i An update to this article is included at the end

Renal Disorders in Pregnancy: Core Curriculum 2019

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As the incidence of chronic kidney disease increases and women pursue pregnancy at more advanced ages, the management of kidney disease in pregnancy has become increasingly relevant to the practicing nephrologist. Women with kidney disorders face several challenges in pregnancy due to increased physiologic demands on the kidney and risk for disease progression, the potential teratogenicity of medications, and the increased risk for complications such as preeclampsia and preterm delivery. Challenges posed by an underlying disease process in pregnancy, such as autoimmune disease or diabetes mellitus, necessitate an interdisciplinary team to ensure good maternal and fetal outcomes. Rates of acute kidney injury in pregnancy are generally declining worldwide, but remain a significant public health concern in developing countries. Pregnancy may also be the first time that a woman has kidney disease or hypertension diagnosed. An understanding of what constitutes normal physiologic changes in pregnancy is critical in a diagnostic evaluation. In this review, we review physiologic changes in pregnancy, causes and management of acute kidney injury in pregnancy, hypertensive disorders of pregnancy, and how to care for women with chronic kidney disease of various causes, including the use of antihypertensives and immunosuppressants.

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Am J Kidney Dis. 73(1): 119-130. Published online August 16, 2018.

doi: 10.1053/j.ajkd.2018.06.006

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Physiologic Changes in Pregnancy

There are significant hemodynamic and immunologic shifts that occur during the course of healthy pregnancy (Box 1). The major hemodynamic changes in pregnancy include increased blood volume, decreased systemic vascular resistance, and increased cardiac output. There are increased systemic levels of vasodilators, such as nitric oxide and relaxin, and relative resistance to vasoconstrictors, such as angiotensin II. There is typically a decrease in systemic blood pressure (BP), usually reaching a nadir by 20 weeks' gestation. Glomerular filtration rate (GFR) increases by ~50%, resulting in a physiologic reduction in serum creatinine (Scr) level in the setting of hyperfiltration. The normal Scr level in pregnancy is in the 0.4- to 0.6-mg/dL range. The combination of smooth muscle relaxation due to progesterone and mechanical compression by the enlarging uterus can cause physiologic hydronephrosis and retention of urine in the collecting system during pregnancy.

Urine protein excretion increases during the course of normal pregnancy, from 60 to 90 mg/d to 180 to 250 mg/d, as measured by a 24-hour urine collection. As a consequence of this physiologic increase in proteinuria, the threshold for elevated proteinuria in pregnancy has been set at a higher level of protein excretion of 300 mg/d. This increase in proteinuria has been attributed to hyperfiltration, as described, but may also be due to changes in glomerular permeability. Some studies have demonstrated an increase in tubular proteinuria, reflected as an increase in urinary retinol-binding protein, as opposed to an increase in albuminuria, which would reflect a glomerular source. The use of spot urine protein-creatinine ratio (UPCR) has gained favor in the diagnosis of preeclampsia, which is typically characterized by proteinuria (UPCR > 0.3 g/g). UPCR is a faster test that has acceptable sensitivity and specificity. There may be increased UPCR in the absence of hypertension or kidney disease, a phenomenon known as isolated proteinuria, present in as many as 15% of pregnancies.

Last, there are several changes in the function of the innate and adaptive immune systems in pregnancy that may have important impacts on the behavior of autoimmune diseases, a common cause of reduced kidney function in young women. Normal pregnancy is characterized by a shift from a T helper (T_H) cell type 1 (T_H1; cell-mediated immunity) to a T_H2 (humoral-mediated immunity) phenotype, which is important for tolerance to fetal antigens, trophoblast invasion, and placental formation. In addition, the number of regulatory T cells, which promote immune tolerance, is increased in normal pregnancy, further contributing to establishing fetal tolerance. In autoimmune diseases, such as systemic lupus erythematosus (SLE), alterations in the number and function of regulatory T cells may correlate with increased risk for pregnancy complications, such as preeclampsia, and poor fetal and maternal outcomes.

Box 1. 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

Abbreviations: GFR, glomerular filtration rate; T_H2, T helper cell type 2; Tregs, regulatory T cells.

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Hypertension in Pregnancy

Case 1: *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. She received intravenous magnesium sulfate and lorazepam. Following cessation of seizure activity, her BPs were in the 160s/100s mm Hg. She had an emergent surgical delivery. She remained hypertensive after delivery despite antihypertensive medication therapy, which included labetalol and hydralazine. 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 92 ×10³/μL (1 month prior, platelet count was 160 ×10³/μL). Urinalysis was negative for proteinuria and hematuria. Renal ultrasound showed normal-size kidneys, with no signs of chronic kidney disease (CKD).*

Question 1: What is the most likely diagnosis for this patient?

a) Severe preeclampsia
b) Acute cortical necrosis
c) Hypertensive emergency
d) HELLP (hemolysis, elevated liver function test results, low platelet count) syndrome

For answer, see Appendix.

Hypertensive disorders of pregnancy are common, occurring in 6% to 8% of pregnancies. The differential diagnosis of hypertensive events during pregnancy includes chronic hypertension, gestational hypertension, or preeclampsia. Patients who have a known history of hypertension before pregnancy or those who are found to have BPs ≥ 140/90 mm Hg before 20 weeks of gestation are considered to have chronic hypertension. Women with chronic hypertension have an increased risk for superimposed preeclampsia, which can occur in up to 35% of their pregnancies. Some hypertensive patients with unknown histories of hypertension before pregnancy may present with BPs in the normal range during the first and second trimesters due to the normal physiologic decrease in BP during this time, thus masking the diagnosis of preexisting hypertension. This may lead to the erroneous assumption that the finding of an elevated BP later during the pregnancy is related to gestational hypertension. The correct diagnosis ultimately is confirmed during the postpartum period because BP should normalize in those with true gestational hypertension. Gestational hypertension occurs during the second half of pregnancy in patients with no history of pre-existing hypertension, and has an incidence of 6% to 7%.

Preeclampsia is defined as BP ≥ 140/90 mm Hg in a previously normotensive woman, measured on 2 different occasions at least 4 hours apart, after 20 weeks of gestation, in the presence of proteinuria with protein excretion ≥ 300 mg/d or UPCR ≥ 0.3 g/g. A diagnosis of preeclampsia also can be made in the absence of proteinuria in the presence of clinical features of severity (Box 2).

