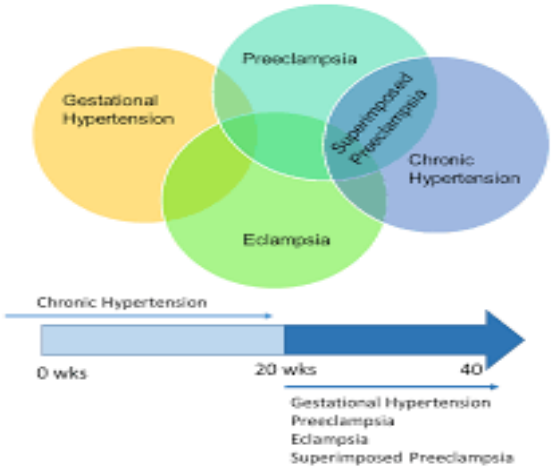

Hypertension in pregnancy

Dr. F. Ahmadi

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- Hypertensive disorder of pregnancy(HDP) was considered to be present if hypertension existed during pregnancy and up to 12 weeks after delivery
- Hypertension is the most common medical problem encountered during pregnancy, complicating up to 10% of pregnancies

ACOG Classification of Hypertension in Pregnancy

Condition	Definition	Prevalence, %
GH	De novo BP elevations (>140/90 mm Hg) after 20 wks of gestation without other organ system dysfunction	6–7
Preeclampsia	De novo BP elevations after 20 wks of gestation coupled with proteinuria or other end-organ dysfunction	5–7
Chronic hypertension	Elevated BP before 20 wks of gestation or persisting beyond 12 wks postpartum	1–5
Chronic hypertension with superimposed preeclampsia	Increased BP and new-onset proteinuria or other end-organ dysfunction in addition to preexisting hypertension	0.2–1

Severe hypertension in pregnancy

- Severe hypertension in pregnancy is defined as a sustained systolic blood pressure of 160 mmHg or over or diastolic blood pressure of 110 mmHg or over
- The most common cause of sever hypertension in pregnancy is pre-eclampsia, which presents after 20 weeks' gestation
- Severe hypertension before 20 weeks' gestation is usually due to chronic hypertension, and requires assessment for target organ damage and exclusion of secondary causes of hypertension.

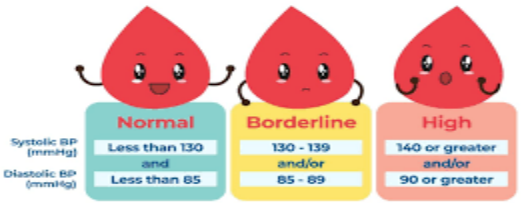
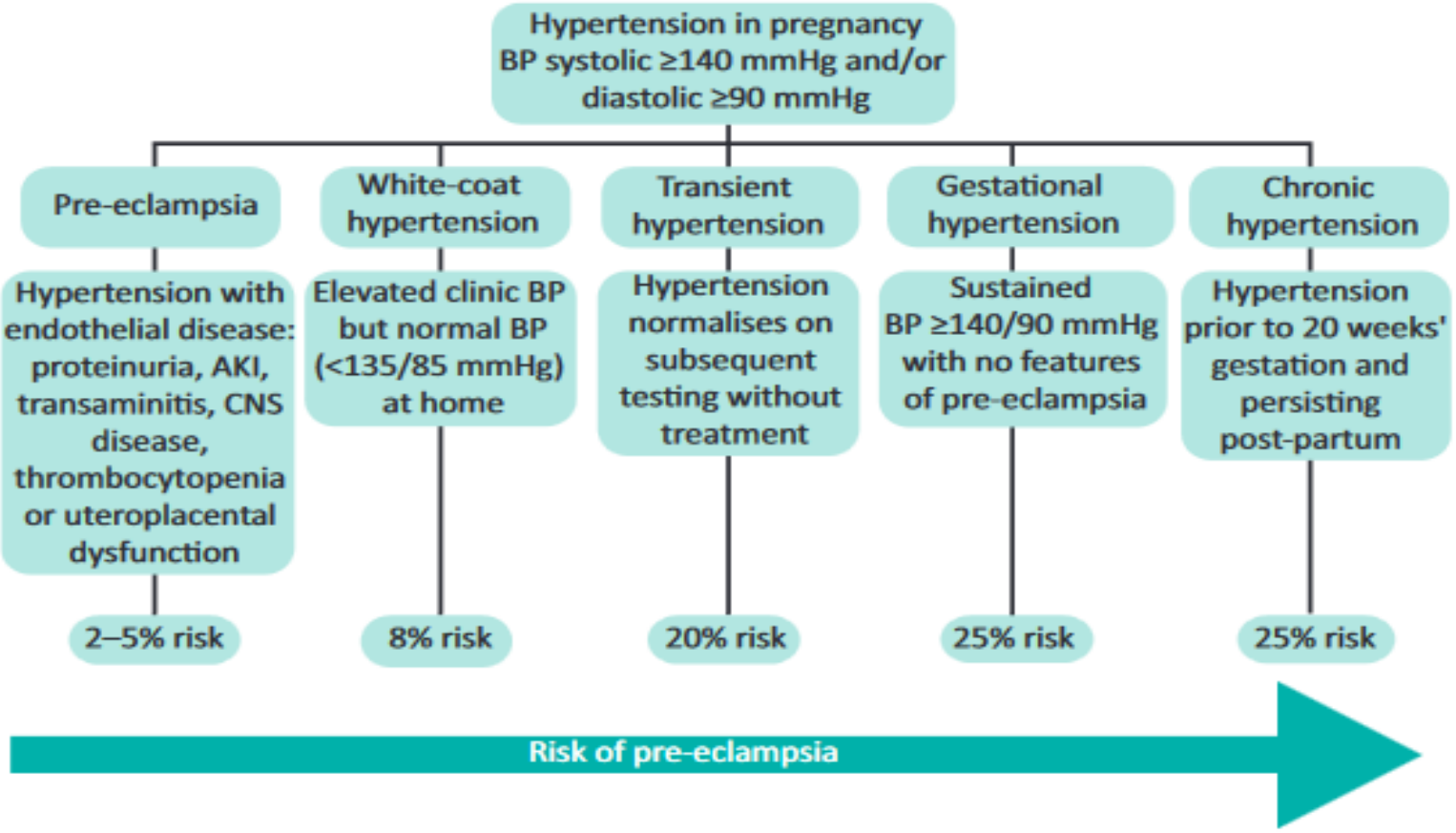


Table 1. Secondary causes of hypertension in pregnancy

Aetiology	Clinical assessment in pregnancy	Diagnosis and management in pregnancy
Coarctation	Upper limb hypertension Radio-/brachiofemoral delay Systolic murmur from associated bicuspid aortic valve Turner's syndrome phenotype	Echo/MRI
Chronic kidney disease	Symptoms: oedema, arthralgia, rash, hair loss, visible haematuria, recurrent UTI and family history Renal bruit Urine dip Quantification of proteinuria Serum creatinine Kidney ultrasound for morphology and symmetry	>2+ blood or protein on urine dip warrants further assessment uACR >8 mg/mmol and uPCR >30 mg/mmol are abnormal in pregnancy Creatinine >77 µmol/L is abnormal in pregnancy[6] Imaging of renal vasculature usually delayed until postpartum, provided safe blood pressure control can be achieved ACEi and ARB contraindicated due to fetotoxicity
Hyperaldosteronism / Conn's syndrome	Hypokalaemia Treatment resistance	Gestational increases in renin and aldosterone prevent accurate interpretation Formal diagnosis usually delayed until postpartum, provided safe blood pressure control can be achieved Spironolactone contraindicated due to anti-androgenic fetal effects Limited data on the use of amiloride and eplerenone in pregnancy
Cushing's syndrome	Phenotype: thin skin, bruising, striae, fat distribution, proximal weakness, elevated plasma glucose/early diagnosis of GDM	Phenotype overlaps with normal pregnancy Gestational increase in cortisol prevents accurate interpretation Formal diagnosis usually delayed until postpartum, provided safe blood pressure control can be achieved
Phaeochromocytoma/ paraganglioma	Headache, sweating, tachycardia, anxiety Episodic hypertension	Urine and plasma metanephrine concentrations unaffected by pregnancy. Non-contrast MRI MIBG contraindicated due to placental transfer; maternal benefit of alpha-blockade outweighs risk; labetalol has insufficient alpha-blockade in isolation
Hyperparathyroidism	Nausea/hyperemesis, constipation, low mood, polyuria Serum calcium and PTH	Significant maternal (pancreatitis, kidney injury, nephrolithiasis, pre-eclampsia) and fetal (miscarriage, intrauterine death) risks warrant early diagnosis and support definitive surgical treatment in pregnancy

