HYPERTENTION IN PREGNANCY

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WHAT IS THE MOST LIKELY DIAGNOSIS FOR THIS PATIENT?

A 36-year-old woman, G1P0, with a history of chronic hypertension and type 2 diabetes mellitus (DM) presented at 35 weeks of gestation to the emergency department and was found to have BPs in the 200s/110s mm Hg on arrival. She began having seizures.

Her baseline Scr level was not known. Scr level on arrival to the hospital was 2.6 mg/dL and peaked at 3.2 mg/dL during the hospitalization. Hemoglobin level was 9.3 mg/dL, with no signs of hemolysis on peripheral smear, and platelet count was

92000/µL (1 month prior, platelet count was 160000/µL). Urinalysis was negative for proteinuria and hematuria.

Renal ultrasound showed normal size kidneys

Introduction

- HTN is the most common medical disorder of pregnancy and is estimated to complicate 1 in 10 pregnancies
- In normal pregnancy, mean arterial BP decreases, reaching its lowest point between the 16th and 20th weeks
- BP slowly returns to pre-pregnancy levels by the 40th week of gestation.

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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DIAGNOSIS OF THE HYPERTENSIVE DISORDERS OF PREGNANCY

- **Hypertension**
  systolic BP ≥140 and/or diastolic BP ≥90 mmHg
  Blood pressure should be repeated to confirm true hypertension

  If blood pressure is severe (SBP ≥160 and/or DBP ≥110 mmHg) then the blood pressure should be confirmed within 15 min for less severe blood pressure, repeated readings should be taken over a few hours.

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Hypertensive disorders of Pregnancy

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

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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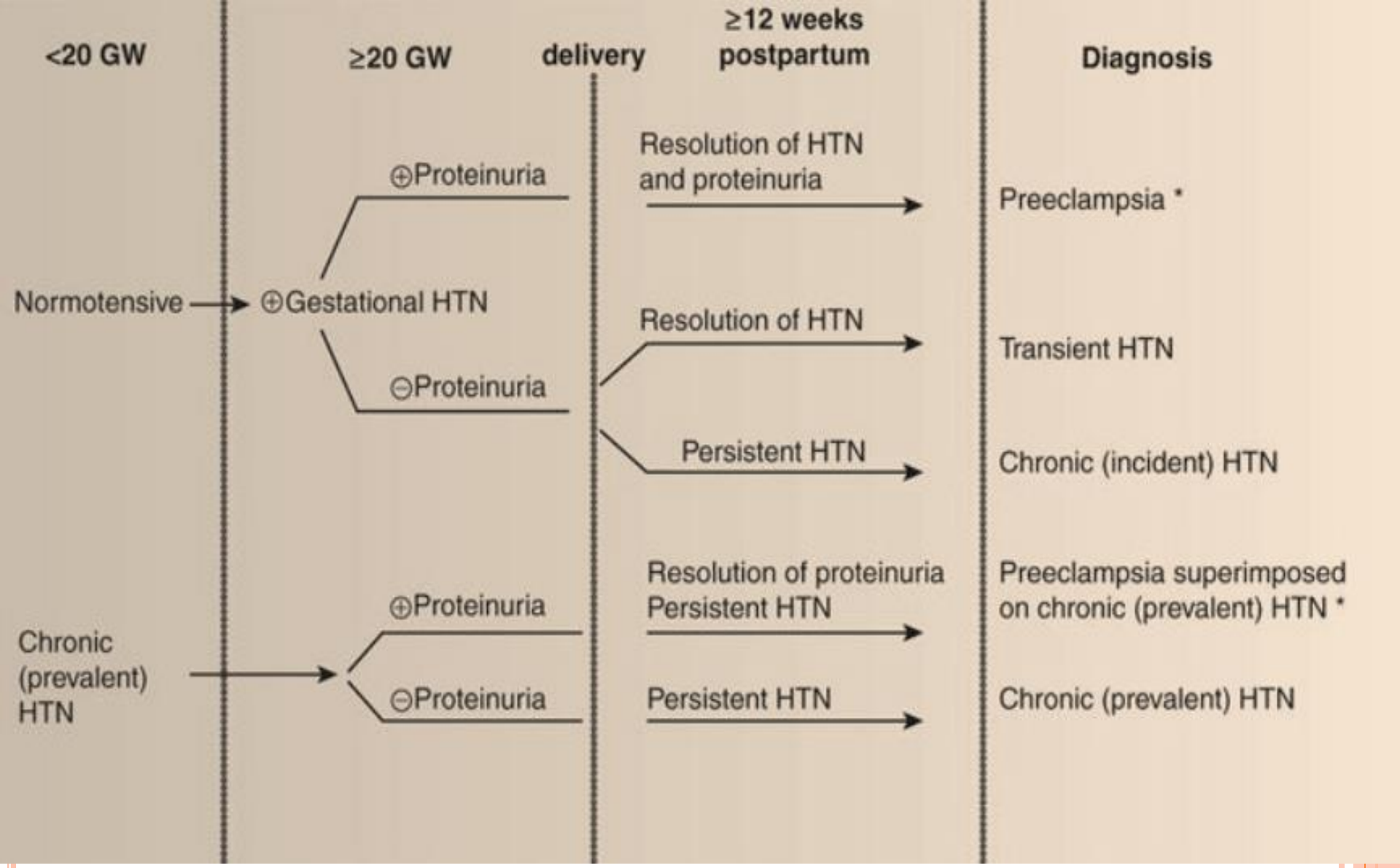