During the last 2 decades, the heterogeneity of preeclampsia with respect to underlying mechanisms and resultant clinical phenotypes has been increasingly recognized. Major breakthroughs in the pathophysiology of preeclampsia have occurred that attributed impaired angiogenesis in preeclampsia to an imbalance between proangiogenic (serum vascular endothelial growth factor and placental growth factor [P1GF]) and antiangiogenic (soluble fms-like tyrosine kinase 1 [sFlt-1] and soluble endoglin) factors, favoring the latter. However, angiogenic abnormalities seem to be informative for severe and early (<34 weeks of gestation) forms of preeclampsia, but not for late disease (≥34 weeks of gestation). Consequently, screening tests to predict preeclampsia, including the sFlt-1:P1GF ratio, currently are not recommended for clinical practice. The only available screening approach that has a substantial net benefit is serial BP measurements during pregnancy. Similarly, several approaches aiming at preventing preeclampsia have been studied. The only approach with proven benefit is low-dose aspirin when prescribed during the late first trimester in patients with moderate or high risk for preeclampsia, patients with a history of preeclampsia and preterm delivery at less than 34 weeks, and those with a history of preeclampsia in 2 or more pregnancies.

Box 2. 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 ×10³/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)

Abbreviations: Scr, serum creatinine; UPCR, urinary protein-creatinine ratio.
[a]Measured on 2 occasions, at least 4 hours apart, after 20 weeks of pregnancy in a previously normotensive patient.
[b]Signs of severe preeclampsia.

Delivery remains the mainstay of therapy for preeclampsia, particularly for its severe forms and anticipated life-threatening complications. Expectant management can be considered for milder forms of preeclampsia, with the goal of extending pregnancy to full term (37 weeks of gestation) to decrease the risks for fetal complications related to prematurity.

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Hypertension Management

The management of hypertension during pregnancy has evolved over time. Uncontrolled hypertension increases the risk for maternal hemorrhagic stroke, whereas tight BP control has been linked historically to placental hypoperfusion and fetal compromise. In a metaregression analysis evaluating the effects of antihypertensives on fetal growth, a significant association between mean arterial BP and fetal weight was identified, with a 10–mm Hg decrease in mean arterial BP associated with a 176-g decrease in fetal birth weight. Due to these concerns, an open-label, international, multicenter, randomized, controlled trial (Control of Hypertension in Pregnancy [CHIP] Trial) analyzed 987 pregnant women with pre-existing or gestational hypertension who were randomly assigned to less tight BP control (target diastolic BP, 100 mm Hg) versus tight BP control (target diastolic BP, 85 mm Hg) during pregnancy. No significant differences were found between groups in terms of pregnancy loss, need for high-level neonatal care, or incidence of maternal complications other than a higher frequency of severe maternal hypertension in the less tight control arm (40.6% vs 27.5%, respectively). However, it should be noted that the achieved mean separation of BP in the tight versus less tight BP groups was 4.6 (95% confidence interval [CI], 3.7-5.4) mm Hg diastolic, less than the intended target difference of 15 mm Hg.

Guidance regarding management of hypertension differs slightly depending on the organization. The American College of Obstetricians and Gynecologists recommends starting antihypertensive therapy in patients with gestational hypertension or preeclampsia with persistent BP ≥ 160/110 mm Hg. Delivery is recommended for these women at 37 weeks or later if no severe features of preeclampsia are observed. Initiation of antihypertensive therapy is recommended for pregnant women with pre-existing hypertension if systolic BP is ≥160 mm Hg and/or diastolic BP is ≥105 mm Hg, without evidence of end-organ damage. The National Institute for Health and Care Excellence (NICE) in the United Kingdom, in contrast, recommends initiation of treatment in pregnant women with systolic BPs ≥ 150 mm Hg and/or diastolic BPs ≥ 100 mm Hg. Despite these conflicting guidelines, the authors of this review believe that it is safe to treat women with pre-existing hypertension and/or kidney disease with antihypertensive therapy to a target diastolic BP of 85 mm Hg based on results of the CHIP Trial.

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Acute Kidney Injury in Pregnancy

Case 2: *A 42-year-old woman with a history of poorly controlled hypertension presented at 29 weeks of gestation with vaginal bleeding and abdominal cramping. She had not received prenatal care and had stopped her antihypertensive therapy. In the emergency department, she was found to have intrauterine fetal demise and placental abruption. Her laboratory studies were notable for hemoglobin level of 9.5 mg/dL, platelet count 75 ×10³/μL (baseline platelet count, 140 ×10³/μL), Scr level of 1.8 mg/dL, and elevated liver enzyme levels. She also had low fibrinogen levels (110;*

reference range, 200-393 mg/dL) and a prolonged protime, consistent with disseminated intravascular coagulation. She had severe elevations in BP, with systolic BP close to 200 mm Hg. She was taken for urgent delivery and had significant blood loss requiring multiple transfusions. She became hypotensive, with systolic BPs in the 80– to 90–mm Hg range for at least 30 minutes. The next day she was anuric and was started on dialysis therapy, which she required for 4 weeks, with gradual recovery of kidney function. A kidney biopsy was performed (Fig 1).

Question 2: What is the pathologic diagnosis?

a) Glomerulonephritis
b) Hypertensive nephrosclerosis
c) Thrombotic microangiopathy
d) Acute cortical necrosis

For answer, see Appendix.

Pregnancy-related acute kidney injury (AKI) in young women worldwide is an important cause of maternal and fetal morbidity and mortality. The cause of AKI varies geographically and according to the availability of health resources. The main cause of AKI during pregnancy in developing countries is severe sepsis from septic abortions. Other causes of AKI include hypertensive disorders of pregnancy and hemorrhage. In developed countries, causes of AKI also include hypertensive disorders of pregnancy and sepsis, as well as thrombotic microangiopathy, heart failure, acute fatty liver, and postpartum hemorrhage. Rates of pregnancy-related AKI overall have decreased in the last several decades, most likely due to improved prenatal care and a decrease in septic abortions. However, more recent data from Canada show an increasing incidence of pregnancy-related AKI, from 1.66 per 10,000 deliveries in the 2003 to 2004 era to 2.68 per 10,000 deliveries during the 2009 to 2010 era. Although these incidence rates are still low, the trend is concerning. This could be due to several factors, including the increased use of assisted reproduction technology that allows women to become pregnant at more advanced ages, an increasing incidence of hypertensive pregnancy disorders, and increasing obesity. AKI requiring dialysis in pregnancy or postpartum is even less common, occurring in 1 per 10,000 pregnant women, but it is associated with increased mortality.

