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A. Eric Anderson and Sophia M. Rothberger Lannon

Case 1

A 23-year-old G1P0000 without prior past medical history is 31 weeks pregnant with prenatal care presents with complaints of worsening leg and face swelling for the past 2 days now seeks care because of headache, diarrhea, nausea, and vomiting. On exam she is found to have a blood pressure of 120/86, edema, and brisk deep tendon reflexes. Laboratory testing revealed hemoglobin 11.3 g/dl, platelet count 141,000/µl white blood count 18,000/µl, creatinine 1.1 mg/dl, aspartate aminotransferases (AST) 65 U/l, lactate dehydrogenase (LDH) 400 U/l, total bilirubin 1.1 mg/dl, prothrombin time (PT) 14.7 s, ammonia of 90 mcg/dl, blood glucose 139 mg/dl, calcium 7.3 mg/dl, and uric acid of 6.0 mg/dl. The urinalysis demonstrated WBC's 3–5/hpf, RBC's 3–5/hpf—non-dysmorphic, renal tubular epithelial cells were seen and a urine protein to creatinine ratio of 2. One day after hospitalization the patient's blood pressure was 145/87 with a similar blood pressure 6 h later.

A.E. Anderson, M.D. (✉)
Outpatient, General Nephrology Clinic, Department of Medicine, University of Washington Medical Center, 1959 NE Pacific St., Seattle, WA 98195, USA
e-mail: iamerica@u.washington.edu

S.M.R. Lannon, M.D., M.P.H.
Department of Obstetrics & Gynecology, University of Washington, Seattle, WA 98195, USA

Case 2

A 38-year-old G4P2022 at 32 weeks gestational age who presents to clinic for her scheduled prenatal visit, and her blood pressure is found to be 147/92. Urine dip was negative for protein. She returned the following day with a 24 h urine collection which was negative for proteinuria again and her blood pressure was 156/94. She denied headache, vision changes, abdominal pain, or peripheral edema. Laboratory testing revealed hemoglobin 10 g/dl, platelet count 79,000, white blood count 13,270, creatinine 1.9 mg/dl, AST 92 U/l, and alanine aminotransferases (ALT) 120 U/l, and LDH of 672 U/l. A peripheral smear was significant for moderate shistocytes. The patient was admitted and given antenatal corticosteroids for fetal lung development in anticipation of preterm delivery. On hospital day 3, the patient developed severe right upper quadrant (RUQ) pain. Laboratory values were repeated and revealed hemoglobin 10.5 g/dl platelet count 85,000, white blood count 11,360, creatinine 1.8 mg/dl, AST 94, and ALT 98.

Introduction

Kidney injury in pregnancy is not a rare phenomenon. However, kidney injury reaching the level to warrant nephrology involvement is. The cases of patients with preexisting kidney disease prior to pregnancy differs in the differential diagnosis

from new onset kidney disease that develops because of pregnancy. The focus of this chapter is to review the evaluation of new onset kidney injury as a result of pregnancy. This chapter does not attempt to review the newly diagnosed patient with kidney disease that may be discovered during pregnancy, that in and of itself is not thought related to pregnancy. When kidney involvement occurs, from proteinuria alone to elevation of creatinine, pathologic systemic changes related to the fetal-placenta interaction provokes the obstetric provider to heighten their level of concern for the maturing fetus and the welfare of the mother. While the diagnosis of preeclampsia is easily the first consideration given how common it is, a broaden differential is employed. Before doing so, a discussion of kidney physiology during pregnancy is prudent as well as a review of the diagnostic tools used in kidney function assessment during pregnancy.

Kidney-Related Physiology During Pregnancy

Glomerular filtration rate (GFR) increases during pregnancy beginning in the first trimester after 6 weeks, the GFR increases [1]. This is before there is an increased placental blood supply or a decreased serum albumin and hence a lower glomerular oncotic capillary pressure that can explain this consequence. GFR continues to increase throughout pregnancy and a lower serum creatinine is evidence of this. A rise in serum creatinine will raise the suspicion of potentially dire systemic concerns. There are other physiologic perturbations that have accompanying laboratory changes seen during normal pregnancy that are shown in Table 48.1. This is not intended to be all-inclusive but present labs more germane to this review.

Anatomic changes in ureteral contraction and stasis from the gravid uterus will cause an anatomic anomaly that is normal in pregnancy with the ultrasound of the kidneys revealing hydronephrosis.

The plasma volume, cardiac output (CO), and GFR increase by 30–50% during pregnancy [1]. Additionally, the mean arterial pressure (MAP) decreases during pregnancy. This is related to the

Table 48.1 Laboratory changes in normal pregnancy

	First trimester	Third trimester
Albumin	↓	↓
Fibrinogen	↑	↑
PT	Normal [2]	Normal [2]
AST/ALT	Normal or slight ↓	Normal or slight ↓
Total bilirubin	Normal or slight ↓	Normal or slight ↓
Creatinine	↓	↓
Sodium	↓	↓
Uric acid	↓	Normal or slight ↓
GFR	↑	↑

Adapted from Creasy RK, Resnik R et al. Maternal-fetal medicine: principles and practice. 6th ed. Philadelphia, PA: Saunders/Elsevier; 2009

physics of an increased diversion of plasma volume through the uterus an organ that is in parallel with the other organs, so systemic vascular resistance (SVR) decreases. These hemodynamic changes of lower MAP, higher CO, and lower SVR occur beginning at 6 weeks [1]. Other reasons for decreased SVR and blood pressure are attributed to hormones such as relaxin.