Hypertension 2012;59:555–557

Risk Factors for Preeclampsia

- Nulliparity
- Multifetal gestations
- Preeclampsia in a previous pregnancy
- Chronic hypertension
- Pregestational diabetes
- Gestational diabetes
- Thrombophilia
- Systemic lupus erythematosus
- Prepregnancy body mass index greater than 30
- Antiphospholipid antibody syndrome
- Maternal age 35 years or older
- Kidney disease
- Assisted reproductive technology
- Obstructive sleep apnea

- 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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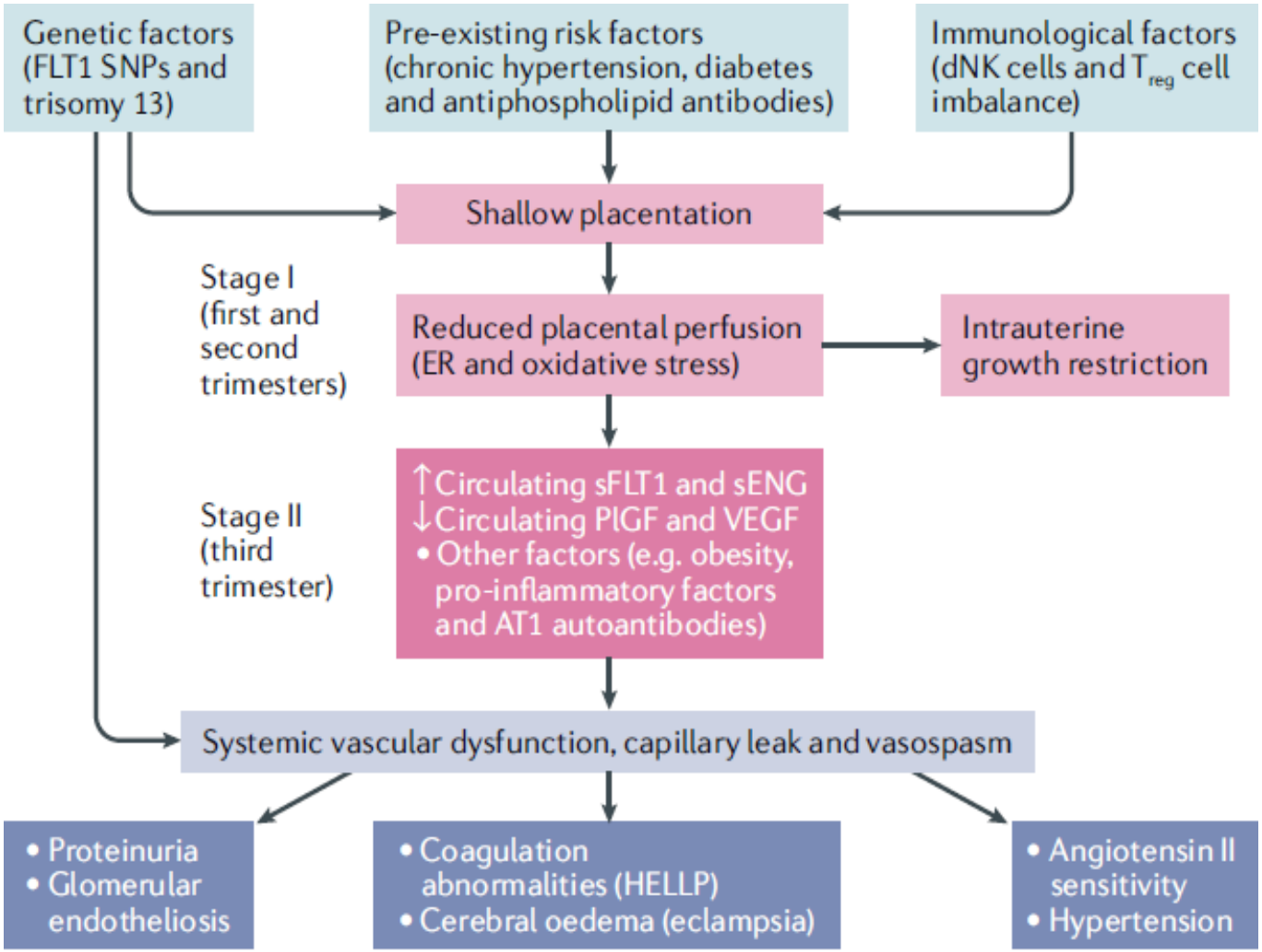
Criteria for the diagnosis of preeclampsia

Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive patient AND the new onset of 1 or more of the following*:

- Proteinuria ≥0.3 g in a 24-hour urine specimen or protein/creatinine ratio ≥0.3 (mg/mg) (30 mg/mmol) in a random urine specimen or dipstick ≥2+ if a quantitative measurement is unavailable
- Platelet count <100,000/microL
- Serum creatinine >1.1 mg/dL (97.2 micromol/L) or doubling of the creatinine concentration in the absence of other renal disease
- Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
- Pulmonary edema
- New-onset and persistent headache not accounted for by alternative diagnoses and not responding to usual doses of analgesics¶
- Visual symptoms (eg, blurred vision, flashing lights or sparks, scotomata)

- *American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 222: Gestational Hypertension and Preeclampsia. Obstet Gynecol 2020; 135:e237.*
- Graphic 79977 Version 36.0



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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 protein

- 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. PIGF 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)**

MANAGEMENT

- For women with preeclampsia without severe features at less than **37** weeks of pregnancy, expectant management is suggested;
- After **37** weeks, delivery rather than observation is suggested.
- Women with pre- eclampsia with severe features at less than **34** weeks who are otherwise stable are recommended to receive corticosteroids to promote fetal lung maturity and to continue pregnancy at a facility with adequate maternal and neonatal intensive care.

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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

INDICATION OF DELIVERY IN PREECLAMPSIA

- Women with preeclampsia at 37 weeks' gestation should be delivered
- Women with preeclampsia between 34 and 37 weeks can be managed with an expectant conservative approach
- Women with preeclampsia at <34 weeks' gestation should be managed with a conservative (expectant) approach at a centre with maternal and foetal medicine expertise, delivery being necessary when one or more of the following indications emerges:
  - (a) Inability to control maternal blood pressure despite antihypertensives
  - (b) Maternal pulse oximetry <90% or pulmonary oedema unresponsive to initial diuretics
  - (c) Progressive deterioration in liver function, glomerular filtration rate, haemolysis or platelet count
  - (d) Ongoing neurological symptoms or eclampsia
  - (e) Placental abruption
  - (f) Reversed end-diastolic flow in the umbilical artery Doppler velocimetry, a non-reassuring cardiotocography or stillbirth

Of note is that neither the serum uric acid nor the level of proteinuria should be used as an indication for delivery

2020 by the American College of Obstetricians and Gynecologists

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 .

Am J Kidney Dis. XX(XX): 1-12. Published online Month X, 2018.