Most AKI episodes in pregnancy occur in otherwise healthy women with an isolated pregnancy-related condition. Hyperemesis gravidarum in the first trimester can lead to volume depletion that can require hospitalization and intravenous fluid replacement. Hemodynamic compromise in the setting of hemorrhage, pulmonary embolism, heart failure, or sepsis can cause prerenal AKI, which can lead to ischemic acute tubular necrosis if the injury is of sufficient severity and duration. Acute tubular necrosis can also be seen in the setting of acute fatty liver of pregnancy or amniotic fluid embolism or as a secondary injury related to severe preeclampsia, in particular HELLP (hemolysis, elevated liver function test results, low platelet count) syndrome (Fig 2). Acute cortical necrosis can occur in the setting of severe hypotension and appears to occur more commonly in pregnancy than in other conditions characterized by a similar degree of hemodynamic compromise (Fig 1). The increased risk for cortical necrosis in pregnancy may be due to the hypercoagulable nature of pregnancy.

Criteria for the diagnosis of AKI in pregnancy have not been standardized. Scr level typically is lower in pregnancy

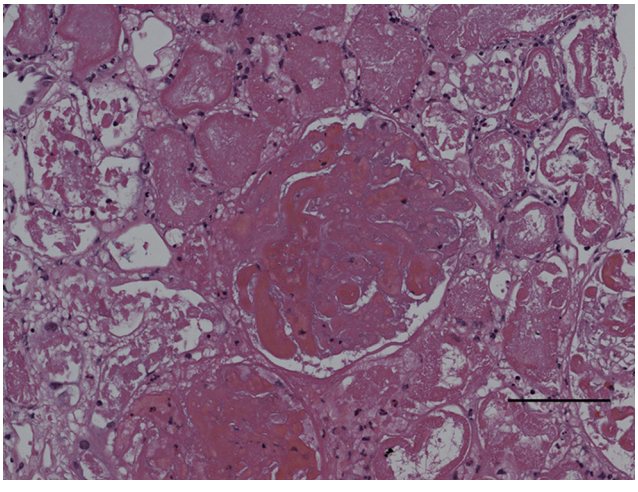

Figure 1. Light microscopy image shows acute cortical necrosis in the setting of pregnancy (hematoxylin and eosin stain; scale bar: 100 μm) (see case 1).

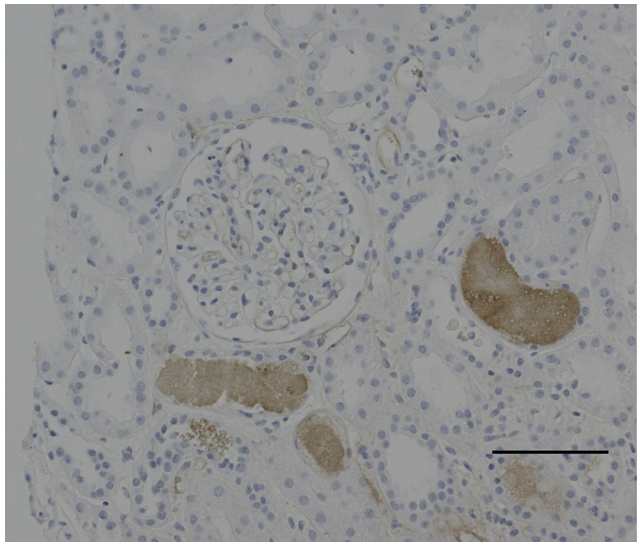

Figure 2. Kidney biopsy image from a 30-year-old woman with hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome. Kidney biopsy was performed due to acute kidney injury and revealed severe acute tubular necrosis with hemoglobin casts, likely related to hypoperfusion and hemolysis (light microscopy image shows hemoglobin-containing casts in renal tubules and acute tubular necrosis; scale bar: 100 μm).

due to hyperfiltration, as mentioned previously. An increase in Scr level of 0.3 mg/dL, consistent with stage 1 in the AKI Network scheme, may represent a significant kidney injury. There are currently no distinct criteria for the diagnosis of AKI in pregnancy, though it is possible that smaller increases in Scr levels (<0.3 mg/dL) may be more sensitive for picking up early injury. In the absence of data, changes in Scr levels should be interpreted within the context of each clinical scenario. For example, an increase in Scr level by 0.2 mg/dL in a woman with new-onset hypertension and low platelet count, concerning for HELLP syndrome or atypical hemolytic uremic syndrome (aHUS), is likely to herald kidney injury and calls for close follow-up of serial Scr values and relevant serologic test results. Renal ultrasounds that are obtained to rule out postrenal causes of AKI may show hydronephrosis, but this may be physiologic rather than pathologic. Serum complement levels tend to be elevated in pregnancy due to increased synthesis by the liver, which can complicate making the diagnosis of certain conditions, such as lupus nephritis.

The hemodynamic, inflammatory, and immunologic shifts in pregnancy may unmask underlying kidney disease, and it can be difficult to diagnose an acute as opposed to a chronic kidney injury. This may be particularly true for glomerular disease. Kidney biopsy should be considered in women at less than 32 weeks of gestation, when delivery is not a viable alternative and treatment may result in prolongation of a desired pregnancy. A systematic review of 39 studies provided data for 243 biopsies performed during pregnancy. The main indication for biopsy was to differentiate between glomerulonephritis and preeclampsia, and the results led to changes in therapy in 66% of cases. Reports of potential complications of kidney biopsies during pregnancy vary from mild to severe, depending on the pregnancy stage, and appear to be significantly higher later in pregnancy, with a peak at 25 weeks of gestation (ie, major bleeding requiring transfusion, embolization, severe obstetric complications, early preterm delivery, and in one case, presumably related fetal death). Therefore, careful consideration of the clinical scenario and counseling of the patient are necessary before proceeding with a kidney biopsy. If a woman presents with decreased kidney function in the late preterm period (34 weeks), the provider should consider whether it might be prudent to wait to biopsy after delivery. Biopsy may still be indicated in certain scenarios, but fetal outcomes are generally good after 34 weeks and thus careful discussion of risks and benefits with the patient, obstetrician, and neonatologist are needed before proceeding.

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Lupus Nephritis

SLE disproportionately affects women of childbearing age. Counseling regarding family planning should be discussed early after an SLE diagnosis to implement measures to reduce the risks for adverse maternal and fetal outcomes in a desired pregnancy. Patients with SLE should have quiescent disease for at least 6 months before attempting to conceive.

Assessment of disease activity through the use of biological markers and assessments of kidney function and degree of proteinuria are necessary to diagnose underlying disease flares and monitor for any potential complications during the pregnancy. Timely identification of high-risk patients is important to reduce the risk for possible disease progression and minimize any potential side effects.