Kidney Function Testing

Practically assessing GFR during pregnancy has all the flaws as in the non-obstetric realm but has the added nuisances of increased GFR and urinary stasis. The best test was discerned by comparing inulin versus 24 h creatinine clearance as well as using the modification of diet in renal disease (MDRD) formula in healthy pregnant women and women with preeclampsia or chronic kidney disease (CKD) [3]. In healthy pregnant women the 24 h creatinine clearance was better than the MDRD by 40 cc/min. In women with preeclampsia or prior CKD the MDRD underestimated the GFR in both by 25 cc/min. Because the GFRs were >60 the MDRD formula loses its' integrity in this population. Following serum creatinines is certainly useful, but the absence of changes in creatinine may not be indicative of

true GFR changes and so 24 h urine collections may be instructive.

Estimating proteinuria during pregnancy also has its limitations as in the non-obstetric world. If one assumes the urine protein to creatinine ratio (PCR) is expected to hold in pregnancy, it is useful for quantification for diagnosis of preeclampsia and monitor preexisting kidney disease. Urine dipsticks routinely have high rates of false positives and negatives compared to 24 h urines and do not take into consideration the specific gravity in the guidelines when assessing proteinuria such as in preeclampsia. Most nephrologists do not speak in terms of urine protein dipsticks. However, urinary stasis complicates the utility of the urine PCR. There is sufficient data in the literature that demonstrates that the spot urine PCR has been shown to correlate well with 24 h urine collections [4, 5]. Certainly, if the cutoff value is questionable, a 24 h urine collection for creatinine and protein should be done.

Acute Kidney Disease Resulting from Pregnancy

The evaluation schema for this differential diagnosis is similar to the nonpregnant patient but with diagnoses that are only related to the pregnant condition (Table 48.2). Most kidney injury associated with increased creatinine is related to

Table 48.2 Pregnancy-associated kidney injury

Prenal
Anatomic—none
Physiologic
Hyperemesis gravidarium
Obstetrical hemorrhage
Abruptio placentae
Postpartum
Liver Failure
AFLP
Intrahepatic cholestasis
Viral hepatitis
Cardiomyopathy
Milk alkali syndrome
Post-renal
Gravid uterus and ureteral obstruction

(continued)

Table 48. 2 Continued

Postpartum surgical clips of ureters
Nephrolithiasis
Intrinsic
Glomerular
Nephrotic
Preeclampsia/HEELP
Nephritic
PIGN
Tubular—Acute tubular necrosis
Ischemic
Cortical necrosis
Protracted volume depletion
Sepsis/SIRS
Septic abortion
Puerperal
Chorioamionitis
Endometritis
Pyelonephritis
Toxins
Endogenous
Rhabdomyolysis
Cocaine
Methamphetamine
Baking soda
CPT deficiency
Uric Acid
Sickle cell disease/trait
Exogenous
Tocolytics
NSAIDS
Interstitial nephritis
Vascular
TTP/HUS

Abbreviations: *AFLP* acute fatty liver of pregnancy, *HELLP* hemolysis elevated liver enzymes low platelets, *PIGN* post-infectious glomerular nephritis, *SIRS* systemic inflammatory response syndrome, *CPT* carnitine palmitoyl transferase, *TTP/HUS* thrombotic thrombocytopenia purpura/hemolytic uremic syndrome

hypovolemia or hemorrhage. Most kidney injury with proteinuria is related to preeclampsia. With both of these presentations, nephrology involvement is rare. The obstetric provider will manage these scenarios without the need for specialized consultation. Additionally, the nephrologist may not be as aware of the other obstetric pathologic diseases that involve the kidney.

Prerenal

Hyperemesis Gravidarium

Prerenal causes of kidney disease during pregnancy are mainly of the physiologic type as opposed to anatomical causes, i.e. renal artery stenosis. Prerenal kidney disease is defined as reversible hypoperfusion where the kidney injury recovers after the underlying problem is reversed within 24–48 h. Examples of this would be volume resuscitation in the setting of hyperemesis gravidarium (HG). HG is severe nausea and vomiting beginning ≤12 weeks of gestation, ketonuria, and >5% loss of pre-pregnancy body weight without a known cause. It tends to improve in the later part of pregnancy but may persist up until delivery. The etiology of this is not well elucidated. Patients develop severe volume depletion potentially leading to kidney injury. An increase in transaminases is seen in up to 50% of cases. They are usually elevated from 2 to 10 times the upper limit of normal.

Obstetrical Hemorrhage

Obstetrical hemorrhage occurs when there is a blood loss of greater than 500 ml with vaginal delivery or 1,000 ml with cesarean delivery. Any number of pregnancy diagnoses can cause an obstetrical hemorrhage, most commonly uterine pathology such as uterine atony, inappropriate placental separation, and placental retention. Obstetrical hemorrhage can occur during pregnancy, immediately postpartum or delayed postpartum. Severe cases can cause hemorrhagic shock, thus leading to renal hypoperfusion and oliguria. Identifying and correcting the source of bleeding is the mainstay of treatment, as is aggressive replacement of blood products. These strategies will also correct renal function unless the bleeding is protracted and then the patient may have superimposed acute tubular necrosis (ATN).

