Pre- eclampsia: pathogenesis, novel diagnostics and therapies

SAMIRA TABIBAN MD

Introduction

- ***Pre- eclampsia*** is a leading complication of pregnancy that affects an estimated 4–5% of pregnancies worldwide
- Pre- eclampsia is defined as the presence of new-onset hypertension and proteinuria or other end-organ damage occurring after20 weeks gestation
- Eclampsia is defined as the development of grand mal seizures in a woman with preeclampsia.

Epidemiology

- Pre- eclampsia and eclampsia are estimated to cause over 50,000 maternal deaths worldwide per year
- Women with pre- eclampsia or eclampsia had a 3–25 fold increased risk of severe complications in their index pregnancy, including abruptio placentae, disseminated intravascular coagulation, pulmonary edema and aspiration pneumonia
- Prematurity of the fetus and long- term cardiovascular disease (CVD) in the mother

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Physiologic Changes in Pregnancy

Increased

- Blood volume
- Cardiac output
- Levels of nitric oxide and relaxin
- Relative resistance to vasoconstrictors
- GFR by 50%
- Urine protein excretion
- T_H2 phenotype
- Circulation of Tregs

Decreased

- Systemic vascular resistance
- Systemic blood pressure
- Serum creatinine

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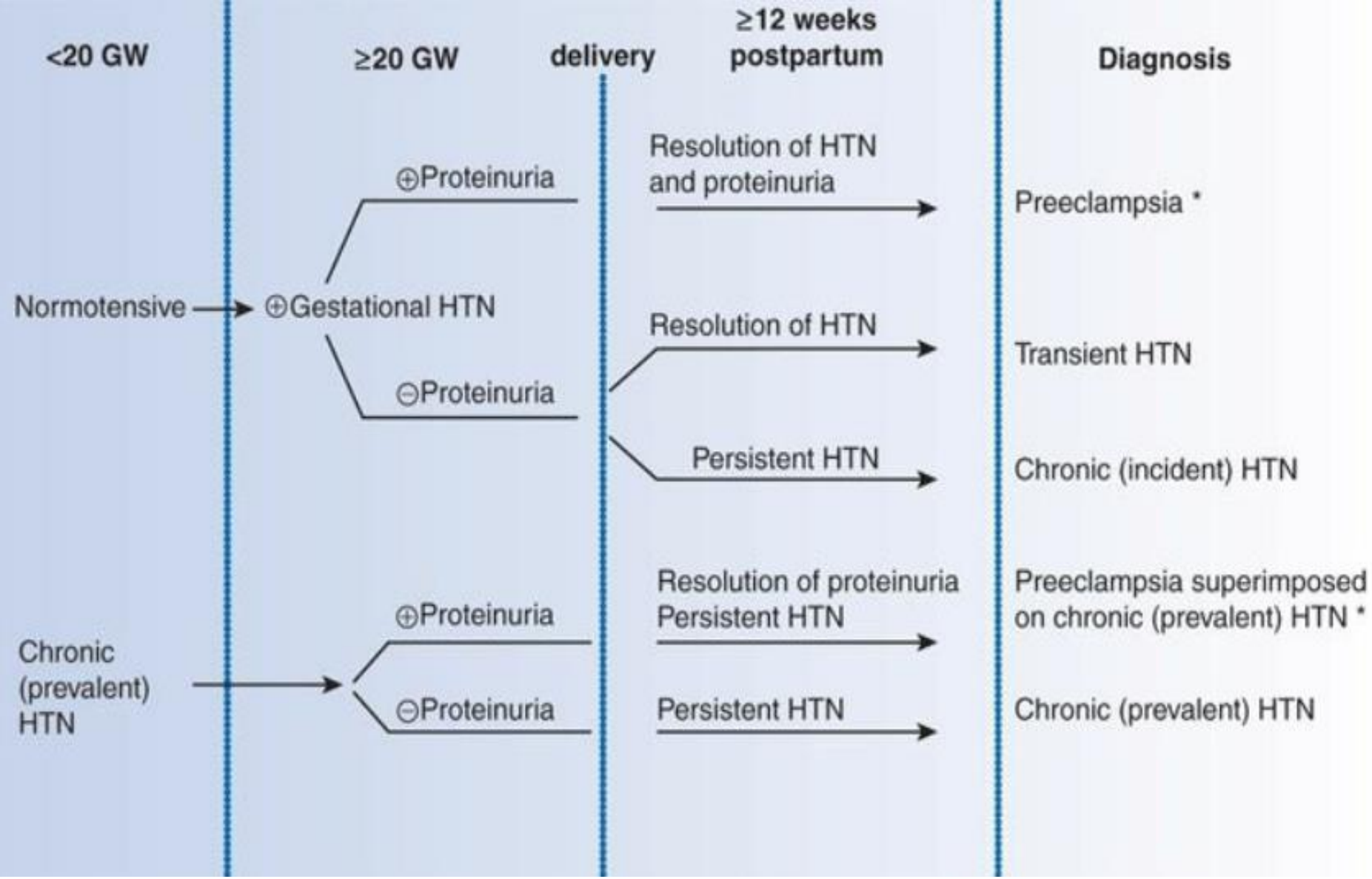
Hypertensive disorders of Pregnancy