Clinical Medicine 2021 Vol 21, No 5: e451–6

Hypertensive disorders in pregnancy



Clinical Medicine 2021 Vol 21, No 5: e451–6

American Heart Association | American Stroke Association

Hypertensive Disorders of Pregnancy and Future Maternal Cardiovascular Risk

Wendy Ying, MD; Janet M. Catov, PhD, MS; Pamela Ouyang, MBBS

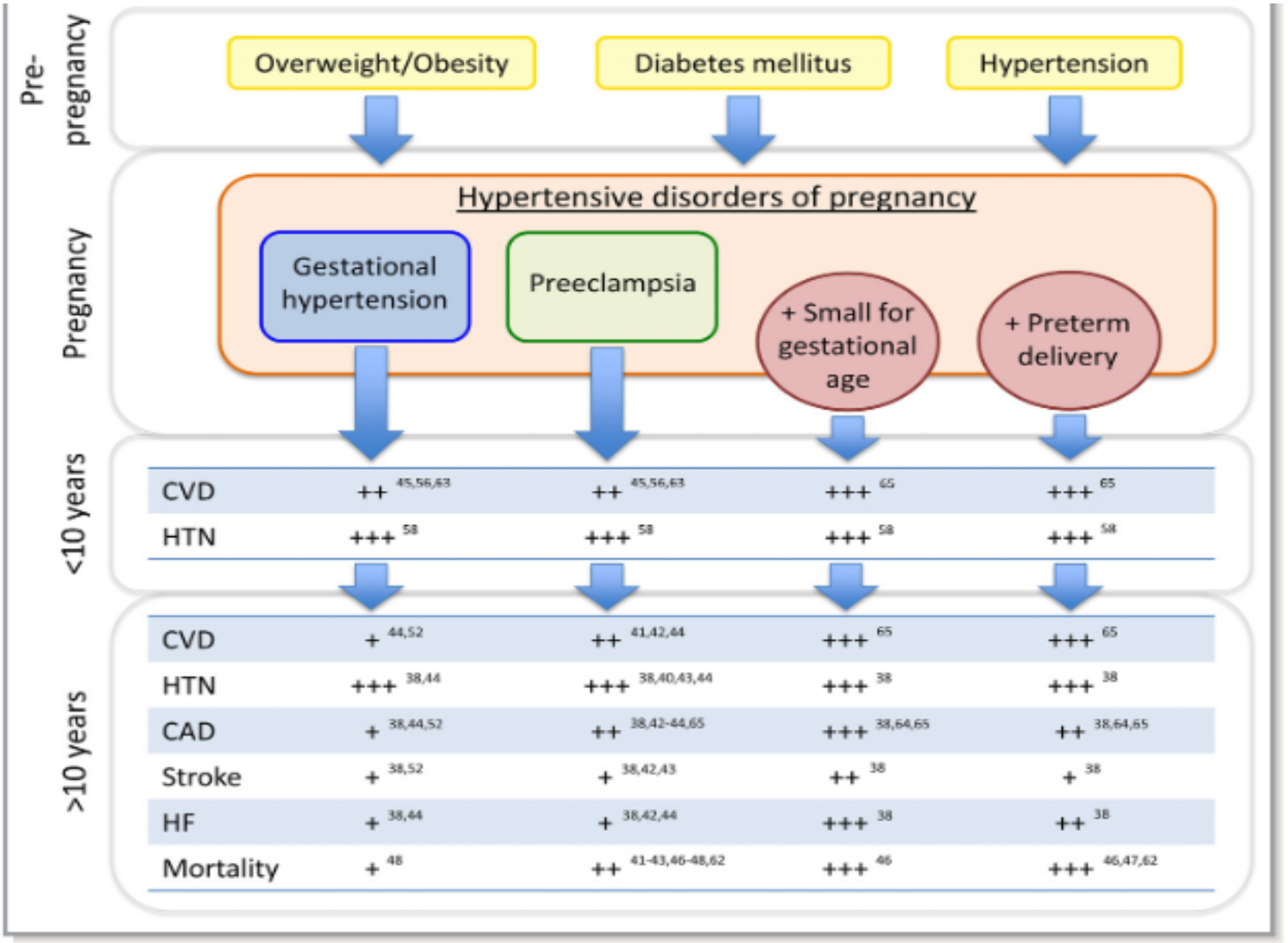


Table 4. Pregnancy outcomes and risk in severe hypertension compared with pre-eclampsia in the absence of severe hypertension

	Gestational hypertension, %[8,9]	Preeclampsia without severe features, BP <160/110 mmHg, %[8,9]	Severe gestational hypertension, BP ≥160/110 mmHg, %[8,9]	Odds ratio (95% CI) for outcome in severe hypertension adjusted for pre-eclampsia[10]
Maternal outcomes				
Elevated liver enzymes	1.1	3.2	6.3	2.47 (1.12–5.43)
Placental abruption	0.3–1.3	0.5–3.2	3.1–4.2	
DIC	0.1	0.5	3.1	
Induction of labour	23.8	41.5	50	
Caesarean delivery	29.1	30.9	28.1	
Neonatal outcomes				
Delivery <37 weeks' gestation	17.8	25.8	54.2	2.59 (1.83–3.68)
Delivery <34 weeks' gestation	1	1.9	3.2	3.07 (1.97–4.80)
Small for gestational age	6.5–6.9	4.8–9.2	10.2–20.8	1.75 (1.19–2.58)
Birthweight <2,500 g	7.7	11.1	25.8	
Intensive care unit admission	12.5–18.2	24.2–27.3	20.8–29	
Respiratory distress	4.8–5.5	3.2–4.8	6.5–12.5	
Perinatal death	0.1–1.7	0.5	0.1–3.1	

BP = blood pressure; CI = confidence interval; DIC = disseminated intravascular coagulation.

Clinical Medicine 2021 Vol 21, No 5: e451–6

Classification of pre-eclampsia

Based on gestational age at clinical presentation
International Society for the Study of Hypertension in Pregnancy definition

- Preterm (<37 weeks of gestation)
- Term (≥37 weeks of gestation)
- Postpartum (diagnosed after delivery)

Based on symptoms
Symptom severity[a]

- Severe: blood pressure >160/110 mmHg and at least one other condition, including haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome or fetal growth restriction <tenth percentile
- Mild: blood pressure >140/90 mmHg, and at least one other condition, including proteinuria (urine protein to creatinine ratio ≥30 mg/mmol, albumin to creatinine ratio ≥8 mg/mmol) or 24-h urine collection ≥0.3 g/day

Eclampsia

- Severe complication of pre-eclampsia characterized by new onset multifocal, focal or tonic–clonic seizure activity or unexplained coma during pregnancy or postpartum

HELLP syndrome

- Severe complication of pre-eclampsia characterized by haemolysis, elevated liver enzymes and low platelet count (lactate dehydrogenase ≥600 IU/l; aspartate aminotransferase >70 IU/l; platelet count <150,000 cells/μl)[350]