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) is a rare but potentially fatal complication of the third trimester occurring from 1 in 10,000 to 20,000 pregnancies [6]. The median gestation is 36 weeks reportedly occurring between 22 and 40 weeks. The classic presentation of this rare

Table 48.3 Criteria for diagnosis of AFLP [6, 7]

Six or more of the following features in the absence of another explanation
Vomiting
Abdominal pain
Polydipsia/polyuria
Encephalopathy
Elevated bilirubin (>0.8 mg/dl)
Hypoglycemia (72 mg/dl)
Elevated urate (5.7 mg/dl)
Leucocytosis (11,000/μl)
Ascites or bright liver on ultrasound scan
Elevated transaminases (AST or ALT > 42 U/l)
Elevated ammonia (>80)
Renal impairment (>1.7 mg/dl)
Coagulopathy (PT > 14 s or aPTT > 34 s)
Microvesicular steatosis on biopsy

disease is hypoglycemia, transaminitis, elevated coagulation studies, hypofibrinogenemia, kidney injury, and fatty infiltration of the liver. However, the exclusion of these signs does not rule out the diagnosis. The largest series of AFLP studied to date came from a population of over 1.1 million deliveries in the United Kingdom Obstetric Surveillance System Study between 2005 and 2006 [6]. Providers diagnosed only 61 women with AFLP, 90% of which were retrospectively confirmed by the authors using the previously described Swansea criteria [7] (see Table 48.3). Of the 57 women meeting the criteria for the diagnosis of AFLP, 1 woman died; and of the 67 infants, there were 7 deaths, yielding a perinatal mortality rate of 104 per 1,000 births.

Liver ultrasound is not typically very helpful when performed, and in the aforementioned study showed evidence of disease by ascites or echogenicity in only 27% of women. Liver biopsies are seldom performed, as the maternal condition is typically too unstable. However, autopsies have shown swollen pale hepatocytes with central nuclei and positive fat staining.

The pathogenesis of AFLP has been better elucidated. There is a subset of AFLP that has been linked to long-chain 3-hydorxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency, a transport protein for long-chain fatty acids [8]. This is an autosomal recessively inherited condition that

results in the inability of the fetus to transport free fatty acids (FFA) into the liver mitochondria, thereby preventing its metabolism. Fetuses homozygous for LCHAD deficiency return high levels of FFA to maternal circulation, yielding excess levels of FFA. High levels of FFA in the already mildly comprised maternal heterozygous liver puts a strain on maternal hepatic activity, resulting in AFLP. Infants with LCHAD deficiency are commonly born to mothers diagnosed with AFLP [8].

Consequences of fat deposition in the maternal liver include inadequate fibrinogen synthesis and impeded bilirubin conjugation. Coagulation factor synthesis may decrease as fat deposits in the liver. Because the fetus is unable to oxidize the long-chain fatty acids, the fetal glucose demand increases and the mother may become hypoglycemic. Hypoglycemia is not required for the diagnosis of AFLP and excluding it in the setting of euglycemia may delay the diagnosis. Our case #1 presented with complaints of nausea and vomiting and meets six of the diagnostic criteria for AFLP: elevated AST, bilirubin, PT, WBC, ammonia, and uric acid level. Management of such patients requires hospitalization, close monitoring, and urgent delivery. However, because the signs and symptoms are nonspecific, other etiologies must be entertained.

The resulting elevated creatinine and renal injury is not well understood, because kidney biopsies are rarely performed in the setting of coagulopathy and impending delivery (similar to reason liver biopsies are not performed). However, severe liver dysfunction frequently results in renal hypoperfusion and thus ATN.

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is a disease of unknown etiology that occurs in the second and third trimester with pruritus alone or accompanied by icterus. Symptoms of liver dysfunction are uncommon. Serum bilirubin may be elevated but usually less than 5 mg/dl and alkaline phosphatase may be increased. Serum aminotransferases are also elevated and may reach values tenfold normal [9]. Severe cholestasis may lead to steatorrhea and loss of fat soluble vitamins

with vitamin K deficiency and prolonged PT. Decreased creatinine clearance with increased serum creatinines along with decreased urine output and decreased NH_4^+ urinary excretion invoke kidney involvement as well [10]. The maternal outlook is excellent but fetal prematurity is of concern and demise occurs rarely. It is unlikely our patient in case #1 had this without the symptom of pruritus, elevation of bilirubin, and with such an elevated creatinine, which is atypical for ICP. The diagnosis, if entertained, would require an 8-h fast with elevated bile acids.

Viral Hepatitis

Acute viral hepatitis with fulminant hepatic failure associated with high viral loads of Hepatitis E in developing countries is associated with poor pregnancy outcomes including intrauterine demise and maternal death particularly in the third trimester [11]. Kidney involvement was not discussed by this aforementioned paper, but likely occurs. The pathogenesis of kidney failure is likely due to systemic and intrarenal hemodynamic changes leading to hepatorenal syndrome (HRS), but ATN could also occur.