Extrarenal lupus flares are more common during the second and third trimesters, whereas kidney disease activity seems to be more common during the postpartum period. Evidence suggests that severe maternal flares occur in 3% to 5% of pregnancies. Immunologic activity at conception (as measured by low C3 levels and anti-DNA antibodies) has been described as the best predictor of renal flares. Low C4 levels and high anti-C1q antibody levels are associated with early flares (encountered during the first or second trimesters of pregnancy). High body mass index has been associated with increased risk for late flares, defined as flares encountered during the third trimester or postpartum period. The presence of a renal flare does not constitute an absolute contraindication to maintaining a pregnancy.

Several studies have evaluated the risk for maternal complications in women with SLE. A systematic review and meta-analysis of pregnancy outcomes in patients with SLE and lupus nephritis by Smyth et al showed that lupus flares, hypertension, and preeclampsia were among the main maternal complications. Patients with SLE and preexisting lupus nephritis have higher risk for a preterm delivery and earlier onset of preeclampsia compared with women with SLE without nephritis. The overall maternal mortality rate in pregnant patients with SLE and lupus nephritis is estimated to be ~1%. The PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus

Erythematosus) Study consisted of a prospective cohort of 385 pregnant patients with SLE and evaluated adverse pregnancy outcomes and pregnancy-related flare rates. It demonstrated that 19% of patients had an adverse pregnancy outcome: fetal death in 4%, neonatal death in 1%, preterm delivery in 9%, and small for gestational age (SGA) infants in 10%. Independent predictors of adverse pregnancy outcomes included the presence of a lupus anticoagulant, a physician global assessment of disease activity score > 1, antihypertensive use, and platelet count $< 100 \times 10^3/\mu L$.

Lupus activity during the last year before conception is a good predictor of fetal outcomes. For example, miscarriages are best predicted by the amount of steroids taken in the year before conception, stillbirths are predicted by the number of SLE flares in the year before conception, and preterm births are predicted by the existence of both antiphospholipid antibody syndrome (APS) and anti–double-stranded DNA antibody levels before conception. Complete congenital heart block is a severe manifestation of neonatal lupus, with an incidence of 1% to 2% after exposure to SSA/Ro and/or SSB/La antibodies. This incidence increases to 20% if there is a maternal history of previous delivery of an infant with neonatal lupus. Therefore, anti-Ro (SSA) and anti-LA (SSB) antibodies should be screened for in pregnant patients with SLE.

Antiphospholipid antibodies may be present in up to one-quarter of SLE pregnancies. APS is associated with pregnancy complications, including fetal loss and increased relative risk for preeclampsia. During the initial pregnancy evaluation in women with SLE, screening is recommended to determine whether these antibodies are present. The mainstay of APS management is anticoagulation using either unfractionated heparin or low-molecular-weight heparin during pregnancy. Risk for thrombotic events is increased in pregnancy, both because pregnancy is a hypercoagulable state and because of obstruction of venous return by the enlarged uterus. In addition, women with glomerular disease may experience worsening proteinuria and may commonly reach nephrotic-range values, which have been associated with increased risks for thrombotic events. Therefore, anticoagulation is indicated for all patients with SLE who have antiphospholipid antibodies and a history of thrombotic event(s) and for those lacking a history of thrombotic event(s), but who meet obstetric criteria for APS, such as 3 or more pregnancy losses, or a late pregnancy loss.

The safety profiles of immunosuppression during pregnancy, including steroid use, are presented in Table 1. Hydroxychloroquine therapy should be continued throughout pregnancy to maintain quiescence of lupus nephritis and decrease the risk for systemic flares. Discontinuation of hydroxychloroquine therapy has been associated with increased lupus activity and flares during pregnancy, requiring higher steroid doses to control symptoms.

Table 1. Immunosuppression Therapy in Pregnancy

Drug	Adverse Effects During Pregnancy
Safe	
Hydroxychloroquine	No known risk for teratogenicity; withdrawal may cause flare
Glucocorticoids	Risk for gestational diabetes; risk for cleft lip and palate; risk for premature rupture of membranes
Azathioprine	No known risk for teratogenicity
Cyclosporine	Increased risk for cholestasis
Tacrolimus	Risk for gestational diabetes and hypertension
Hazardous	
Cyclophosphamide	Fetal malformations, higher rates of pregnancy loss
Mycophenolate mofetil	Teratogenic (lip, palate, ear abnormalities), higher rates of pregnancy loss
Unknown	
Rituximab	Transient fetal B-cell depletion

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Atypical HUS

aHUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and decreased kidney function as a result of uncontrolled complement activation. Unlike classic HUS, which is triggered by diarrheal illness, aHUS may be triggered by any process that activates the alternative complement pathway. Pregnancy is a classic example of a condition that can trigger aHUS, and many women may have this condition diagnosed, especially in the postpartum period. A retrospective cohort study of 100 patients with aHUS reported that 21 women developed aHUS in association with pregnancy, with complement abnormalities detected in 85.7% ($n = 18$). These patients were at elevated risk for fetal loss and preeclampsia, and 76% had reached end-stage renal disease (ESRD) by last follow-up.

The diagnosis of pregnancy-associated aHUS may be difficult. Several conditions may be associated with

AKI, microangiopathic hemolytic anemia, and thrombocytopenia, including aHUS, thrombotic thrombocytopenic purpura (TTP), and severe preeclampsia with HELLP syndrome. TTP presents most commonly in the third trimester, whereas aHUS presents in the postpartum period. When one of these conditions is suspected, plasma exchange should be started while awaiting ADAMTS13 (von Willebrand factor protease) activity results (<10% is associated with TTP). If ADAMTS13 activity is normal and aHUS is suspected, eculizumab treatment should be initiated. The prognosis for this condition before the use of eculizumab was poor and associated with high morbidity and mortality rates. There are only a few reports about the use of eculizumab in pregnancy-associated aHUS, and all of them show promising results. A recent retrospective cohort of 22 patients with pregnancy-associated aHUS found that 16 patients presented during their first pregnancies and 9 patients required dialysis at the time of presentation. Seventeen patients were treated with plasmapheresis, with a renal response in only 3, whereas all 10 women who received eculizumab had a favorable outcome. Eculizumab is therefore becoming the preferred therapy for pregnancy-associated aHUS.

Based on recent work, it appears that mutations in the genes encoding for complement regulatory proteins may enhance the risk for preeclampsia in other disease entities, such as SLE and/or antiphospholipid antibodies. Considering the overlap in disease processes and lack of a single diagnostic test to clearly identify one process from another, studying complement disorders in these different groups is challenging. One small study (n = 11 women) suggested that ~36% of patients who develop HELLP syndrome during pregnancy may have complement abnormalities. Research is ongoing in this area.