Also commonly used
Early onset (<34 weeks of gestation) and late onset (≥34 weeks of gestation)

Nature Reviews Disease Primers | (2023) 9:8

Box 1 | **Risk factors for pre-eclampsia**[21,245]

Positive risk factors

- Family history of pre-eclampsia
- Nulliparity
- Multiple pregnancy
- Advanced maternal age
- In vitro fertilization
- Maternal comorbidities, including diabetes mellitus, chronic hypertension, obesity, chronic kidney disease, history of acute kidney injury or systemic lupus erythematosus
- Previous placental abruption or intrauterine fetal growth restriction
- Trisomy 13
- Molar pregnancies

Negative risk factors

- Maternal smoking
- Prolonged sexual cohabitation

Nature Reviews Nephrology **volume 15**, pages 275–289 (2019

Table 1 | Risk assessment checklists from ISSHP[2], ACOG[25] and NICE[26]

Risk factor level	ISSHP	ACOG	NICE
High-risk factors	Previous pre-eclampsia	Previous pre-eclampsia	Previous pre-eclampsia
	Chronic renal disease	Chronic renal disease	Chronic renal disease
	Chronic hypertension	Chronic hypertension	Chronic hypertension
	Diabetes mellitus	Diabetes mellitus	Diabetes mellitus
	SLE or APS	SLE or APS	SLE or APS
	Body mass index ≥30 kg/m^2	–	–
	Assisted reproductive therapy	–	–
	–	Multiple pregnancy	–
Moderate-risk factors	First pregnancy	First pregnancy	First pregnancy
	Age ≥40 years	Age ≥40 years	Age ≥35 years
	Multifetal pregnancy	–	–
	Prior placental abruption	–	–
	Prior stillbirth	–	–
	Prior fetal growth restriction	–	–
	–	Body mass index ≥35 kg/m^2	Body mass index ≥30 kg/m^2
	–	Inter-pregnancy interval >10 years	Inter-pregnancy interval >10 years
	–	Family history of pre-eclampsia	Family history of pre-eclampsia
	–	–	Black ethnicity
	–	–	Low socioeconomic status

ACOG, American College of Obstetricians and Gynecologists; APS, antiphospholipid syndrome; ISSHP, International Society for the Study of Hypertension in Pregnancy; NICE, National Institute for Health and Care Excellence; SLE, systemic lupus erythematosus.

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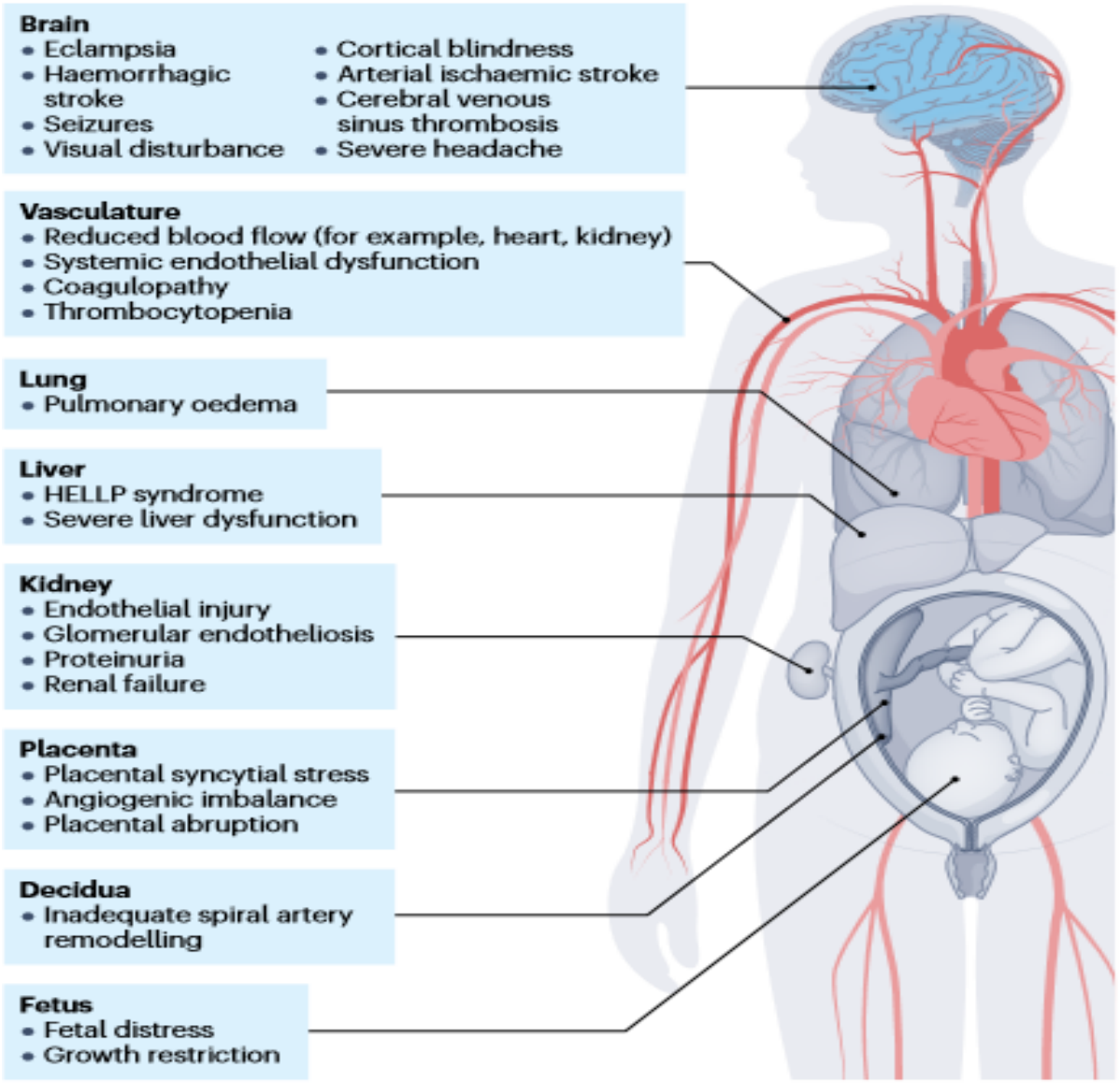
Organs affected by pre-eclampsia