Herpes simplex virus (HSV) is a rare but commonly fatal condition with mortality in untreated individuals >80% [12]. It is most common in the third trimester of pregnancy. HSV causing hepatitis occurred in 132 patients noted in the literature from 1969 to 2006 [12]. Twenty three percent of the patients were pregnant. The majority of these patients, 98%, had fever, 97% developed coagulopathy, 80% encephalopathy, and acute kidney injury in 65%. Herpetic rash was detected in only 44% of patients, of which 61% were mucocutaneous and 39% were disseminated. Liver transaminases in HSV hepatitis generally increase 100 to 1,000-fold above normal [12]. It is most common in the third trimester of pregnancy [13]. When suspected, polymerase chain reaction (PCR) testing is done and prophylactic treatment is begun with parenteral acyclovir while awaiting the results. Kidney biopsies are prohibitive in these setting with fulminant liver failure so the kidney pathogenesis is speculative. The kidney pathology is presumptive in these cases being either prerenal or ATN.

Cardiomyopathy

Peripartum cardiomyopathy is defined as a condition that occurs in the last gestational month and first 5 months after delivery in the absence of another identifiable cause of heart failure and absence of recognizable heart disease prior to the last month of pregnancy. Also, left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria, such as depressed shortening fraction or ejection fraction below 45% is present [14, 15]. Undiagnosed heart failure can lead to prerenal disease in pregnancy, as it does in the nonpregnant state.

Milk Alkali Syndrome

Pregnant women have an increased susceptibility to developing milk/calcium alkali syndrome if there is hyperemesis causing volume depletion and enhanced kidney absorption of calcium in that setting [16]. The need for fetal calcium is satiated by maternal increases in intestinal calcium absorption by twofold, probably through an increase twofold of 1,25-dihydroxyvitamin and vitamin D independent mediated affects along with prolactin and placental lactogen [17]. This renders the mother susceptible to hypercalcemia. With increased use of calcium and vitamin D supplements to treat osteoporosis and when used to treat gastroesophageal reflux (GERD) exacerbated by pregnancy, milk alkali syndrome occurs [18]. GERD is a common problem in pregnancy occurring in 30–56% of all pregnancies and therefore with indiscriminate use of calcium products lead to the syndrome [19]. The kidney injury from hypercalcemia has several mechanisms. It causes afferent arteriolar vasoconstriction and decreases renal blood flow and GFR. Increased calcium binds to calcium-sensitive receptors in the medullary thick ascending limb and inhibits Na-K-2Cl cotransporter and blocks sodium reabsorption leading to volume depletion. Increased calcium in the tubulointerstitium can affect kidney function as well. The treatment is avoidance of calcium and vitamin D, control of emesis and volume resuscitation. Our patient was normocalcemic.

Post-Renal

Gravid Uterus and Ureteral Obstruction

As previously mentioned, hydronephrosis and hydroureter are not uncommon findings in pregnancy. Several factors are thought to contribute to these physiologic changes that most commonly do not lead to renal injury. Progesterone reduces ureteral tone and contractility. Enlarged blood vessels in the pelvis may cause ureteral compression, especially at the pelvic brim. The enlarging uterus displaces the ureters laterally, and on rare occasions can directly compress the ureters. The resulting urinary obstruction is marked by severe abdominal pain and inability to void. Resolution with maternal position changes aids in making the diagnosis. In these severe cases ureteral stents can relieve the ureteral compression, but in case of stent failure, delivery may be required.

Ureters can also be injured during delivery, most commonly during a challenging cesarean delivery. Lacerations of the uterine incision that extend into the lateral lower uterine segments, cervix or vagina are at highest risk for lacerating the ureters. Repair of uterine extensions that are in close proximity to the ureter could inadvertently obstruct them. Women with ureteral injury or obstruction will present with abdominal pain and possibly hematuria. The diagnosis does not require an elevated creatinine or signs of renal failure, as ureteral injury is commonly unilateral. CT scan showing urinary obstruction or urinoma is diagnostic, and this requires surgical correction.

Nephrolithiasis

Nephrolithiasis in pregnancy poses risks to the mother and fetus. Renal colic from ureteral obstruction in pregnancy may induce hypertension, premature labor, preeclampsia and may be associated with urinary-tract infections [20–22]. The incidence is similar to the nonpregnant childbearing women despite hypercalciuria with normal serum calcium levels, hyperuricosuria with normal to low serum uric acid levels and increased urinary citrate, magnesium and glycoproteins which exert a protective effect against stone formation and aggregation [20]. Most symptomatic stone episodes occur during the second or third

trimesters when ureteral dilation and compression by the gravid uterus is more likely [20]. The symptoms are similar to the nonpregnant patient with abdominal or flank pain, nausea, vomiting, and hematuria with 42% of these patients having pyuria on urinalysis [23]. The most appropriate first-line test is renal ultrasound and management is conservative if possible, with analgesia and intravenous volume. A majority of the patients, 84%, passed the stones spontaneously during pregnancy [23]. Obstruction of the ureter above or below the level of the pelvic brim with tapering of the ureter to a normal caliber is suggestive of pathologic obstruction [20]. The risk of acute kidney injury is low, given the unilateral presentation.

Intrinsic Kidney Injury

Glomerular: Nephrotic
Preeclampsia and Hemolysis Elevated Liver Enzymes Low Platelets Syndrome

Preeclampsia is a systemic syndrome that occurs in 3–14% of pregnancies worldwide and 5–8% of pregnancies in the USA. It manifests after 20 weeks gestation with new onset hypertension and proteinuria. It is a leading cause of maternal and neonatal morbidity and mortality. Placental anti-angiogenic factors are upregulated and disrupt maternal endothelium damaging target organs; glomerular endotheliosis, cerebral edema, liver injury, and the vasculature of other organs are thereby impacted. Preeclampsia is a spectrum of disease with eclampsia and hemolysis elevated liver enzymes low platelets (HELLP) syndrome on the severe end of it. In pregnancy, preeclampsia is the third leading cause of death after bleeding and infection and accounts for 20% of maternal deaths [24]. Women affected by preeclampsia have a 20% risk of developing cardiac disease years later as well as microalbuminuria [25]. Cardiovascular and cerebrovascular disease double in women with preeclampsia and may be a risk factor for CKD.