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Immunoglobulin A Nephropathy

Immunolobulin A (IgA) nephropathy is often diagnosed in the second and third decades of life and thus affects many women of child-bearing age. Several studies have evaluated pregnancy outcomes in women with IgA nephropathy, and the overall body of evidence suggests that pregnancy does not affect long-term kidney function, although the majority of the included women had mild disease (CKD stages 1 and 2). A systematic review and meta-analysis included 4 studies that evaluated pregnancy outcomes in IgA nephropathy and found that pregnancy did not increase the risk for adverse renal events (defined as doubling of Scr level, 50% decline in estimated GFR, or ESRD). However, there was a high risk for pregnancy complications, including pregnancy loss (12.2%; 95% CI, 7.4%-19.4%), preterm delivery (8.5%; 95% CI, 5.9%-12.1%), low birth weight (9.5%; 95% CI, 6.7%-13.3%), and preeclampsia/eclampsia (7.3%; 95% CI, 4.9%-10.6%). A recent study showed that in women with IgA nephropathy, pregnancy did not increase the risk for adverse renal events. However, women with hypertension, baseline estimated GFR < 60 mL/min/1.73 m^2, or proteinuria with protein excretion > 1 g/d had significantly higher risk for kidney disease progression.

Most patients with mild, stable, or slowly progressive IgA nephropathy do not receive immunosuppressive treatment. In most cases, angiotensin-converting enzyme (ACE) inhibitor treatment should be discontinued before pregnancy and immunosuppressive agents should be reviewed and switched to pregnancy-safe alternatives, ideally before conception or at the first sign of pregnancy to minimize risk to the fetus. Steroids can be used in pregnancy if immunosuppression is needed for more active disease.

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Diabetic Nephropathy

Diabetic nephropathy is characterized by a slowly progressive course, with the gradual development of hypertension, albuminuria, and loss of GFR. Diabetic nephropathy is present in 6% of pregnant women with type 1 DM. Type 2 DM and associated nephropathy are less common among women of child-bearing age. Similar to other glomerular diseases, the risk for pregnancy complications in young women with type 1 DM is related to the degree of prepregnancy decrease in kidney function. The risk for deterioration in kidney function and progression to ESRD as a consequence of

pregnancy is highest in women with Scr levels > 1.4 mg/dL.

ACE inhibitors and angiotensin receptor blockers are contraindicated in pregnancy, but 3 to 6 months of therapy before conceiving may have renal protective effects. In the absence of renin-angiotensin-aldosterone system blockade and under the physiologic conditions of pregnancy, urinary albumin excretion may increase substantially during the course of pregnancy in women with diabetic nephropathy. In one study of 12 women with pregestational moderately increased albuminuria, defined as urinary albumin excretion between 30 and 300 mg/d, urinary albumin excretion increased on average 7-fold, with several women exceeding 3 g/d. All women returned to their prior baselines by 12 weeks postpartum. This increase in albuminuria, as noted previously, can complicate the diagnosis of preeclampsia in the absence of other severe features (extreme elevations of BP, thrombocytopenia, neurologic symptoms, etc). Women with type 1 DM are at increased risk for preeclampsia irrespective of the baseline proteinuria, with as many as two-thirds of women with diabetic nephropathy developing preeclampsia in some studies. Available evidence does not show that aspirin decreases the risk for preeclampsia specifically in women with type 1 DM, though it may be reasonable as preeclampsia prophylaxis given the theoretical benefit and overall low risk for harm.

In addition to the risk for preeclampsia, women with DM are at increased risk for other pregnancy complications, such as miscarriage, congenital malformations, preterm delivery, macrosomia, and perinatal mortality. Prepregnancy counseling is critical so that women can understand the risks and optimize their chances of having a successful pregnancy. Tighter glycemic control for at least 6 months before conceiving is associated with improved outcomes, and the American Diabetes Association recommends targeting a hemoglobin A_{1c} goal of <6.5% while watching carefully for hypoglycemia. Insulin is the mainstay of therapy, though oral hypoglycemics such as metformin and glyburide may be continued in some women with pregestational type 2 DM and excellent glycemic control.

Some women with diabetic retinopathy may have worsening in the setting of pregnancy. A baseline ophthalmic examination before pregnancy is needed in all women with DM. Women with moderate to severe retinopathy at the time of conception may need more careful monitoring and even intervention in pregnancy. This is particularly relevant for women with high hemoglobin A_{1c} levels at the beginning of pregnancy because rapid improvement in glycemic control in early pregnancy has been associated with worsening of retinopathy.

Given the complexities of care in women with diabetes, a multidisciplinary approach with endocrinology, nephrology, and obstetrics is likely to achieve the best pregnancy outcomes.

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Nephrotic Syndrome in Pregnancy

Case 3: *A 25-year-old pregnant woman presented with new-onset proteinuria, with protein excretion up to 7 g/d, and hypertension at the time of delivery, consistent with preeclampsia. Postpartum, the proteinuria persisted, and at 6 months after delivery, protein excretion exceeded 2 g/d. Serum albumin and lipid profile levels were within reference ranges, and she had negative results from serologic evaluation. She had normal body mass index, was a nonsmoker, and had previously been normotensive. Kidney biopsy was performed.*

Question 3: Which one of the following renal lesions has been most commonly associated with a history of preeclampsia?

a) Minimal change disease
b) Membranous nephropathy
c) Focal segmental glomerulosclerosis (FSGS)
d) Amyloidosis

For answer, see Appendix.

It can be difficult to differentiate intrinsic kidney disease causing nephrotic syndrome from preeclampsia, particularly after 20 weeks of gestation. Preeclampsia may cause heavy proteinuria and edema, and hypoalbuminemia is often present. If one is considering the new diagnosis of nephrotic syndrome in pregnancy, particularly before 20 weeks' gestation, kidney biopsy can be safely performed to determine whether immunosuppression is needed. A recent case series of 19 women with nephrotic syndrome in pregnancy found that the average gestational age at presentation was 18 weeks. Kidney biopsies were performed in 8 women and resulted in a change of management in 6 cases. Of the 26 pregnancies in the cohort, 7 were complicated by preeclampsia; 6, by AKI; 2, by premature rupture of membranes; and 3, by cellulitis. There were 14 infants with low birth weight (<2,500 g) and 8 required a neonatal intensive care unit admission.