- Gestational Hypertension
- Chronic Hypertension
- Chronic Hypertension with superimposed pre-eclampsia
- Pre-eclampsia , Eclampsia



Hypertension 2012;59:555–557

Diagnostic Criteria of Preeclampsia

Systolic blood pressure[a] ≥ 140 mm Hg *or* diastolic blood pressure[a] ≥ 90 mm Hg *and*

- Proteinuria ≥ 300 mg/d, or UPCR ≥ 0.3 g/g
- If no proteinuria is present, new onset of any of the following[b]:
  - Platelets < 100 ×10^3/μL
  - Scr > 1.1 mg/dL or doubling of Scr concentration in the absence of other kidney disease
  - Liver transaminases 2× upper limits of normal
  - Pulmonary edema
  - Cerebral or visual symptoms (new-onset and persistent headaches, blurred vision, flashing lights)

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- Early- onset or ‘placental ’pre- eclampsia (occurring before 34 weeks):risk of intrauterine growth restriction
- Late- onset or ‘maternal’ pre- eclampsia (occurring after 34 weeks):associated with maternal obesity and large- for gestational age neonates.

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Risk factors for pre- eclampsia

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

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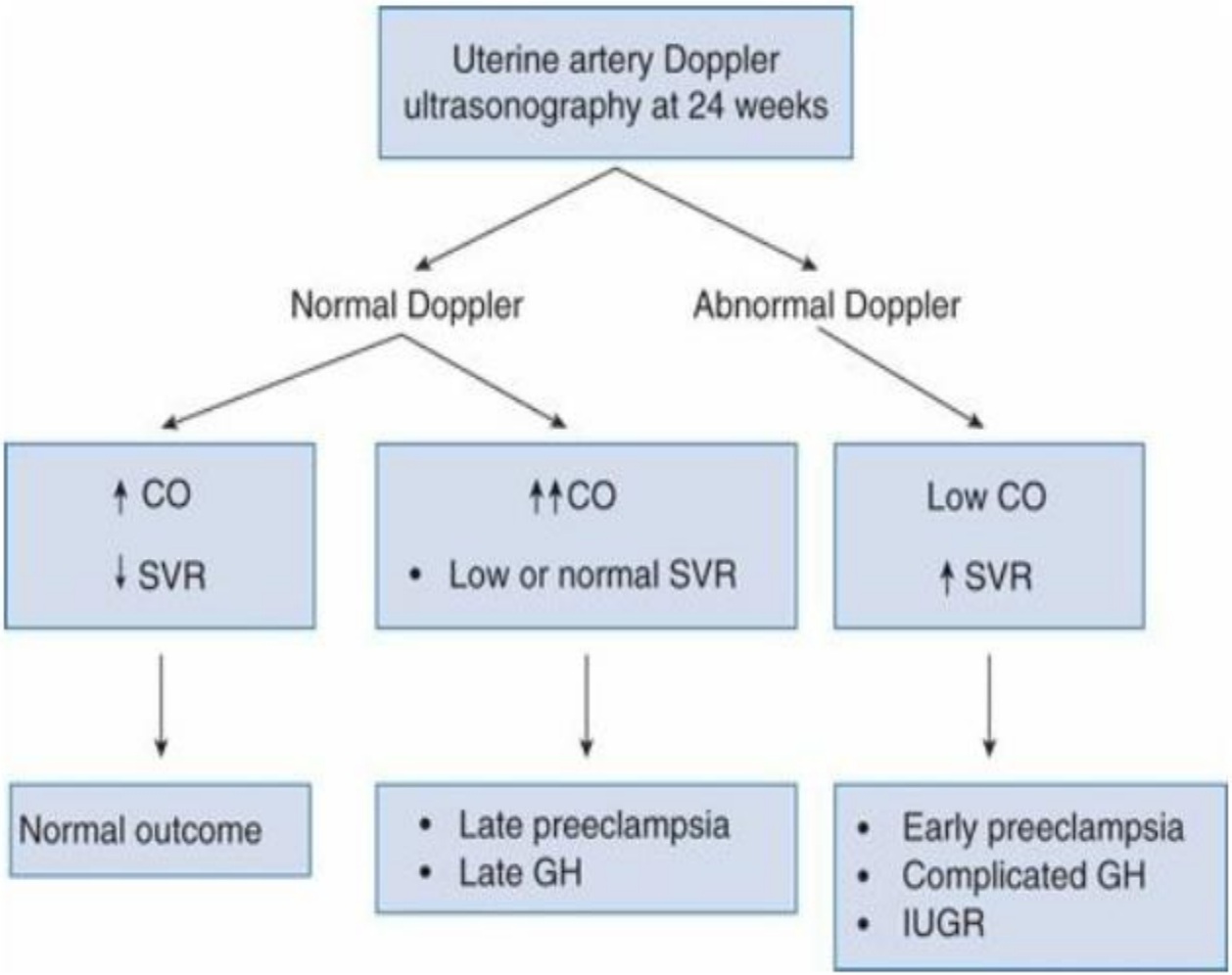
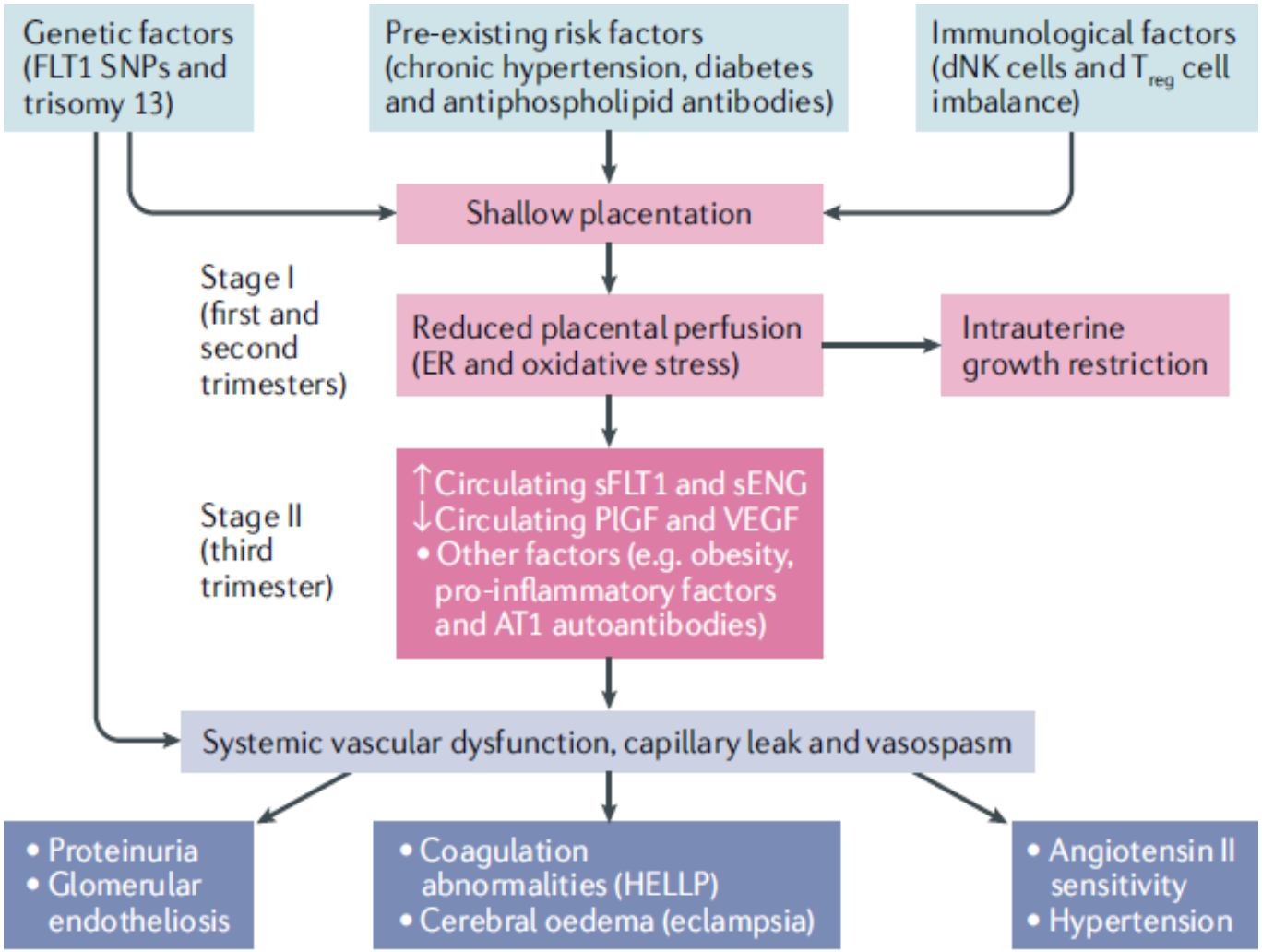