Because the pathophysiology of the disease is not well known, diagnosis depends on the presence of clinical signs of disease. Strict criteria for the diagnosis presented in Table 48.4 have been estab-

Table 48.4 Preeclampsia

1. New onset of hypertension and proteinuria after 20 weeks gestation
   - Systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg, on two occasions at least 6 h apart
   - Proteinuria of 3 g or greater in a 24-h urine specimen
   - Preeclampsia before 20 weeks, consider molar pregnancy
2. Severe preeclampsia in addition must have one of the following
   - Symptoms of central nervous system dysfunction = Blurred vision, scotomata, altered mental status, severe headache
   - Symptoms of liver capsule distention = Right upper quadrant or epigastric pain
   - Nausea, vomiting
   - Hepatocellular injury = Serum transaminase levels ≥ 2× normal
   - SBP ≥ 160 mmHg or DBP ≥ 110 mmHg on two occasions at least 6 h apart
   - Thrombocytopenia < 100,000 platelets/μl
   - Proteinuria ≥ 5g in 24 h
   - Oliguria = <500 mL in 24 h
   - Severe fetal growth restriction
   - Pulmonary edema or cyanosis
   - Cerebrovascular accident

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lished for clinical consistency. However, it should be noted that the pathophysiological changes of preeclampsia may be present in the absence of hypertension and proteinuria, as in the HELLP syndrome. Note that evidence of systemic vascular involvement without hypertension or proteinuria does not exclude preeclampsia as a diagnosis.

HELLP syndrome is a diagnosis based on clinical findings rather than pathophysiology. The incidence is 1–2 per 1,000 live births and acute renal failure occurs in 4% of these women [26]. The progression of disease and its termination with delivery suggest its relation to preeclampsia. There are degrees to the extent of the laboratory abnormalities seen with HELLP. Extremes of thrombocytopenia, elevated AST, and LDH levels are distinguished by some authorities as complete HELLP with all of the following AST > 70 IU/l, platelets < 100,000, and

LDH > 600. Partial HELLP may manifest with milder or incomplete laboratory abnormalities such as AST > 40, platelets < 150,000, and hemolysis present or absent [7, 26].

The physiologic invasion of placental vascularization into the uterine spiral arteries requires VEGF and TGF-β1 to maintain endothelial health in several tissues, including the kidney and the placenta. During normal pregnancy, vascular homeostasis is maintained by physiologic levels of VEGF and TGF-β1 signaling in the vasculature. In preeclampsia, excess placental secretion of sFLT1 and sENG, two endogenous circulating anti-angiogenic proteins, inhibits VEGF and TGF-β1 signaling. This results in endothelial cell dysfunction, leading to hypertension, proteinuria, and other systemic manifestations.

The most frequent and pronounced renal changes from preeclampsia occur in the glomerulus. The kidney injury is glomerular capillary endothelial cell swelling (endotheliosis) and vacuolization and loss of capillary space with subendothelial deposits of fibrin [27]. Capillary lumen occlusion is thought to render the glomeruli nonfunctional, thus leading to a lower GFR seen in preeclampsia. With increased glomerular damage, there is an increase in the permeability of the glomeruli, likely the cause of proteinuria in preeclampsia. These glomerular changes regress postpartum. Not all patients with preeclampsia have proteinuria that reaches the level of nephrotic syndrome; it depends on the severity. The pathogenesis of preeclampsia is likely multifactorial and is beyond the scope of this review.

The renin–angiotensin system is suspected to play a role in preeclampsia, although research in this area is limited. Plasma renin activity, plasma renin concentration, and angiotensin levels are all decreased in preeclampsia compared to normal pregnancy [28, 29]. Women with preeclampsia are suspected to be more sensitive to angiotensin. Urinary sodium excretion is reduced in preeclampsia and returns to normal postpartum. Although the mechanism of renal changes in preeclampsia are not clear, they could all be explained by decreased renal perfusion.

Preeclampsia should certainly be on the differential diagnosis for case #1. Although her initial blood pressure was below the cut-off for preeclampsia at 120/86, it subsequently increased to 145/87 and remained elevated 6-h later. Her blood pressure in combination with her proteinuria was adequate for the diagnosis of preeclampsia. Hyperreflexia and elevated uric acid are also consistent with the diagnosis of preeclampsia, but these measurements are nonspecific. Measuring SFLT-1 and sENG may have been insightful, but at this time are not standardly performed.

Glomerular: Nephritis
Post-Infectious Glomerular Nephritis

Pregnant women with exposure to children aged 5–7 years are at risk for parvovirus B19 infection during pregnancy [30]. A case report of a patient in the tenth week of pregnancy developed parvovirus B19 IgM positive and 2 weeks later developed hypertension, nephrotic range proteinuria and evidence of pure red cell aplasia. The kidney biopsy revealed diffuse proliferative glomerulonephritis with immunofluorescent and electron microscopic changes consistent with post-infectious glomerulonephritis. The kidney function and blood pressure recovered by the 16th week gestation and the delivery was at term with a healthy infant [31].