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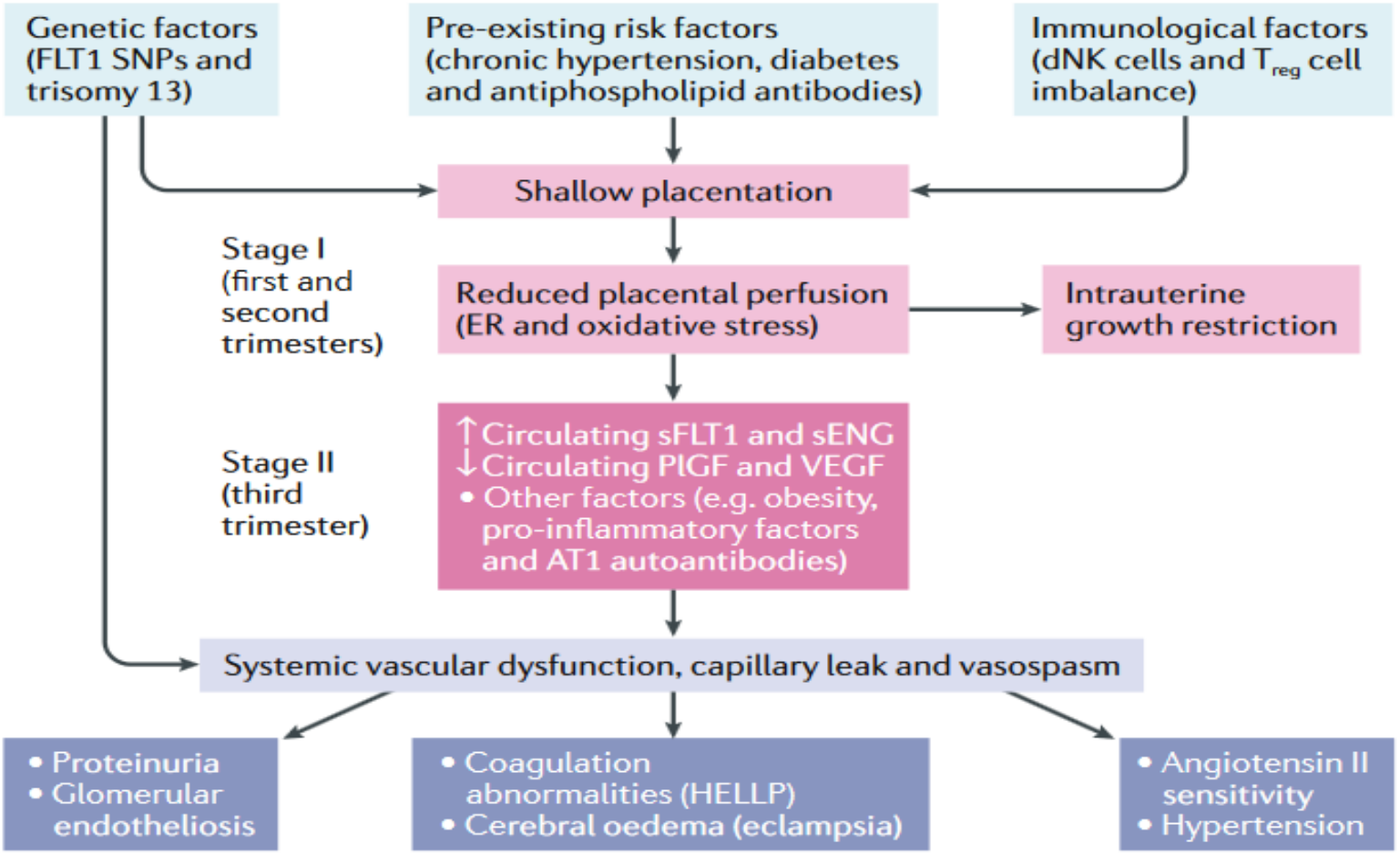
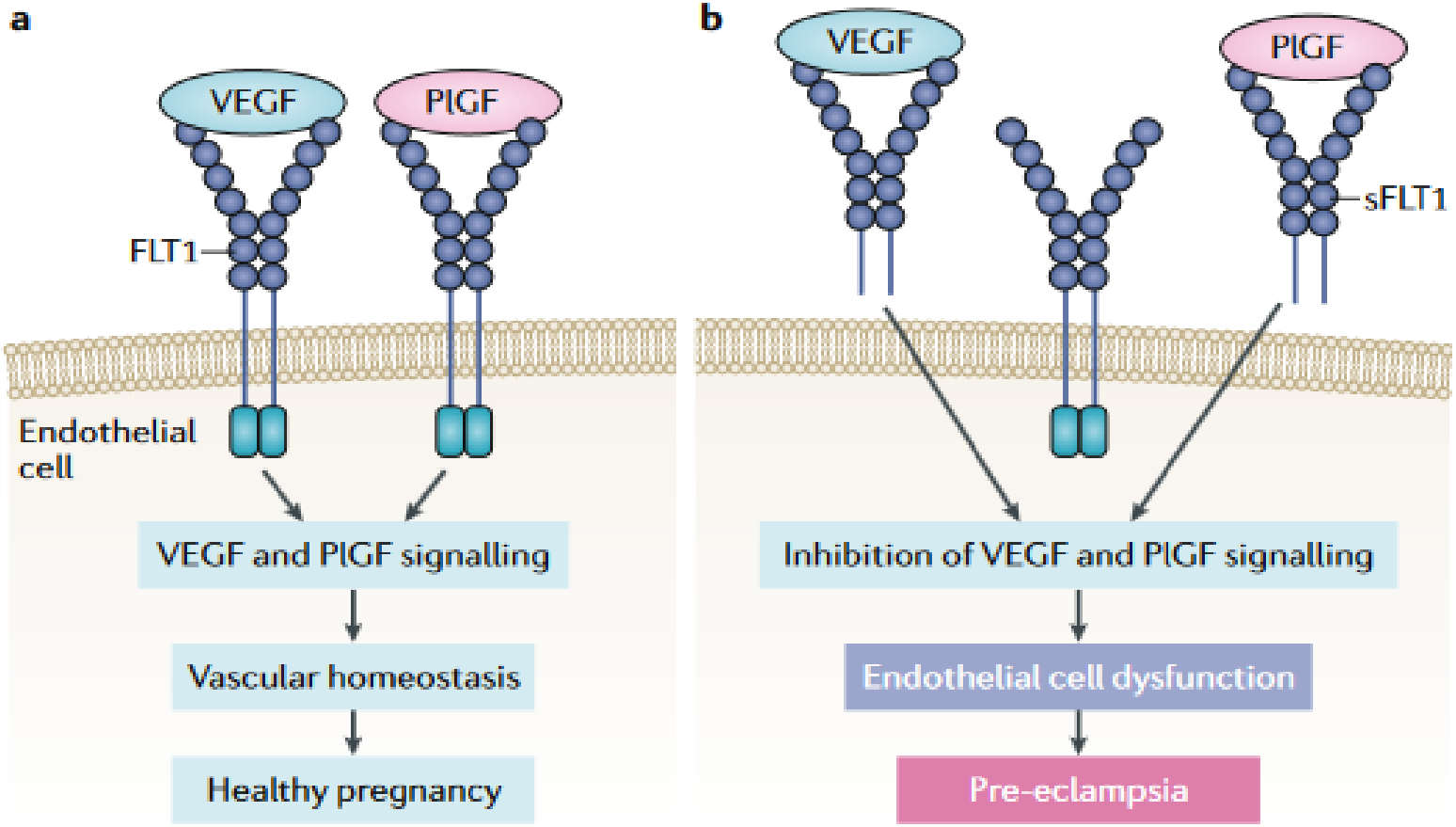
The pathogenesis of pre-eclampsia