Kaplan's clinical hypertension / Norman M. Kaplan, Ronald G. Victor ; with a chapter by Joseph T. Flynn.—Eleventh edition



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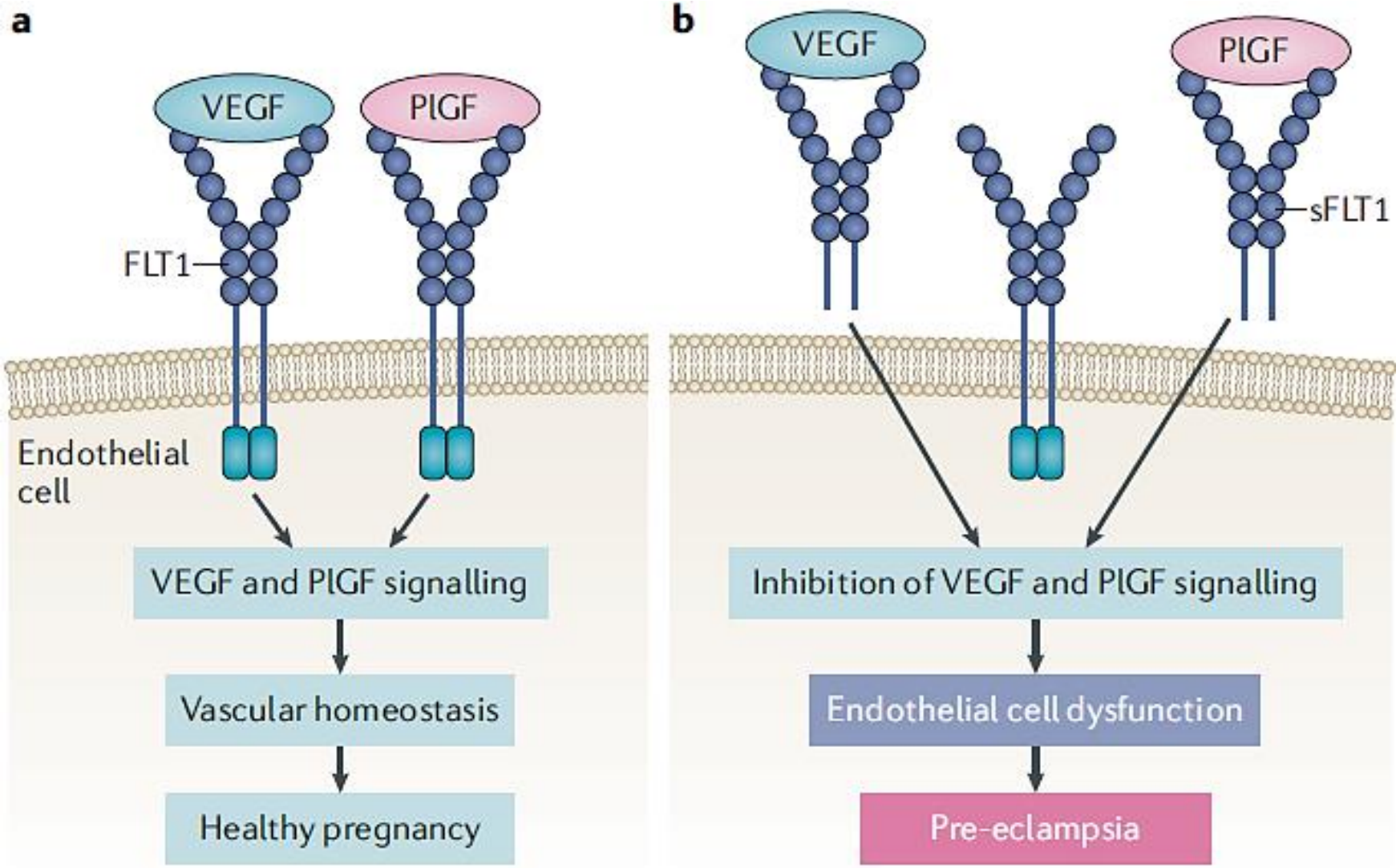