Several case reports of pregnant patients developing (PIGN) appear in the literature. The classic findings of antecedent infection with resolution and then development of gross hematuria and the urinalysis confirming proteinuria and red blood cell casts along with serology with low C3. In one case, the biopsy demonstrated proliferative and exudative glomerular lesions along with immunofluroescence demonstrating coarse staining of C3 along the capillary loops and mesangium [32]. There was IgG staining as well. The electron microscopy demonstrated subepithelial electron dense deposits and humps, all the findings consistent with PIGN. The patient required dialysis but recovered without residual kidney injury with a creatinine peak of 4.9–0.9 mg/dl 1 week after discharge. As in previously reported cases with biopsy-proven post-infectious glomerular nephritis (PIGN), the disease had remitted [24, 33–36].

Hematuria

In a prospective case–control study pregnant women following in an antenatal care clinic in Australia enrolled to have routine urinalysis performed and were referred to nephrology clinic for investigation if dipstick microscopic hematuria was detected more than once before 32 weeks gestation [37]. Of 902 women (20%) had dipstick hematuria on at least two occasions in pregnancy. Sixty-six of 126 women (53%) who had hematuria before 32 weeks followed up with nephrology where the hematuria was confirmed in 40 women. Microscopic hematuria persisted in half (15 women) of those who followed up after 3 months postpartum. They concluded from their results that dipstick hematuria is common during pregnancy but rarely signifies a disorder such as preeclampsia, hypertension, or small for gestational age infants. Kidney biopsies and follow up was not reported. Antecedent hematuria prior to pregnancy was not assessed or commented on.

ATN: Ischemia

Cortical necrosis is a devastating insult to the kidneys with the cardinal signs and symptoms of abrupt onset anuria, flank pain, and gross hematuria. It is severe kidney ischemia from hypoperfusion or disseminated intravascular coagulopathy that is seen with abruption of the placenta, prolonged intrauterine fetal death, or amniotic fluid embolism. It is diagnosed by ultrasound or noncontrast CT scan demonstrating hypoechoic areas in the cortex or renal calcifications, which is a late finding. This disease is not usually reversible and treating the underlying problems may prevent extensive damage. Cocaine has been reported to cause abruption of the placenta and cortical necrosis leading to end stage renal disease (ESRD) [38].

ATN: Sepsis

Peurperal sepsis is a leading cause of maternal death worldwide, accounting for over 80,000 deaths per year [39], although uncommon in the USA, it remains a top cause of maternal death. Women are especially at risk for infection during the peripartum period, as labor and delivery exposes the typically sterile uterine environment to the multitude of bacteria harbored in the vagina. Undiagnosed or undertreated chorioamnionitis and postpartum endometritis can both lead to fulminant sepsis, threatening a woman's future fertility and life. Peurperal sepsis is most often a polymicrobial in nature, but coliform bacteria such as *Escherichia coli* and *Enteroccocus* are known pathogens as are *Staphylococcus* and *Streptococcus*.

Similarly, pregnancy is a risk factor for pyelonephritis. Asymptomatic bacteriuria occurs in approximately 5% of pregnant women; similar to nonpregnant women [40], but more commonly leads to pyelonephritis (40% of untreated bacteriuria develop acute urinary tract infection (UTI) or pyelonephritis) [41]. This is likely a result of the increased urinary stasis and ureteral dilation which allows ascent of lower urinary tract bacteria [42]. Approximately 2% of women with pyelonephritis develop acute renal failure which may or may not be reversible [43]. If biopsied, microabscesses may be found. Treatment is with empiric i.v. antibiotics until culture results are available, and until the patient is 24–48 h afebrile. Recurrence during pregnancy is not uncommon, thus prophylactic/suppressive antibiotics after diagnosis are standard of care. Of note, unlike other forms of sepsis and infection, volume resuscitation should be performed with caution, as women with pyelonephritis are at quite susceptible to ARDS. Prevention of infectious complications may be mitigated by universal screening for UTIs at the first prenatal visit and treated accordingly.

ATN: Toxins
Endogenous Toxins: Rhabdomyolysis

Rhabdomyolysis is muscle injury from ischemia or metabolic perturbations that leads to release of myoglobin that is a tubular toxin. Pregnant patients are at risk for rhabdomyolysis similar to the general population. Coma induced by alcohol and opioid overdose leads to immobilization and compartment syndrome that may lead to muscle injury. Cocaine causes rhabdomyolysis as well [38]. Cocaine-induced hyperthermia with excess muscle energy demands may lead to this. Methamphetamine use may occur in pregnancy, as it is known that 3% of pregnant women in the USA had used illicit substances in the preceding

month and methamphetamine is associated with rhabdomyolysis [44, 45].

A case of baking soda ingestion in a woman at 31 weeks gestation developed severe hypokalemic metabolic alkalosis and rhabdomyolysis with elevation in serum transaminases and hypertension and 1 g of proteinuria on a 24 h urine collection [46]. She presented as though she had preeclampsia until further history was obtained that she was ingesting large amounts of baking soda.