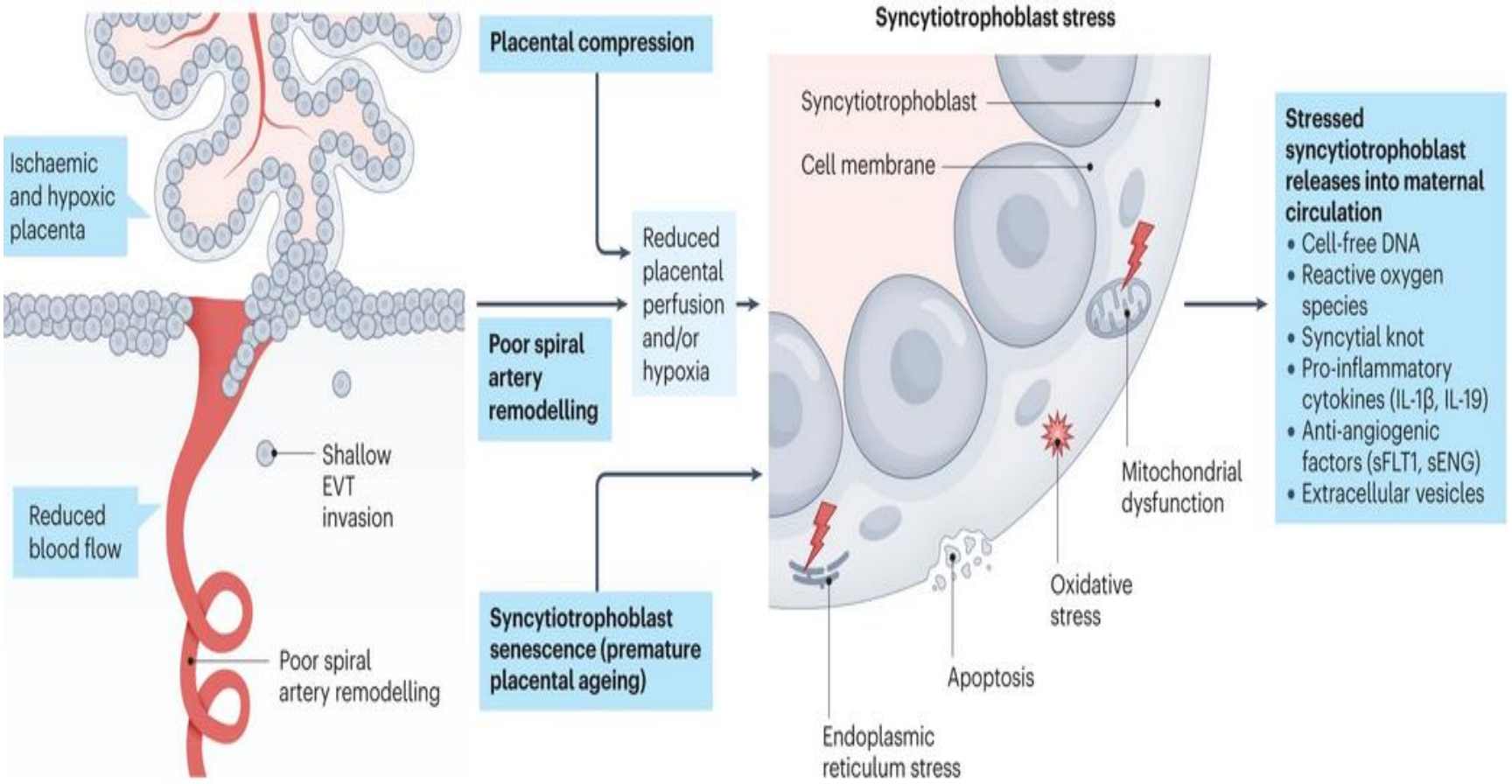
Nature Reviews Nephrology **volume 15**, pages 275–289 (2019

The role of sFlT1 in endothelial dysfunction in pre-eclampsia



Nature Reviews Nephrology **volume 15**, pages 275–289 (2019

Syncytiotrophoblast stress is driven by dysfunctional placental perfusion



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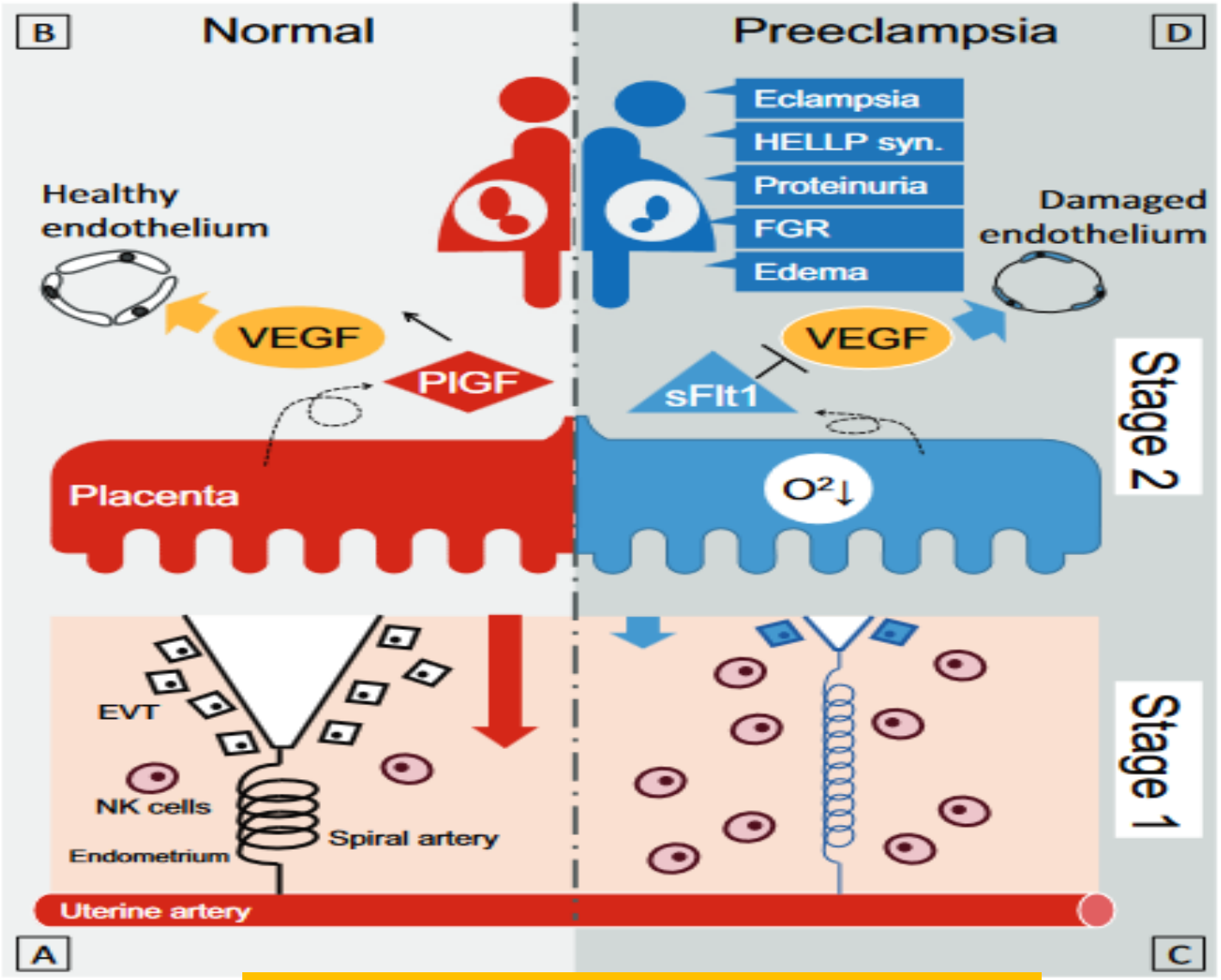
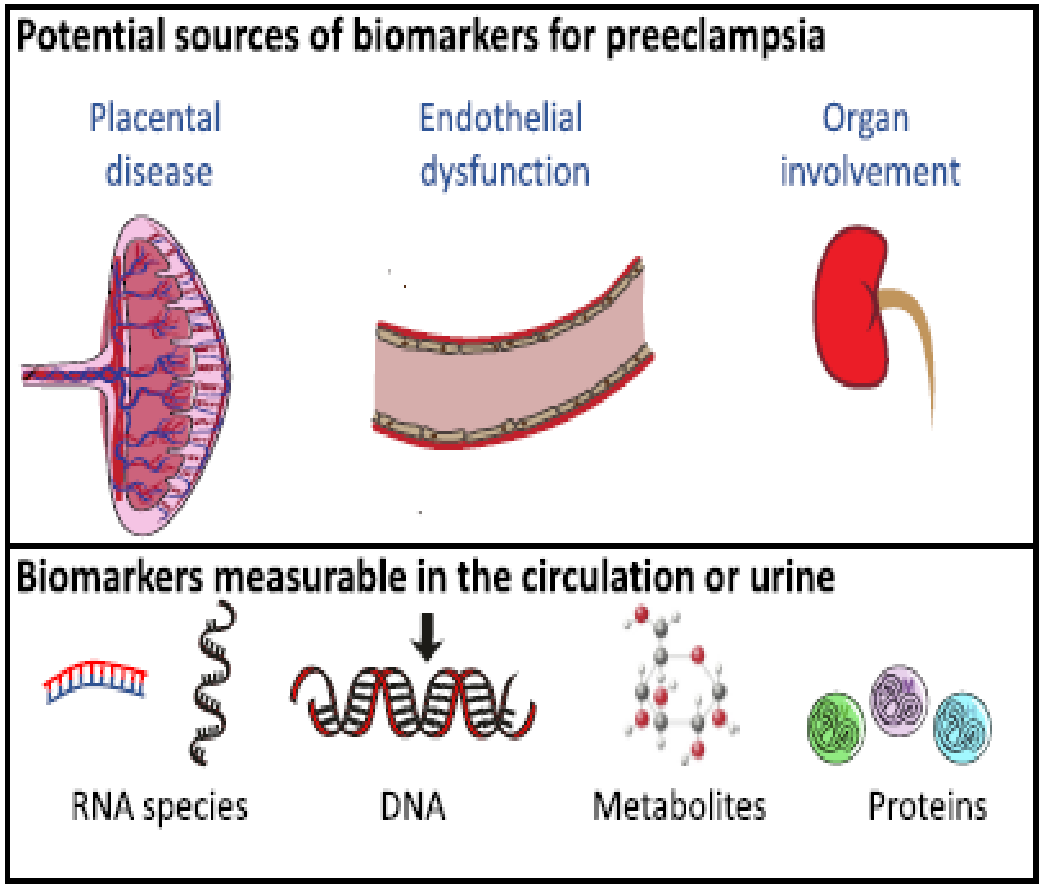
Schematic diagram of the two-stage theory of preeclampsia