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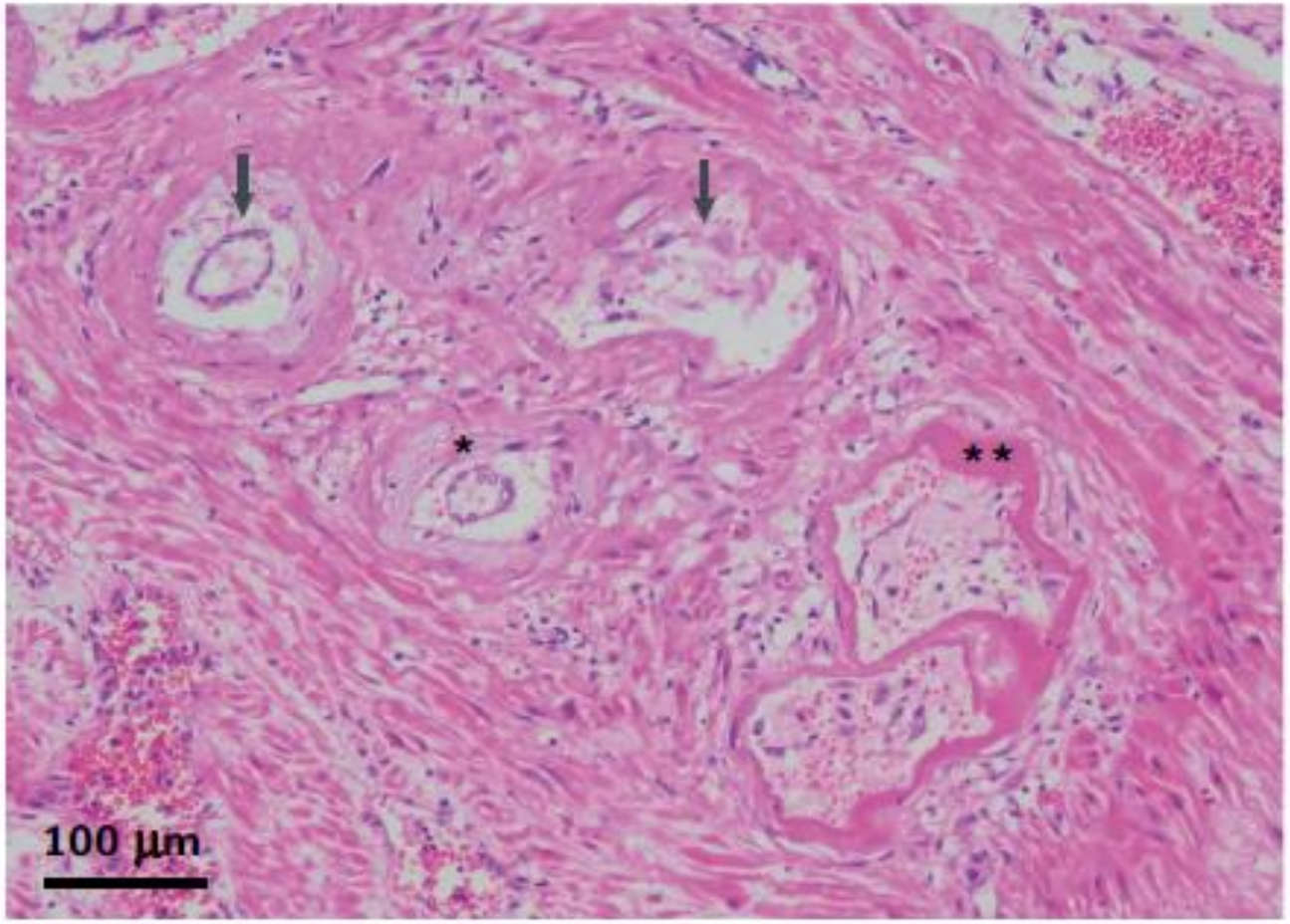