In the setting of massive proteinuria and hypoalbuminemia (albumin < 2 mg/dL), women may be at risk for thrombosis, and anticoagulation therapy should be strongly considered (Fig 3).

Focal segmental glomerular sclerosis (FSGS) is a pathologic pattern that can be due to either primary or secondary causes. Primary FSGS is typically characterized by diffuse foot-process effacement (>80%), whereas secondary FSGS will have moderate foot-process effacement. Primary FSGS will present with an acute or subacute onset of nephrotic syndrome, as opposed to secondary FSGS, which often presents with non–nephrotic-range proteinuria and decreased kidney function. Glucocorticoids and/or calcineurin inhibitors can be safely used for primary FSGS in pregnancy.

Minimal change disease is another common cause of nephrotic syndrome, but it is rare in pregnancy. The management of minimal change disease in pregnancy should include antihypertensive therapy and glucocorticoids. Diuretics can be used judiciously. There is a theoretical concern of causing intravascular volume depletion with excessive diuretic use that can worsen and/or contribute to systemic vasoconstriction and placental hypoperfusion in preeclampsia. Although salt restriction does not seem to protect against preeclampsia, the authors recommend that women with nephrotic syndrome limit their fluid intake and adhere to a low-salt diet. Similar to FSGS, women with a pre-existing diagnosis of minimal change disease should be in clinical remission before conceiving. Patients with relapsing disease desiring to become pregnant can be safely treated with azathioprine (AZA) or calcineurin inhibitors.

Membranous nephropathy in women of child-bearing age is most often secondary to other diseases, such as SLE, drug exposure (in particular, nonsteroidal anti-inflammatory drugs or biologic agents), hepatitis B or hepatitis C virus infection, syphilis, or less commonly, malignancy, but can also be primary in some cases. Pregnancy presents therapeutic challenges for this disease because ACE inhibitors, lipid-lowering therapy, warfarin, and cyclophosphamide are contraindicated. Prednisone and calcineurin inhibitors can be used.

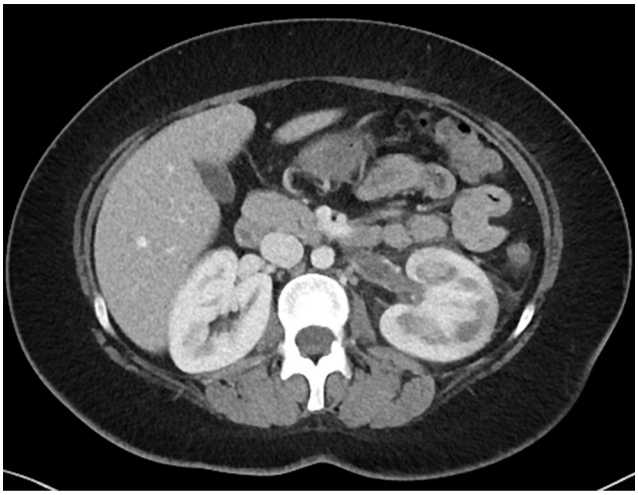

Figure 3. Computed tomographic image from a young woman with a history of human immunodeficiency virus (HIV)-associated nephropathy who developed heavy proteinuria (protein excretion, 11 g/d) at the time of delivery and developed acute left-sided renal vein thrombosis 5 weeks postpartum.

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CKD in Pregnancy

Women with CKD, compared with pregnant women with no CKD, are at increased risk for adverse maternal and fetal events, including preeclampsia, preterm delivery, low birth weight, and an increase in overall mortality (Box 3). Women with advanced CKD may also have a deterioration in kidney function. In a classic study by Jones and Hayslett of 67 women (with 82 pregnancies) with Scr levels ≥ 1.4 mg/dL in pregnancy, 51% of women had no change in GFR as a result of pregnancy, but 31% had a decline in kidney function that persisted 6 months postpartum. Women with antepartum Scr levels > 2.0 mg/dL were at particularly high risk for losing kidney function as a consequence of pregnancy.

A meta-analysis published in 2015 evaluated both the effect of kidney disease on pregnancy outcomes and the effect of pregnancy on kidney outcomes. The authors reviewed 23 observational studies, which included data for 506,340 pregnancies in women with

Box 3. Adverse Perinatal Outcomes in Women With CKD

Maternal adverse events
- Deterioration in kidney function
- Flare of underlying disease
- Preeclampsia
- HELLP syndrome[a]
- Complications from immunosuppression
- Preterm delivery

Fetal adverse events
- Miscarriages
- Stillbirths
- Neonatal death
- Preterm births
- Small for gestational age infants
- Low birth weight

Abbreviations: CKD, chronic kidney disease; HELLP, hemolysis, elevated liver enzymes, and low platelets.
[a]Defined as microangiopathic hemolytic anemia with schistocytes, elevated bilirubin ≥ 1.2 mg/dL, elevated aspartate aminotransferase twice the upper limit of normal, and low platelet count (<100 × 10^3/μL).

CKD, excluding women with SLE, hereditary kidney diseases, kidney transplants, ESRD, AKI, or a solitary kidney. They found that women with CKD had increased odds of developing preeclampsia (odds ratio [OR], 10.36; 95% CI, 6.28-17.09), premature delivery (OR, 5.72; 95% CI, 3.26-10.03), SGA infants (OR, 4.85; 95% CI, 3.03-7.76), and failure of pregnancy, including stillbirth and fetal and neonatal deaths (OR, 1.80; 95% CI, 1.03-3.13). The second aim of this study was to evaluate the effect of pregnancy on CKD progression. There were 216 renal events (defined as doubling of Scr, 50% decrease in estimated GFR or creatinine clearance, or ESRD) in 1,268 participants included in the various studies analyzed in this meta-analysis. However, most women had only mild CKD with near-normal Scr levels and moderately increased albuminuria.

Women with CKD who are contemplating pregnancy, given these risks, should be evaluated by a high-risk obstetrician and nephrologist before pursuing pregnancy, when possible. They should receive extensive counseling regarding the risks particular to their disease processes and kidney function. Women with milder CKD (Scr < 1.4 mg/dL) may expect to have good maternal and fetal outcomes, whereas women with advanced disease (Scr, 1.4-2.9 mg/dL) are at high risk for pregnancy complications. Women with Scr values ≥ 3.0 mg/dL may permanently lose kidney function with pregnancy. The underlying disease, such as DM or lupus nephritis, may impose additional disease-specific risks, as is discussed in more detail in the preceding sections. Although risks for growth restriction, preterm delivery, and SGA infants still exist, infant survival has improved over the last 2 decades, likely owing to advances in neonatal care.