Hypertension Research (2022) 45:1298–1309

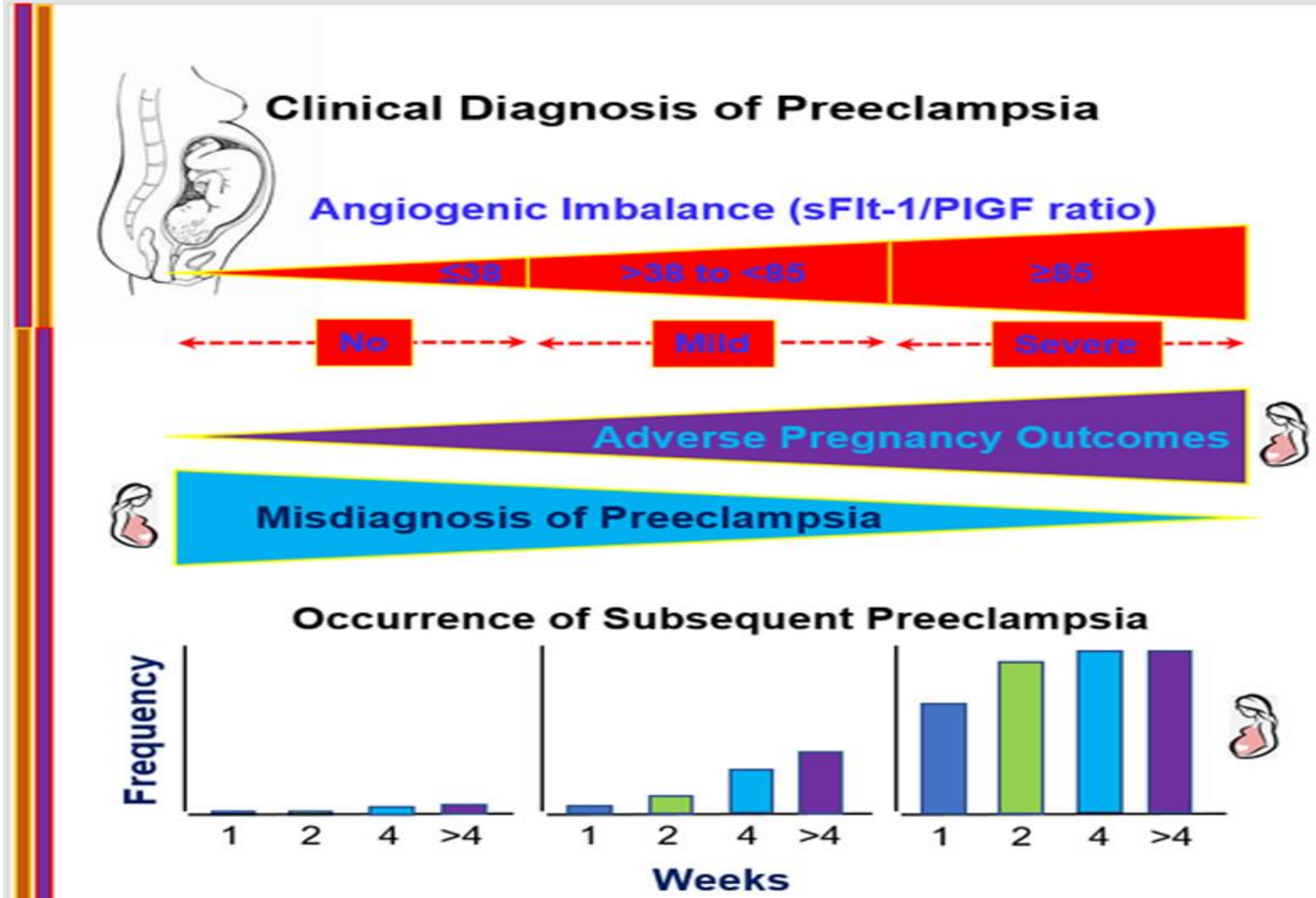
Novel biomarkers

- PlGF, sFLT1
- sENG
- sFLT1:PlGF
- Fetal RNA,
- Placental RNA



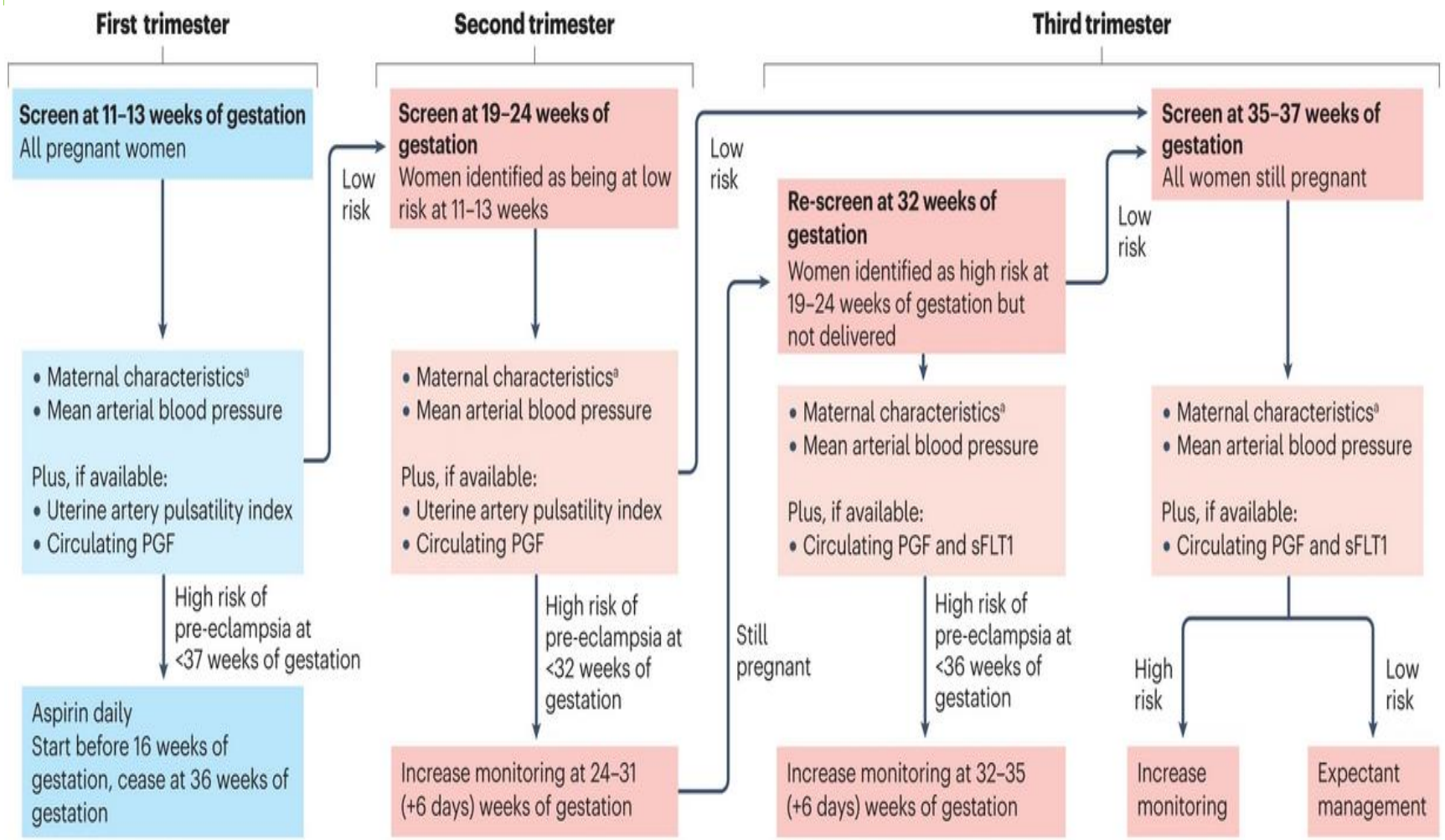
NICE's recommended cut-off values for PlGF testing