The pathology of eclampsia: an autopsyseries, Hecht, J. L. et al., *Hypertension in Pregnancy*, 2017 ,by permission of the publisher (Taylor & Francis Ltd,)

Laboratory test

All women with hypertension in pregnancy have the following tests performed at first diagnosis:

- A full blood count (hemoglobin and platelet count)
- Liver enzymes [AST, ALT] and functions tests [international normalized ratio (INR), serum bilirubin, and serum albumin
- Serum creatinine, electrolytes, and uric acid, LDH
- Urinalysis & microscopy, UPCR or 24h urine prot

❖ Renal ultrasound if serum creatinine or any of the urine testing are abnormal

Novel biomarkers

- **PlGF** test was significantly (*P*< 0.001) better than other commonly used tests in predicting preeclampsia requiring delivery within 14 days
- **PlGF** level below 100 pg/mL was just as good as a PlGF level below the fifth centile for gestational age at predicting preeclampsia requiring delivery within 14 days. PlGF levels lower than 12 pg/mL indicated an average time to delivery of just 9 days
- **sFlt-1:PlGF** ratio of 38 or lower can be used to predict the short-term absence of preeclampsia in women in whom the syndrome is suspected clinically

Zeisler H; Llurba E; Chantraine F; Vatish M; Staff AC; Sennström M; Olovsson M; Brennecke SP; Stepan H; Allegranza D; Dilba P; Schoedl M; Hund M; Verlohren **N Engl J Med. 2016; 374(1):13-22** **(ISSN: 1533-4406)**

Timing Of Delivery

- >37w Terminate without delay
- <37w Expectant management
- unstable maternal or fetal conditions should be delivered as soon as the maternal status is stabilized
- Steroids prophylaxis if <34w

Hypertension Management

- Initiation of antihypertensive therapy is recommended for pregnant women with pre-existing hypertension if systolic BP is **≥160** mmHg and/or diastolic BP is **≥105** mmHg, without evidence of end-organ damage.
- United Kingdom, in contrast, recommends initiation of treatment in pregnant women with systolic BPs **≥ 150** mm Hg and/or diastolic BPs **≥ 100** mmHg.
- CHIP Trial: women with pre-existing hypertension and/or kidney disease with antihypertensive therapy to a target diastolic BP of **85** mmHg .

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Oral Drugs for Treatment of Chronic Hypertension in Pregnancy

Agent	Comments
Methyldopa	Preferred on the basis of long-term follow-up studies supporting safety
β-Blockers	Reports on intrauterine growth retardation (atenolol)
Labetalol	Increasingly preferred to methyldopa because of reduced side effects
Calcium antagonists (nifedipine)	Limited data No increase in major teratogenicity with exposure
Diuretics	Not first-line agents Probably safe to reduce fluid retention from other agents
ACEIs, A-II receptor blockers, direct renin inhibitors	Contraindicated: Reported fetal toxicity and death

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Treatment of Acute Severe Hypertension in PE

Hydralazine	5 mg IV bolus, then 10 mg every 20–30 min to a maximum of 25 mg, repeat in several hours as necessary
Labetalol	20 mg IV bolus, then 40 mg 10 min later, 80 mg every 10 min for two additional doses to a maximum of 220 mg
Nifedipine	10 mg PO, repeat every 20 min to a maximum of 30 mg. Caution when using nifedipine with magnesium sulfate, can see precipitous BP drop. Short-acting nifedipine is not approved by U.S. Food and Drug Administration for managing hypertension
Sodium nitroprusside (rarely when others fail)	0.25 μg/kg/min to a maximum of 5 μg/kg/min. Fetal cyanide poisoning may occur if used for >4 h

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Novel Therapeutic Strategies