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ESRD in Pregnancy

By the time a woman requires dialysis therapy, her fertility is significantly diminished and she may have erratic and/or absent menstrual cycles. However, pregnancy still occurs, particularly in women during their first year of dialysis therapy and those receiving intensive therapy, such as daily nocturnal dialysis. The diagnosis of pregnancy may be delayed in dialysis patients due to irregular menstrual periods. Serum human chorionic gonadotropin levels can be used to diagnose pregnancy in patients with minimal urinary output. Mild elevations in human chorionic gonadotropin levels can be seen in the absence of pregnancy in patients with ESRD, but significant elevations with appropriate doubling of values every 48 to 72 hours are indicative of true pregnancy. Ultrasonography should be used as a confirmatory test.

Recent data have suggested that dialysis patients can have positive maternal and fetal outcomes if intensive dialysis therapy is instituted in an effort to maintain a near-normal serum urea nitrogen level. Although a goal of 36 hours per week is ideal, in practice this may be difficult to accomplish. Therefore, more than 20 hours per week, with a serum urea nitrogen target < 50 mg/dL, is a more viable goal. Providers may also take into account the amount of residual kidney function when writing a dialysis prescription for a pregnant patient. A recent systematic review and meta-analysis from studies published between 2000 and 2008 evaluated 574 pregnancies in 543 patients on dialysis therapy. Results showed that maternal perinatal mortality was very low (0.4%). A trend toward better outcomes with increased frequency and length of dialysis sessions was observed.

Fetal outcomes have also improved over time, with an increase in fetal survival in patients receiving high-efficiency dialysis treatments. However, some studies have shown that early mortality in the perinatal period remains high, while the incidence of preterm delivery can reach 80%. It has been shown that a successful pregnancy is possible in those undergoing peritoneal dialysis or hemodialysis, but the prevalence of SGA babies has been shown to be higher in mothers receiving peritoneal dialysis compared with those receiving hemodialysis (66% vs 31%, respectively).

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Kidney Transplant Recipients/Donors and Pregnancy

Women with advanced kidney disease are often encouraged to wait until after successful kidney transplantation to pursue pregnancy. The rationale behind this recommendation is that fertility is improved after transplantation and risks for pregnancy complications, such as preterm delivery and preeclampsia, are much lower. Pregnancy is also a sensitizing event, which can

result in the formation of anti-HLA antibodies that may make finding a future suitable donor more difficult. Recommendations from the current KDIGO (Kidney Disease: Improving Global Outcomes) guidelines state that women should wait for 1 year posttransplantation before pursuing pregnancy, provided kidney function is stable. However, a more recent study suggested that waiting 2 years may be prudent to reduce the risk for allograft failure.

There have been several single-center studies that have evaluated the impact of pregnancy on graft survival, but it has been difficult to draw firm conclusions from these results given methodologic differences, including different eras, study populations, immunosuppressive agents, and control groups. A meta-analysis published in 2011 combined results of 50 different studies that reported pregnancy-related outcomes in kidney transplant recipients. There were more than 4,700 pregnancies in 3,570 kidney transplant recipients. They found that the live birth rate was similar to that for the general population (73.5% vs 66.7%), but rates of preeclampsia (27% vs 3.8%), gestational diabetes (8% vs 3.9%), and preterm delivery (45.6% vs 12.5%) were much higher. Risk for graft loss in the cohorts was low (5.8% at 1 year and 6.9% at 5 years).

Women with kidney transplants require close monitoring in pregnancy by both obstetricians and nephrologists. The immunosuppressive regimen needs to be modified to medications that are safe in pregnancy, usually a combination of AZA, tacrolimus/cyclosporine, and prednisone. Tacrolimus doses often need to be increased substantially in pregnancy, though recent pharmacologic studies have shown that whole-blood measurements of tacrolimus do not accurately reflect free tacrolimus levels in the setting of pregnancy, meaning that women may experience toxicity with seemingly therapeutic levels.

Kidney donors may also have a need for more careful monitoring in pregnancy, given increased risk for preeclampsia that has been reported in several observational studies. A study by Garg et al published in 2015 suggested that kidney donors had 2.4 times increased odds of having preeclampsia or gestational hypertension (11% vs 5%), but did not have increased risk for preterm delivery or low birth weight.

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Medications in Pregnancy

Treatment with ACE inhibitors and angiotensin receptor blockers should be discontinued before pregnancy because of their teratogenicity in favor of safe alternative(s), such as methyldopa, labetalol, or nifedipine.

Anticoagulation may be required in the setting of severe nephrotic syndrome, APS, or other thrombophilic conditions. Warfarin is contraindicated in pregnancy due to its teratogenicity, but low-molecular-weight heparin or unfractionated heparin administered as a subcutaneous injection can safely be given. Novel oral anticoagulants are increasingly used. They are known to cross the placenta; however, available data about maternal and fetal outcomes are insufficient to conclude the risk associated with their use during pregnancy, mainly due to the limited number of reported outcomes after exposure.

Glucocorticoids remain the mainstay of immunosuppressive therapy for many glomerulonephritides (Table 1). Prednisone is considered safe during pregnancy due to placental metabolism, with <10% of the maternal dose found in the fetal circulation. Calcineurin inhibitors (ie, cyclosporine and tacrolimus) also are known to induce hypertension and gestational diabetes. The majority of the data regarding their side effects have been obtained from transplant registries, with just a few small case series evaluating their side effects in the context of lupus nephritis. The calcineurin inhibitors have not been associated with teratogenic effects. Cyclophosphamide and mycophenolate mofetil are teratogenic and treatment should be discontinued before conception when possible, or immediately after a pregnancy diagnosis is made in the event of an unexpected pregnancy. AZA is the drug of choice for pregnant patients previously using mycophenolate mofetil who require continuation of immunosuppressive therapy. AZA treatment ideally should be started 3 months before conception. Despite being considered safe to use during pregnancy, calcineurin inhibitors and AZA have been associated with SGA infants and preterm deliveries. Rituximab may be used during pregnancy as part of a chemotherapy regimen for treatment of incident or recurrent malignancies or severe nonmalignant hematologic diseases. Although it is considered safe to administer during the first trimester, neonatal B-cell depletion has been seen in those who have been exposed in utero during the third trimester of pregnancy. Long-term outcomes of rituximab use during pregnancy are not known.

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Conclusions

Exacerbations of preexisting kidney disease or an incident diagnosis of nephropathy during pregnancy are relatively common. It is important to be familiar with the diagnoses and management of kidney disorders during pregnancy. Close monitoring and awareness of possible complications will allow for earlier intervention with the aim of improving maternal and fetal outcomes.