Result	Classification	Interpretation
PlGF <12 pg/ml	Test positive – highly abnormal	Suggestive of severe placental dysfunction and at increased risk for preterm delivery
PlGF ≥12 pg/ml and < 100 pg/ml	Test positive – abnormal	Suggestive of placental dysfunction and at increased risk for preterm delivery
PlGF ≥100 pg/ml	Test negative – normal	Suggestive of no placental dysfunction and unlikely to progress to delivery within 14 days of the test



Alfredo Leaños-Miranda. Hypertension. Usefulness of the sFlt-1/PlGF (Soluble fms-Like Tyrosine Kinase-1/Placental Growth Factor) Ratio in Diagnosis or Misdiagnosis in Women With Clinical Diagnosis of Preeclampsia, Volume: 76, Issue: 3, Pages: 892-900, DOI: (10.1161/HYPERTENSIONAHA.120.15552)

Algorithms to screen for pre-eclampsia in first, second and third trimesters



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Clinical Risk Factors and Aspirin-Use Recommendations for Preeclampsia Prophylaxis

Risk Level	Risk Factor	Aspirin Recommendation
Low	• Prior uncomplicated full-term delivery	Do not recommend
Moderate	• Obesity (body mass index >30 kg/m^2) • Sociodemographic traits (low socioeconomic status, African American race) • ≥35 years of age • Family history of preeclampsia • Factors concerning personal medical history (previous adverse pregnancy result, >10-year pregnancy interval, low birth weight or small for gestational age)	If the mother has two or more moderate risk factors, consider low-dose aspirin
High	• Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • History of preeclampsia, in particular when followed by an adverse consequence • Autoimmune disease (antiphospholipid syndrome, systemic lupus erythematosus)	If the mother has one or more high-risk factors, recommend low-dose aspirin

Obstet Gynecol. 2020;135(6):e237-e260.

Drugs for Treating Gestational or Chronic Hypertension in Pregnancy

Drug
First-Line Treatment
Methyldopa 0.5 g to 3 g orally per day in 2 divided doses
Second-Line Treatment
Labetalol 200 mg to 1,200 mg orally per day in 2 to 3 divided doses • Possible fetal growth restriction • Neonatal hypoglycemia with higher doses has been reported • Other beta-blocker oral agents associated with nonclinically significant neonatal bradycardia • Possible decrease in uteroplacental blood flow • May impair fetal response to hypoxic stress • Effective control of maternal blood pressure, decreased incidence of severe hypertension, and decreased rate of preterm hospital admission
Nifedipine 30 mg to 120 mg orally per day (slow-release formulation) • Possible inhibition of labor and may work synergistically with magnesium sulfate to lower blood pressure
Hydralazine 50 mg to 300 mg orally per day in 2 to 4 divided doses • Long experience with few reported adverse events • May cause neonatal thrombocytopenia
Hydrochlorothiazide 12.5 mg to 25 mg orally per day • Minimizes impaired glucose tolerance and hypokalemia • Triamterene and amiloride are not teratogenic based on small numbers of case reports • Spironolactone is not recommended because of its antiandrogenic effects during fetal development
Contraindicated
Angiotensin-converting enzyme inhibitors Angiotensin-receptor blockers

Obstet Gynecol. 2020;135(6):e237-e260

Eplerenone as a treatment for resistant hypertension in pregnancy

Jessica Gehlert and Adam Morton View all authors and affiliations

Volume 14, Issue 1 | https://doi.org/10.1177/1753495X19825967

- Increasing obesity is likely to result in a greater incidence of OSA and possibly resistant hypertension in pregnancy. Where hypertension is unresponsive to antihypertensive agents customarily used in pregnancy remote from term, eplerenone and amiloride may be useful, particularly in the setting of moderate–severe OSA.

Antihypertensive drugs to avoid in pregnancy

Antihypertensive class	Advice	Potential adverse effects	Recommendation
ACE inhibitors	Contraindicated	Teratogenic in the second and third trimester resulting in fetal anuria, oligohydramnios, hypocalvaria, intrauterine growth restriction and patent ductus arteriosus, death	Stop drug ideally before conception or at diagnosis of pregnancy
Angiotensin receptor blockers	Contraindicated	Teratogenic in the second and third trimesters, fetal anuria, oligohydramnios, hypocalvaria, intrauterine growth restriction, patent ductus arteriosus, death	Stop drug ideally before conception or at diagnosis of pregnancy
Diuretics	Avoid	Maternal hypovolaemia, fetal hypoglycaemia, thrombocytopenia, hyponatraemia and hypokalaemia	Use an alternative antihypertensive
Beta blockers (other than labetalol)	Avoid	Fetal bradycardia, intrauterine growth restriction (atenolol)	Use an alternative antihypertensive
Calcium channel antagonists (other than nifedipine and diltiazem)	Avoid	Maternal hypotension and fetal hypoxia	Use an alternative antihypertensive

Aust Prescr. 2021 Oct; 44(5): 148–152

Antihypertensive drugs that can be safely used in pregnancy

Antihypertensive drug*	Class/action	Dose	Adverse effects
Labetalol	Beta blocker	100 mg twice a day – 400 mg three times a day	Bradycardia, bronchospasm, headache
Nifedipine controlled release	Calcium channel antagonist	30 mg daily – 60 mg twice a day	Headache (first-dose effect), flushing, tachycardia, peripheral oedema
Methyldopa	Central action	250 mg twice a day – 750 mg three times a day	Depression, dry mouth, sedation, rarely haemolysis and hepatitis
Hydralazine	Vasodilator	25 mg three times a day – 50 mg three times a day	Flushing, headache, lupus-like syndrome
Prazosin	Alpha blocker	0.5 mg twice a day – 5 mg three times a day	Orthostatic hypotension

* Although oxprenolol is safe, it is no longer available in Australia.

Aust Prescr. 2021 Oct; 44(5): 148–152

Urgent treatment of severe hypertension* in pregnancy

Drug	Dose	Route	Onset of action	Adverse effects
Hydralazine	5–10 mg	Intravenous bolus repeated after 20 min if blood pressure remains >160/110 mmHg	20 min	Flushing, headache, nausea, hypotension, tachycardia
Labetalol	20–80 mg	Intravenous bolus over 2 min, repeat after 10 min if blood pressure remains >160/110mmHg	5 min	Bradycardia, hypotension, fetal bradycardia
Labetalol	200 mg	Oral	30–45 min	Bradycardia, bronchospasm, headache
Nifedipine†	10 mg	Oral	30–45 min	Headache, flushing

* Severe hypertension is 160/110 mmHg or above.