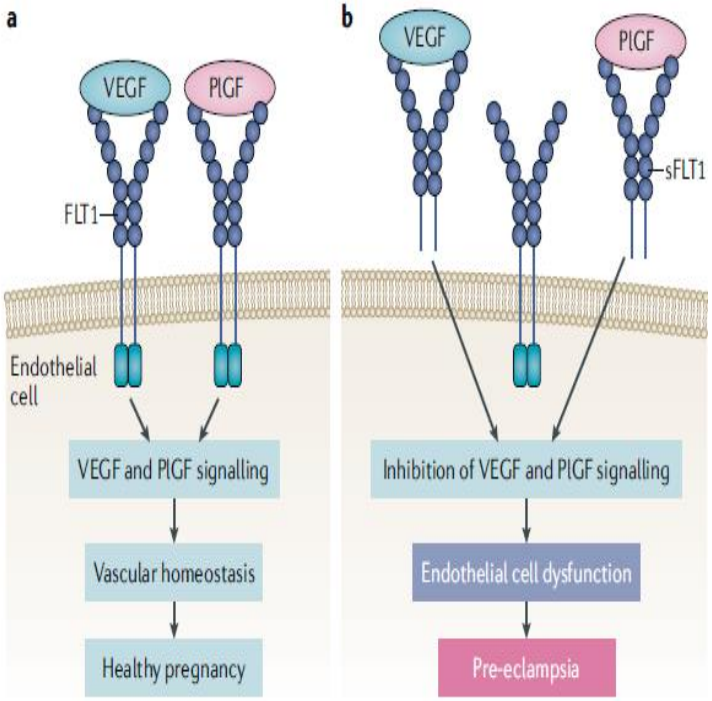
. *sFLT1 ligands*

VEGF is the natural ligand for sFLT1, and **recombinant VEGF121**, which is a novel non-heparin-binding isoform VEGF121 treatment attenuated hypertension and renal damage.

recombinant PlGF, another ligand of sFLT1, PlGF treatment reduced blood pressure and proteinuria in comparison with non- treated pre- eclamptic controls.

. *RNA interference- based strategies*

Single dose of sFLT1 RNAi therapy given intravenously lowered the sFLT1 protein level by 50%.



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Small- molecule inhibitors

- ***Sildenafil*** phosphodiesterase 5 inhibitor that enhances cGMP signalling(NO increase)

Stop … fetal lung disease

- ***Metformin*** has been shown to reduce the production of antiangiogenic factors in vitro
- ***Esomeprazole*** Proton pump inhibitors (PPIs) were shown to block sFLT1 production

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- ***Statins*** enhanced NO synthase and decreased placental production of sFLT1
- In patients with antiphospholipid antibody syndrome, which is often complicated by preeclampsia and fetal growth restriction, **pravastatin** was shown to prevent maternal and fetal adverse outcomes

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- ***Aspirin*** treatment initiated at ≤16 weeks gestation , ~50% reduction in preterm pre-eclampsia

❖ low- dose aspirin is now recommend for pre-eclampsia prophylaxis in women at high risk

- ***Nonspecific antioxidants*** such as vitamin C and vitamin E have not shown efficacy in preventing pre-eclampsia

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Apheresis

- Removal of excess antiangiogenic proteins using extracorporeal methods
- Apheresis treatment in women with preterm (<32 weeks) preeclampsia was safe, reduced sFLT1 levels and had positive effects, including reductions in proteinuria, stabilization of blood pressure and extended gestation
- Adsorption columns using monoclonal antibodies to more selectively deplete sFLT1 are currently being developed.

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Long- term maternal and fetal outcomes

- Threefold increased risk of chronic hypertension
- Twofold increased risks of CVD and stroke
- Periodic assessment of blood pressure, lipids, fasting blood glucose and body mass index in women who have a history of preterm or recurrent pre- eclampsia.
- Pre- eclampsia is also associated with an excess of peripartum cardiomyopathy.

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Long- term maternal and fetal outcomes

- Fourfold increased risk of microalbuminuria at a mean of 7.1 years postpartum in women with pre- eclampsia
- Eightfold increased risk of microalbuminuria in those who had previously experienced pre-eclampsia with severe features.

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Long- term fetal outcomes

Pre- eclampsia is an important risk factor

- Neonatal respiratory distress syndrome
- Bronchopulmonary dysplasia.