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

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

Drug doses for oral treatment of hypertension in pregnancy

Drug	Class	Initial dose	Usual effective dose range	Maximum suggested total daily dose	Comments
Labetalol	Combined alpha and beta blocker	100 mg 2 times daily, increase by 100 mg twice daily every 2 to 3 days as needed	200 to 800 mg in 2 divided doses	2400 mg	Can cause bronchoconstriction. Avoid in women with asthma, chronic obstructive lung disease, heart failure, bradycardia, or greater than first-degree heart block.
Hydralazine **NOTE:** Due to reflex tachycardia, monotherapy with oral hydralazine is not recommended; hydralazine may be combined with methyldopa or labetalol if needed as add-on therapy	Peripheral vasodilator	Begin with 10 mg 4 times per day, increase by 10 to 25 mg/dose every 2 to 5 days	50 to 100 mg in 2 to 4 divided doses	200 mg*	
Nifedipine extended release¶	Calcium channel blocker	30 to 60 mg once daily as an extended release tablet, increase at 7 to 14 day intervals	30 to 90 mg once daily	120 mg	Do not administer sublingually.
Methyldopa	Centrally acting alpha agonist	250 mg 2 to 3 times daily, increase every 2 days as needed$^{\Delta}$	250 to 1000 mg in 2 to 3 divided doses	3000 mg	Sedation is a common side effect.

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

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

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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Clinical Risk Factors and Aspirin Use*

Level of Risk	Risk Factors	Recommendation
High†	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (ie, systemic lupus erythematosus, the antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate‡	• Nulliparity • Obesity (body mass index greater than 30) • Family history of preeclampsia (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age 35 years or older • Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
Low	• Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

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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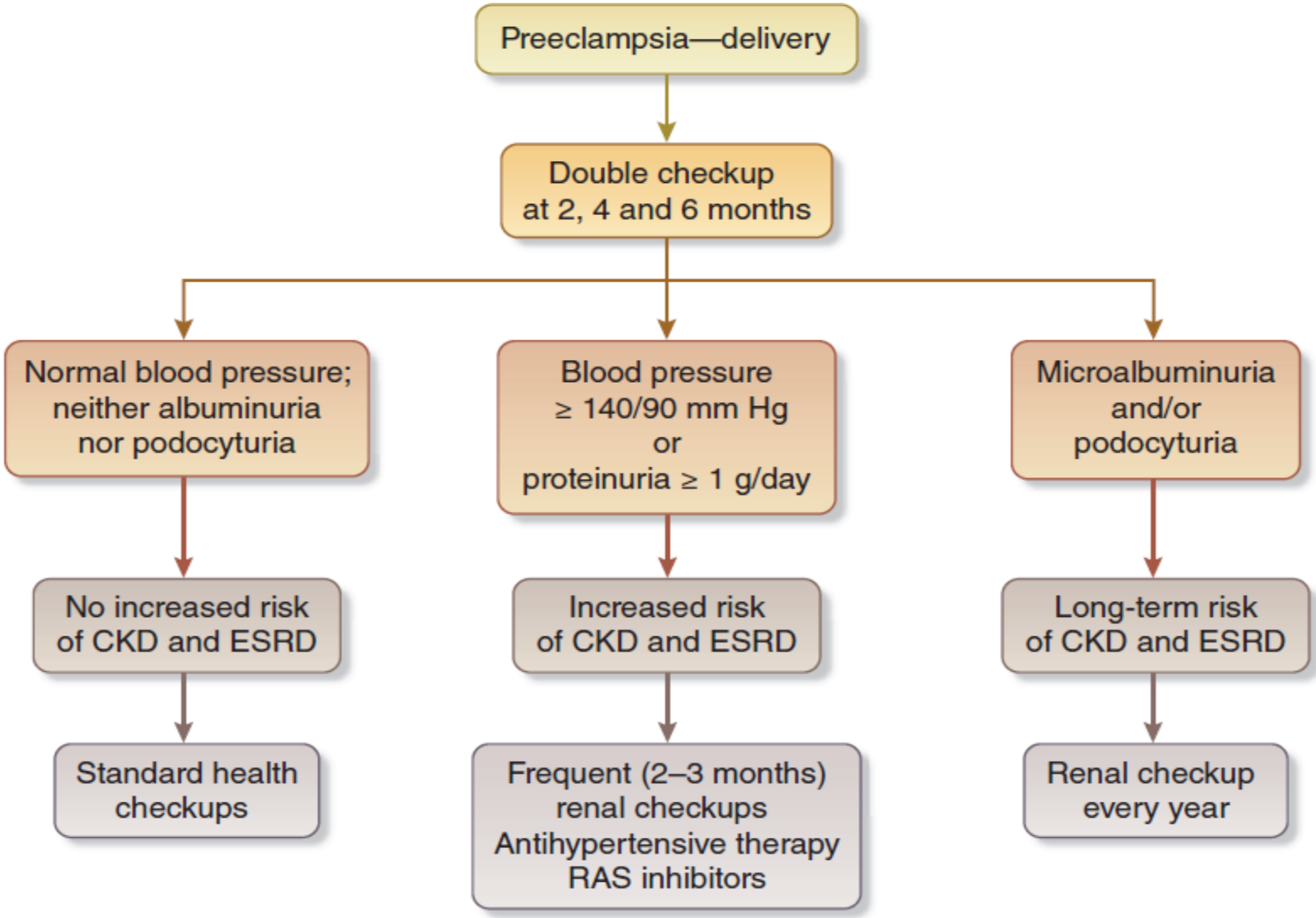