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Support: Dr Garovic is supported by award number P50AG44170 from the National Institute on Aging.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received February 15, 2018, in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form June 1, 2018.

APPENDIX

Answer to Question 1: (a) This patient presented with severe hypertension and at least one of the features of severe preeclampsia: platelet count of $92 \times 10^3/\mu L$. Serum creatinine (Scr) level was also elevated, but there was no baseline for comparison. She did not present with proteinuria. During the next few days of her hospitalization, thrombocytopenia worsened to a platelet count of $80 \times 10^3/\mu L$, 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.

Answer to Question 2: (d) This patient presented with severe preeclampsia in the setting of chronic hypertension. She had kidney injury with an elevated Scr level on presentation, likely due to severe preeclampsia. HELLP (hemolysis, elevated liver function test results, low platelet count) syndrome, a severe form of preeclampsia, is commonly associated with kidney injury. Kidney biopsy frequently demonstrates glomerular endotheliosis and thrombotic microangiopathy. This patient developed disseminated intravascular coagulation in the setting of placental abruption and became acutely hypotensive due to blood loss. She subsequent developed acute cortical necrosis, shown here on light microscopy (Fig 1). Pregnant women are particularly susceptible to acute cortical necrosis in the setting of hypotension.

Answer to Question 3: (c) The patient's kidney biopsy showed focal segmental glomerulosclerosis (FSGS) with perihilar variant and mild to moderate glomerulomegaly, consistent with secondary FSGS. Although preeclampsia is classically characterized by glomerular endotheliosis and thrombotic microangiopathy in the acute setting, several studies have shown FSGS lesions in women with a history of preeclampsia and proteinuria that persists months to years postpartum.

Update

American Journal of Kidney Diseases
Volume 73, Issue 6, June 2019, Page 897

DOI: https://doi.org/10.1053/j.ajkd.2019.02.005

Erratum Regarding "Comparing Newer GFR Estimating Equations Using Creatinine and Cystatin C to the CKD-EPI Equation in Adults" (*Am J Kidney Dis*. 2017;70[4]:587-589)

In the Research Letter entitled "Comparing Newer GFR Estimating Equations Using Creatinine and Cystatin C to the CKD-EPI Equation in Adults" that appeared in the October 2017 issue of *AJKD* (Levey et al, volume 70, issue 4, pages 587-589), there was an error in the number of participants given for the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine validation database. As discussed in a 2011 correction in *Annals of Internal Medicine* (https://dx.doi.org/10.7326/0003-4819-155-6-201109200-00024), the number of participants is 3,771, not 3,896. Using the correct number of participants to compare eGFR equations leads to changes in values shown in the top half of Figure 1, which lists results for the CKD-EPI, Lund-Malmo Revised (LMR), and Full-Age Spectrum (FAS) equations. A corrected version of Figure 1 is supplied herein.

The comparisons of the LMR equation with the CKD-EPI equation are not substantially changed. The comparison of the FAS equation with the CKD-EPI equation shows similar performance in all 4 metrics, rather than significantly worse performance in IQR and $1 - P_{30}$. Of note, the point estimates for IQR and $1 - P_{30}$ remain higher for FAS than for CKD-EPI. Thus, the error does not alter the conclusions of the study. The newer equations are not more accurate than the CKD-EPI equations in adults.

Equation	Bias: Median Difference (mL/min/1.73 m^2)	Precision: IQR of Differences (mL/min/1.73 m^2)	Accuracy: 1 – P_{30} (%)	Accuracy: RMSE
Performance of Creatinine Equations in Creatinine Validation Database (n=3,771)				
CKD-EPI	2.3 (1.9, 2.7)	17.1 (16.4, 17.8)	16.0 (14.8, 17.1)	0.251 (0.241, 0.260)
LMR	**7.6 (7.2, 8.2)**	**18.6 (17.9, 19.7)**	**20.5 (19.2, 21.8)**	**0.281 (0.273, 0.290)**
FAS	1.5 (1.1, 2.0)	18.3 (17.7, 19.1)	18.2 (17.0, 19.4)	0.262 (0.253, 0.271)
Performance of Cystatin C Equations in Cystatin C Validation Database (n=1,119)				
CKD-EPI	3.4 (2.3, 4.4)	16.4 (14.8, 17.7)	14.1 (12.1, 16.2)	0.234 (0.220, 0.250)
CAPA	3.8 (2.7, 4.9)	18.2 (16.6, 19.6)	16.3 (14.1, 18.4)	0.247 (0.233, 0.264)
FAS	**0.2 (–0.8, 1.4)**	**20.5 (18.6, 21.6)**	**23.9 (21.4, 26.5)**	**0.288 (0.270, 0.310)**

Figure 1. Performance of GFR estimating equations in Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) validation databases. Bias is assessed as the median difference between measured and estimated GFR (mGFR − eGFR). A positive value indicates that eGFR is an underestimate of mGFR. Precision is assessed as the interquartile range (IQR) of the difference between mGFR and eGFR; a larger value indicates lesser precision. Accuracy is influenced by both bias and precision. Accuracy is assessed as the percentage of large errors ($1 - P_{30}$, the percentage of participants for whom the difference between eGFR and mGFR is >30% of mGFR) and root mean square error (RMSE, the standard deviation of differences between mGFR and eGFR; on the log scale, it approximates the standard deviation of the percent error in estimation). Larger values indicate lesser accuracy. Values in parenthesis are 95% confidence intervals, which were calculated by bootstrap methods (2,000 bootstraps) for median difference, IQR of the differences, and RMSE, and by the binomial method for P_{30}. Bold indicates nonoverlapping confidence intervals compared to CKD-EPI. This method is more conservative than identifying differences with $P < 0.05$, which we think is more appropriate given the large sample size and multiple hypothesis tests. Green and red highlighting indicates better or worse performance, respectively, compared to CKD-EPI. Analyses were computed using SAS Enterprise Guide (version 7.12).

Erratum Regarding "Renal Disorders in Pregnancy: Core Curriculum 2019" (*Am J Kidney Dis*. 2019;73[1]:119-130)

In the Core Curriculum article entitled "Renal Disorders in Pregnancy: Core Curriculum 2019" that appeared in the January 2019 issue of *AJKD* (Gonzalez Suarez et al, volume 73, issue 1, pages 119-130), an editing error led to the abbreviation for placental growth factor being listed as "PIGF" instead of "PlGF." This abbreviation has been corrected in the HTML and PDF versions of this article as of March 20, 2019.