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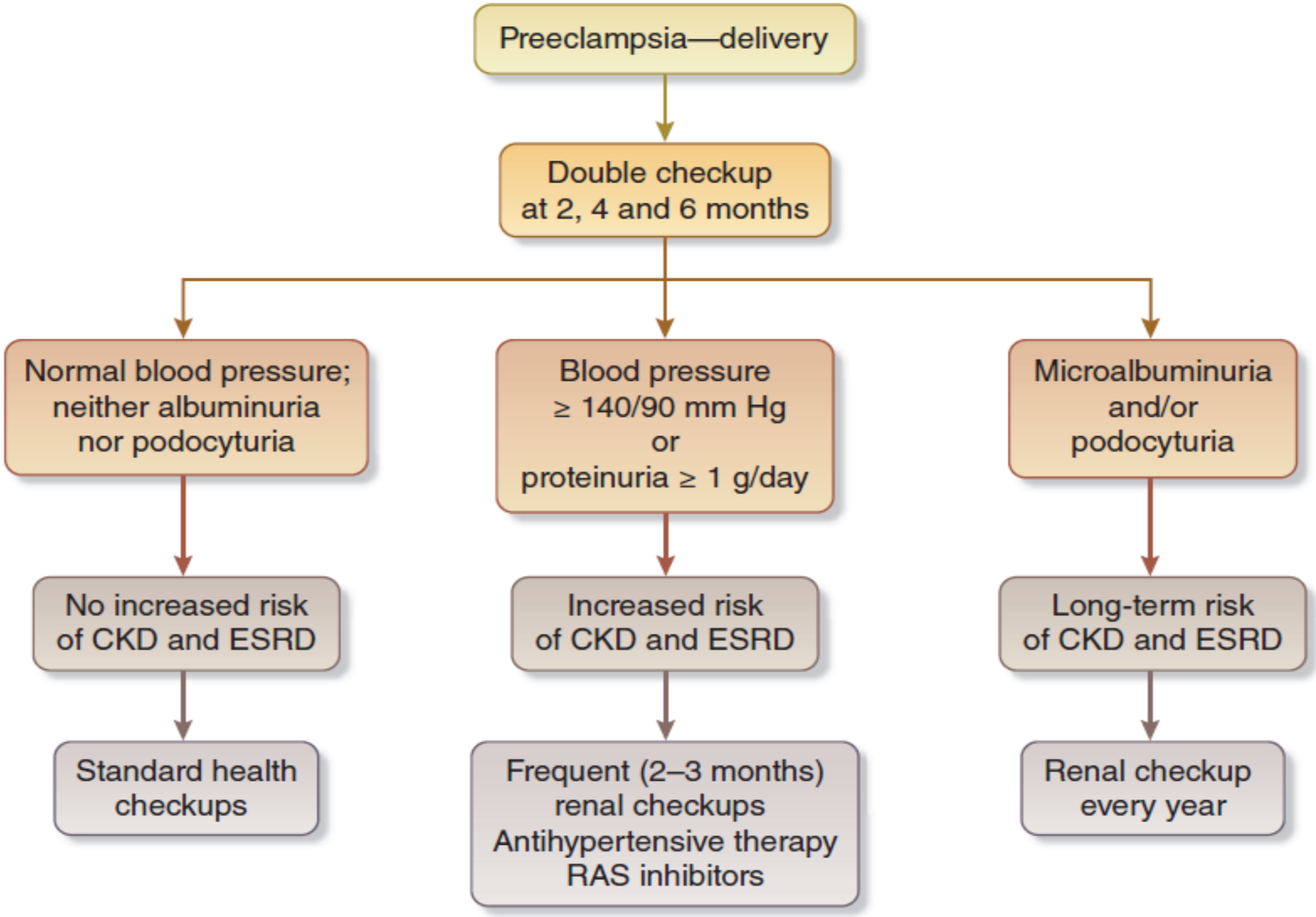

Kidney International (2019) 96, 540–554

Key points

- Pre-eclampsia is defined as new-onset hypertension and proteinuria or other end-organ damage such as to the liver or brain occurring after 20 weeks of pregnancy.
- Pre-eclampsia is characterized by defective placentation, placental ischaemia, abnormal spiral artery remodelling, oxidative stress at the maternal–fetal interface and angiogenic imbalance in the maternal circulation with ensuing endothelial and end-organ damage.
- High levels of antiangiogenic factors and low levels of proangiogenic factors are useful biomarkers for the early detection and prognosis of pre-eclampsia; these markers also serve as theranostics in clinical trials.
- Delivery is currently the only definitive treatment for pre-eclampsia; aspirin is recommended for prevention of pre-eclampsia in women at high risk.
- Potential therapeutic strategies for pre-eclampsia include targeted apheresis, antibody therapies, RNA interference and small-molecule inhibitors of factors that have a role in placental dysfunction.
- Evidence is emerging of long-term increased risk of cardiovascular and kidney disease in women who have experienced pre-eclampsia; pre-eclampsia is also an important risk factor for neonatal respiratory distress syndrome and bronchopulmonary dysplasia.