Patients with carnitine palmitoyl transferase (CPT) type 2 deficiency are at risk of rhabdomyolysis. The disorder of mitochondrial fatty acid oxidation during pregnancy creates a situation where energy stores are inadequate, such as may occur during labor and women are at risk of rhabdomyolysis [47]. It is an autosomal recessive disorder. Normal functioning of the CPT system is required to ensure long-chain fatty acyl CoA is transported to the mitochondrial matrix where it is needed for B-oxidation. Deficiencies of both CPT1 and two leave patients unable to create energy from fatty acid oxidation and after immediate glucose and glycogen stores are exhausted, hypoglycemia may occur leading to rhabdomyolysis and if severe, acute kidney injury. Patients present with dark urine, from myoglobinuria, increased serum creatinine phophokinase, hypertension, low platelets, and elevated liver enzymes. Attentive glucose and volume management may help avoid this along with avoidance of strenuous exercise and labor.

Endogenous Toxins: Sickle Cell Disease/Trait

People with sickle cell disease (SCD) are living longer with advances in medical technology. Improved pregnancy outcomes no longer warrant avoidance or termination of pregnancy [48]. The kidney is at risk for tubulointerstitial injury in patients with SCD and sickle cell trait (SCT). Volume depletion that may occur for a variety of reasons during pregnancy may increase the risk for further tubular injury in these patients. SCD increases the risk of pyelonephritis, and the incidence of pyelonephritis in pregnant women with SCD is 5–7% in pregnancy [48, 49]. Patients with SCT are also at increased risk for urinary tract infections or pyelonephirits [50]. Another poten-

tial cause of kidney injury in this population is the use of nonsteroidal anti-inflammatory drugs (NSAIDS) for pain crisis which may lead to ATN, minimal change disease or interstitial nephritis.

Endogenous Toxins: Uric Acid

Acute uric acid nephropathy in pregnancy was reported in a 38-year-old primigravid woman who was admitted for vomiting and oliguria during the 30th week of gestation with a creatinine of 6.7 mg/dl and serum uric acid of 19 mg/dl [51]. After volume resuscitation, the creatinine was 0.8 mg/dl and the serum uric acid dropped to 3.1 mg/dl. A similar episode occurred 3 weeks later. The etiology of the hyperuricemia was unclear.

Exogenous Toxins

Rhabdomyolysis seemingly provoked by exogenous toxins has been reported during pregnancies. Ritodrine, a potent $beta_2$ stimulant that produces direct relaxation of the uterine smooth muscle and decreases the force and frequency of uterine contractions is used as a tocolytic. There are a few case reports in the literature and one by the referenced authors who noted a CK value of 25,000 IU/l (normal range 40–190) without another explanation [52, 53]. The urinary myoglobin was elevated but the creatinine was normal. The mechanism for the cause of rhabdomyolysis is speculative, but hypokalemia may arise from potassium shifting intracellularly and thus causing rhabdomyolysis.

Another tocolytic and B_2-adrenoceptor agonist, terbutaline, has been reported to cause rhabdomyolysis [54]. This case occurred after receiving terbutaline i.v. and magnesium sulfate during her 25th week of pregnancy to manage premature labor. Her labor was controlled and she was started on oral terbutaline and then because of muscle weakness was noted to have an elevated creatinine kinase up 14,330 U/dl and a creatinine of 1.1 mg/dl. An EMG was consistent with inflammatory myopathy and a muscle biopsy was consistent with acute polymyositis (PM). The patient was treated with prednisone and tocolytics withheld. She had new onset PM after the use of tocolytics.

Indomethacin use as a tocolytic in three cases may have been responsible for reversible acute kidney injury [55]. Other medical circumstances in these patients may have predisposed them to renal vasoconstriction and the vasodilatory protaglandin inhibition of indomethacin in these patients may have exacerbated the acute kidney injury. Cautious use of this medication when patients have potential compromise of hemodynamic perfusion of the kidneys should be considered.

Interstitial Nephritis

A case report of magnesium dypirone (metamizol), a nonsteroidal anti-inflammatory agent used as an analgesic and antipyritic, caused oligohydramnios and acute renal failure [56]. The patient took a high dose of this medication and her creatinine was 3.7 mg/dl. The patient developed a rash and had proteinuria with 0.8 g/24 h and the urinalysis demonstrated leucocytouria and three red blood cells. After discontinuation of the medication the rash resolved and creatinine returned to normal. Magnesium dypirone is a prostaglandin synthetase inhibitor that may cause ischemia or interstitial acute interstitial nephritis.