Kidney International (2019) 96, 540–554

Summary of Recommendations

- Women with any of the high-risk factors for preeclampsia should receive low-dose (81 mg/day) aspirin for preeclampsia prophylaxis, initiated between ***12*** weeks and ***28*** weeks of gestation (optimally before ***16*** weeks of gestation) and continuing until delivery.
- In women with gestational hypertension or preeclampsia without severe features at or beyond ***37*** 0/7 weeks of gestation, delivery rather than expectant management upon diagnosis is recommended.
- Magnesium sulfate should be used for the prevention and treatment of seizures in women with gestational hypertension and preeclampsia with severe features or eclampsia.

Summary of Recommendations

- Delivery is recommended when gestational hypertension or preeclampsia with severe features is diagnosed at or beyond 34 0/7 weeks of gestation, after maternal stabilization or with labor or prelabor rupture of membranes. Delivery should not be delayed for the administration of steroids in the late preterm period.
- The expectant management of preeclampsia with severe features before 34 0/7 weeks of gestation is based on strict selection criteria of those appropriate candidates and is best accomplished in a setting with resources appropriate for maternal and neonatal care.
- Expectant management is not advised when neonatal survival is not anticipated.
- During expectant management, delivery is recommended at any time in the case of deterioration of maternal or fetal condition.

Summary of Recommendations

- Among women with gestational hypertension or preeclampsia without severe features, expectant management up to 37 0/7 weeks of gestation is recommended,
- Fetal monitoring consists of ultrasonography to determine fetal growth every 3–4 weeks of gestation, and amniotic fluid volum assessment at least once weekly.
- In addition, an antenatal test one-to-two times per week for patients with gestational hypertension or preeclampsia without severe features is recommended.

Summary of Recommendations

- Epidural or spinal anesthesia is considered acceptable, and the risk of epidural hematoma is exceptionally low, in patients with platelet counts 70000/L or more & no other acquired or congenital coagulopathy, the platelet function is normal, and the patient is not on any antiplatelet or anticoagulant therapy.

- This patient presented with severe hypertension and at least one of the features of severe preeclampsia: platelet count of 92000/µL. Serum creatinine (Scr) level was also elevated, but there was no baseline for comparison. She did not present with proteinuria.
- She received intravenous magnesium sulfate. Following cessation of seizure activity, her BPs were in the160s/100s mm Hg. ***She had an emergent surgical delivery***. She remained hypertensive after delivery despite antihypertensive medication therapy, which included ***labetalol and hydralazine***.
- During the next few days of her hospitalization, platelet count of 80000/µL, liver function test results remained unremarkable, and she did not develop hemolysis. The patient was not planning to breastfeed, so a diuretic was safely added to her regimen. In addition, she required a calcium channel blocker for blood pressure control. Her blood pressure was under control and Scr level had improved to 2.1 mg/dL at her follow-up visit.

THANK YOU FOR ATTENTION