of antihypertensive therapy for mildly to moderately elevated BP in pregnancy (<160/110 mmHg) have not been demonstrated in clinical trials. Recent reviews including a Cochrane analysis concluded there are insufficient data to determine the benefits and risks of antihypertensive therapy for mild to moderate hypertension (defined as 140–159 mmHg SBP and 90–109 mmHg DBP) (62–64,404461). Of note, with antihypertensive treatment there seems to be less risk of developing hypertension (risk ratio 0.50 with a number-needed-to-treat of 10), but no difference in outcomes of pre-eclampsia, neonatal death, preterm birth and small-for-gestational-age babies with treatment (61).

In the absence of randomized controlled trials, recommendations can only be guided by expert opinion. International and national guidelines vary with respect to thresholds for starting treatment and BP targets in pregnancy. The suggestion in the 2007 ESH/ESC Guidelines (65) of considering drug treatment in all pregnant women with persistent elevation of BP >150/95 mmHg is supported by more recent US data, which show an increasing trend in the rate of pregnancy-related hospitalizations with stroke − especially during the postpartum period − from 1994−2007 (66), and by an analysis of stroke victims with severe pre-eclampsia and eclampsia (67). Despite lack of evidence, the 2013 Task Force reconfirms that physicians should consider early initiation of antihypertensive treatment at values >140/90 mmHg in women with (i) gestational hypertension (with or without proteinuria), (ii) pre-existing hypertension with the superimposition of

Table 55.4   Antihypertensive drugs used in pregnancy

Women with pre-existing hypertension are advised to continue their current medication except for ACE inhibitors, angiotensin II antagonists and aliskiren.

Methyldopa	Drug of choice
Labetalol	Has comparable efficacy with methyldopa; in the case of severe hypertension, it could be given intravenously.
Calcium-channel blockers	Oral nifedipine or IV isradipine could be given in hypertensive emergencies. Potential synergism with magnesium sulphate may induce hypotension.

Abbreviations: ACE, angiotensin-converting enzyme; IV, intravenous.

gestational hypertension or (iii) hypertension with asymptomatic OD or symptoms at any time during pregnancy.

Q3

For non-severe hypertension (Table 55.4), methyldopa, labetalol, and calcium antagonists (most data available for nifedipine) are the drugs of choice. Beta-blockers appear to be less effective than calcium antagonists and may induce fetal bradycardia, growth retardation and hypoglycemia; the type and dose should be carefully selected, with atenolol best avoided (Table 55.5) (68). Calcium-channel blockers are considered to be safe if not given concomitantly with magnesium sulphate (risk of hypotension due to potential synergism). ACE inhibitors, angiotensin II antagonists, and aliskiren should not be used in pregnancy. Women with pre-existing hypertension may continue their current antihypertensive medication except for RAS blockers. The plasma volume is reduced in pre-eclampsia; diuretic therapy is therefore inappropriate unless there is oliguria when low-dose furosemide may be considered. Magnesium sulphate IV is recommended for the prevention of eclampsia and treatment of seizures (69).

Table 55.5   Antihypertensive drugs contraindicated in pregnancy or to be used with caution

ACE inhibitors, angiotensin II antagonists, direct renin inhibitors	Fetal abnormalities including death can be caused and these drugs should not be used in pregnancy.
Diuretics	Diuretics are recommended for chronic hypertension if prescribed before gestation or if patients appear to be salt-sensitive. They are not recommended in pre-eclampsia.
Direct vasodilators	Hydralazine is no longer the parenteral drug of choice because of its perinatal adverse effects.
Beta-blockers	Metoprolol appear to be safe and effective in late pregnancy; it should be avoided in early pregnancy; because of fetotoxicity, atenolol is contraindicated.

Abbreviation: ACE, angiotensin-converting enzyme.

DELIVERY

Induction of delivery is appropriate in pre-eclampsia with visual disturbances, coagulation abnormalities or fetal distress. In asymptomatic gestational hypertension or asymptomatic mild pre-eclampsia, delivery is recommended at 37 weeks (70).

BP POSTPARTUM

Postpartum hypertension is common. BP usually rises over the first 5 days after delivery. Women experiencing hypertension during pregnancy may be normotensive after birth but then become hypertensive again in the first postnatal week. The need to obtain hypertensive control may delay discharge. Methyldopa should be avoided postpartum because of the risk of postnatal depression.

HYPERTENSION AND LACTATION

Breastfeeding does not increase BP in nursing mothers. Bromocryptin, which is still used to suppress lactation in some countries, may induce hypertension. All antihypertensive agents taken by the nursing mother are excreted into breast milk. Most of the antihypertensive drugs are present at very low concentrations, except for propranolol and nifedipine, whose concentrations in breast milk are similar to those in maternal plasma.

RISK OF RECURRENCE OF HYPERTENSIVE DISORDERS IN A SUBSEQUENT PREGNANCY

Women experiencing hypertension in their first pregnancy are at increased risk in a subsequent pregnancy. The earlier the onset of hypertension in the first pregnancy, the greater the risk of recurrence.

LONG-TERM CARDIOVASCULAR CONSEQUENCES IN PREGNANCY-INDUCED HYPERTENSION

Women who develop gestational hypertension or pre-eclampsia are at increased risk of hypertension and stroke in later adult life (71). Furthermore, there is evidence of an increased risk of ischemic heart disease in women who experience pre-eclampsia or isolated intrauterine growth retardation together with increased death from ischemic heart disease (72). Therefore, it is of utmost importance that all women with pregnancy-induced hypertension have their BP measured annually.

Endothelial dysfunction and early alteration of carbohydrate and lipid metabolism are present in otherwise healthy women with previous gestational hypertension. These abnormalities, along with a relative hyperandrogenism,

could explain, at least in part, the increased risk for cardiovascular disease in later life in these women (73).

On the other hand, women who go through pregnancy without developing hypertension are at reduced risk of becoming hypertensive in later life when compared to nulliparous women. Thus, pregnancy may offer a window into the future cardiovascular health of women that is unavailable in men.

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