Vascular

As a way of categorizing vascular involvement as a cause of intrinsic acute kidney injury, one may distinguish this entity from both large and small vessels. The large renal arteries, when occluded, may be defined as prerenal kidney failure. When the small capillaries in the glomerular are primarily involved, this is nephritis or nephrosis. When the interlobular arteries are involved, we speak of intrinsic vascular involvement. Thrombotic microangiopathy (TMA) is an intrinsic cause of renal vascular disease. It is composed of the syndromes thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (TTP-HUS), both of which are seen in pregnancy. The pathology does overlap, with thrombi in the glomeruli, and injury to the interlobular arteries is seen as intimal thickening and onion skinning. The pathogenesis relates to Von Willebrand Factor (VWF) maintenance by ADAMTS-13 enzyme molecules [57]. The VWF multimeric structures are secreted from stimulated endothelial cells. When the activity of ADAMTS-13 is absent or reduced, VWF cleavage does not occur and platelets adhere and aggregate onto the uncleaved VWF molecules forming microvascular platelet thrombi. Severe congenital deficiency of ADAMTS-13 caused by gene mutations or inhibition of the enzyme caused by acquired autoantibodies, inflammatory cytokines, estrogen or bacterial toxins, results in TTP [57]. HUS is described in association with infections by the Shiga toxin-producing hemorrhagic strains of *E. coli* [58]. HUS presents with a greater degree of kidney injury, potentially requiring renal replacement therapy. TTP-HUS is extremely rare during pregnancy and postpartum. They afflict <1 case in 100,000 pregnancies [59]. One review of the literature from 1955 to 2006, only noted 166 cases of TTP, distinguished from HUS by creatinines <3 mg/dl, and 55% of the cases occurred in the second trimester, whereas 33% occurred after 28 weeks [60]. The classic diagnosis of TTP/HUS includes the pentad of thrombocytopenia, Coombs negative hemolytic anemia, kidney injury, neurologic abnormalities, and fever but not all of these findings are present. The ADAMTS-13 activity is absent to markedly reduced in 33–100% of patients with TTP but in HUS that is not the case [59]. TTP-HUS has similarities with HELLP that may confuse the diagnosis and therefore the management. TTP/HUS should be favored as a diagnosis if the patient has a past history of TTP/HUS, ADAMTS-13 activity <5%, severe hemolytic anemia, markedly reduce platelets, a bloody diarrheal prodrome, congenital TTP-HUS, or presentation in the first trimester. Plasma exchange with fresh frozen plasma should be considered if a HELLP-like syndrome persists beyond 3 days postpartum and/or sooner if there is life-threatening microangiopathy. Our case #1 had diarrhea, but the platelets were only modestly reduced and the LDH was only modestly increased and there were no shistocytes on the smear, making TTP-HUS less likely. In case #2, the moderate shistocytes and more elevated creatinine raises the specter of TTP-HUS more so and thus plasma exchange should be considered as the patient is followed.

Case 1 Revisited

This patient is at the gestational age consistent with preeclampsia and has significant proteinuria. The creatinine of 1.1 mg/dl appears normal for a nonpregnant patient but is noticeable elevated for pregnancy. The initial blood pressure does not meet the defined criteria for this disease but that is not always necessary and certainly blood pressures may fluctuate. The patient does have other constitutional signs consistent with a systemic process, and the subsequent blood pressures became consistent with preeclampsia. Other considerations for her presentation are AFLP as the patient meets six or more of the Swansea criteria, those being vomiting, elevated bilirubin, uric acid, ammonia, AST, PT, and leukocytosis. If the patient has HELLP, it is likely considered partial as the AST is not >70 U/l, the platelet count is not <100,000, the LDH is not >600 U/l and there was no hemolysis seen on the peripheral smear. TTP is unlikely without hemolysis but this and HUS should be followed after delivery. Our patient was felt to have preeclampsia and she was delivered after being given antenatal corticosteroids for fetal lung development in anticipation of preterm delivery. The patient's creatinine, liver function tests, and urinalysis normalized.

Case 2 Revisited

This case illustrates the difficulty in clinically distinguishing HELLP syndrome from TTP-HUS. This patient has elevated blood pressures without proteinuria, thus she does not meet criteria for preeclampsia. Proteinuria is *not* necessary for the diagnosis of HELLP syndrome, and in such circumstances the diagnosis is known as "atypical HELLP." She has several features of HELLP syndrome including severe right upper quadrant pain, evidence of hemolysis, mildly elevated liver enzymes, and low platelets. But the clinical picture is confused by renal insufficiency which is a sign of possible TTP-HUS. Whereas the clinical picture for HELLP and TTP-HUS is very similar, treatment strategies are quite different. Delivery for this patient is indicated, as preeclampsia or some variant (such as HELLP), cannot be completely excluded. Given the elevated liver function tests (LFTs) and RUQ pain, HUS is an unlikely diagnosis, but should be considered, especially if the patient does not improve clinically within 48 h after delivery. Postpartum, the patient's AST and ALT continued to rise peaking in the 300 s and her platelets fell to a nadir of 32,000 on postpartum day 1 with a stable creatinine. In this case, a multidisciplinary team with seasoned expert consultants can be helpful in determining if plasma exchange is necessary. She made a full recovery by her 1-week postpartum visit, confirming the diagnosis of HELLP syndrome.

Conclusion

New onset kidney injury during pregnancy that is not coincidentally discovered because of preexisting kidney disease first noticed on medical evaluation of the newly pregnant patient has a broad differential that is well known to the experienced healthcare professional. The commonly anticipated complications of pregnancy warrant more than a cavalier assessment of the patient and the fetus to avoid the kidney organ injury that is usually reversible upon supportive management of the mother or modifiable with expectant delivery avoiding the dire consequences of preeclampsia, HELLP, AFLP, and sepsis. The nephrologist is not as familiar with the management of these entities as the obstetric provider but the rare presentation of TTP/HUS falls in the preview of their specialty and a collaborative approach with the primary maternal caregiver will enhance everyone's experience and potentially improve patient care in these rare predicaments.

Key Points

Pregnancy associated kidney injury is not uncommon during pregnancy, nephrology involvement is

Reversible kidney injury is probably the rule with delivery of the fetus

Catastrophic consequences involving life-threatening kidney failure may arise if simple laboratory assessment is neglected and common untoward symptoms are dismissed without considering the differential outlined herein

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