Aust Prescr. 2021 Oct; 44(5): 148–152

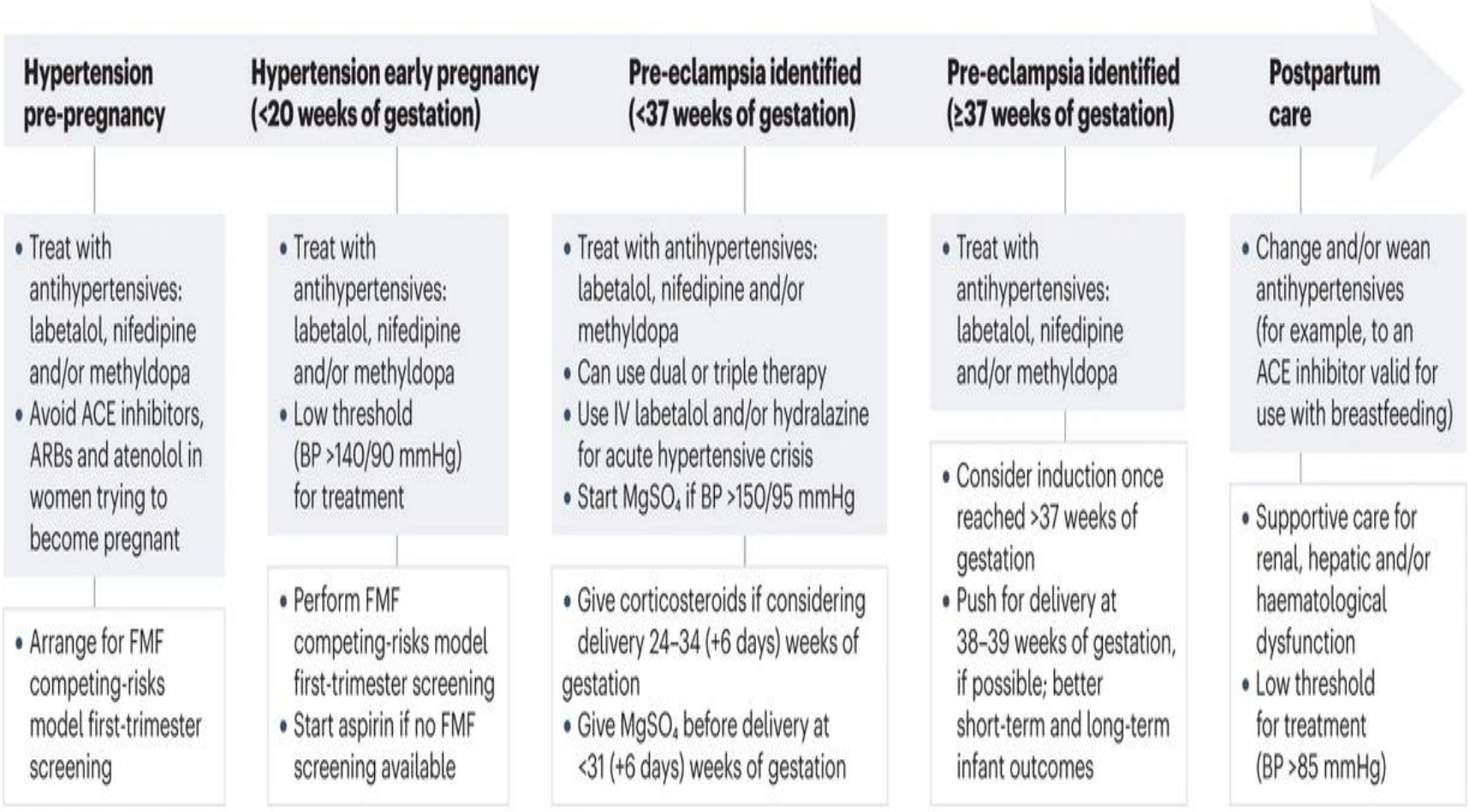
TABLE 2

Agents Prescribed for Chronic Hypertension in Pregnancy[10,13]

Agent	Dosage	FDA pregnancy risk category
Methyldopa	0.5 – 3.0 g/d, 2 divided doses	B
Labetalol	200 – 1,200 mg/d, 2 to 3 divided doses	C
Nifedipine	30 – 120 mg/d, slow-release preparation	C
Hydralazine	50 – 300 mg/d, 2 to 4 divided doses	C
Hydrochlorothiazide	2 mg/d	C
β-Blockers	Differs among choices	C

Sources: Lindheimer et al. *J Clin Hypertens* (Greenwich). 2009[10]; Visintin et al. *BMJ*. 2010.[13]

Treatment algorithm for pregnancies presenting with hypertension



Nature Reviews Disease Primers | (2023) 9:8

nature reviews disease primers

Primer

Pre-eclampsia

Nature Reviews Disease Primers (2023) 9:8

Management of planned delivery in pre-eclamptic pregnancies

Triggers for delivery

- Haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome or significant biochemical derangements
- Eclampsia
- Inability to control blood pressure despite maximum dose of antihypertensive medication
- Abnormal fetal wellbeing parameters and/or fetal distress

Managing delivery

- Induction of labour or caesarean delivery
- Avoiding maternal morbidity
- Avoiding fetal morbidity

Postpartum management and follow-up

- Acute management of hypertension

Short-term follow-up: continued regular monitoring of blood pressure postpartum and treatment with antihypertensive medications to prevent postpartum eclamptic fit. Management of any other acute sequelae of pre-eclampsia such as the developmen of pulmonary oedema or deranged renal/hepatic function

Long-term follow-up and inter-pregnancy advice: ensure blood pressure returns to normal pre-pregnancy levels by ~6 weeks postpartum. Prescribe appropriate antihypertensive medications if there is residual chronic hypertension. Identify other risk factors for maternal cardiovascular disease and encourage risk mitigation

Summary of Clinical Practice Guidelines on BP Treatment Thresholds and Postpartum Follow-up

	Treatment of HDP		Prevention of Future CVD	
	BP Threshold	BP Target	HDP Category Targeted	Recommendations for Healthcare Providers
ACC/AHA[4,74]	No recommendation	No recommendation	Preeclampsia, GH	Take detailed history of pregnancy complications Implement smoking cessation, DASH-like diet, regular physical activity, weight management
ACOG[3]	Preeclampsia: SBP ≥160 or DBP ≥110 mm Hg Chronic HTN: SBP ≥160 mm Hg or DBP ≥105 mm Hg	SBP 105–160 mm Hg and DBP 80–120 mm Hg	Recurrent preeclampsia	Assess BP, lipids, fasting blood glucose, BMI yearly Lifestyle modifications (healthy weight maintenance, exercise, smoking cessation)
ESC[75]	GH, preexisting HTN, or organ damage: SBP ≥140 or DBP ≥90 mm Hg Otherwise: SBP ≥150 and DBP ≥95 mm Hg	No recommendation	Preeclampsia, GH	Lifestyle modifications, regular BP control, and control of metabolic factors
NICE[76]	SBP ≥150 mm Hg or DBP ≥100 mm Hg	SBP <150 mm Hg and DBP 80–100 mm Hg	Preeclampsia, GH	Inform women of the increased CVD risk associated with these conditions If preeclampsia: Keep BMI between 18.5 and 24.9 before next pregnancy

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The impact of antihypertensive treatment of mild to moderate hypertension during pregnancy on maternal and neonatal outcomes: An updated meta-analysis of randomized controlled trials

Armin Attar MD, PhD, Alireza Hosseinpour MD, Mana Moghadami MD

First published: 28 March 2023 | https://doi.org/10.1002/clc.24013

- The results of this meta-analysis are in favor of the beneficial impact of pharmacological treatment of mild hypertension on both maternal and neonatal outcomes and without significant adverse events for the fetus