Acute Kidney Injury in Pregnancy: The Changing Landscape for the 21st Century

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Pregnancy-related acute kidney injury (Pr-AKI) remains a large public health problem, with decreasing incidences in developing countries but seemingly increasing incidences in the United States and Canada. These epidemiologic changes are reflective of the advances in medical and obstetric care, as well as changes in underlying maternal risk factors. The risk factors associated with advanced maternal age, such as hypertension, diabetes, chronic kidney disease, and those associated with reproductive technologies such as multiple gestations, are increasing. Traditional causes of Pr-AKI, such as septic abortions and puerperal sepsis, have been replaced by hypertensive diseases, such as preeclampsia and thrombotic microangiopathies comprising thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS). In this review, we discuss the global impact of Pr-AKI on maternal and fetal outcomes, the predominant etiologies, and key clinical features to distinguish diagnoses, such as preeclampsia/ hemolysis elevated liver function test and low platelet (HELLP) syndrome, acute fatty liver disease of pregnancy (AFLP), and other thrombotic microangiopathies. New insights into the pathogenesis of preeclampsia, TTP/aHUS, and AFLP that have unearthed possible therapeutic targets are summarized. We also delve into special consideration needed to give to pyelonephritis and postobstructive causes of Pr-AKI. With each diagnosis, we offer the latest treatment recommendations, such as the positive reports from the use of eculizumab to treat aHUS. In the end, we hope to arm the clinician with the best tools to understand and address this morbid problem that does not seem to be disappearing.

P regnancy-related acute kidney injury (Pr-AKI) is a heterogeneous disease entity that occurs due to a multitude of underlying etiologies. Regardless of the cause, it is an important obstetric complication associated with significant maternal and fetal morbidity and mortality.[1] Fortunately, there has been a dramatic decrease in the incidence of Pr-AKI over the past 50 years due to improved obstetric care and reduction in septic abortions. However, this reduction has not been uniform worldwide. We delve into the details regarding the changing epidemiology and patient outcomes; this is followed by specific discussions concerning the common causes as well as updated treatment recommendations.

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Epidemiology of Pr-AKI and Maternal/Fetal/Renal Outcomes

Pr-AKI has always been an important public health issue in developing countries. Recent reports from India have revealed a sharp decline in the proportion of Pr-AKI among hospitalized patients with acute kidney injury (AKI), from 15% in the 1980s to 1.5% in the 2010s; however, 30% of the recent cases were severe and required dialysis.[2,3] Most cases of Pr-AKI now occur in the postpartum rather than the post-abortal period, reflecting a decline in septic abortions and the need for further improvement in peripartum care. A similar decreasing trend has been noted in China, with the incidence of Pr-AKI reported to range from 0.2% to 1.8%.[4] Most of these cases (80%) occurred in rural areas and were associated with lack of prenatal care. The most common causes were hypertension and postpartum hemorrhage, with 6% requiring dialysis.[5] In Africa, a recent study from Morocco reported 6.6 cases of Pr-AKI per 1000 deliveries, with 16% requiring dialysis.[6] Concomitant with the decrease in the incidence of Pr-AKI, maternal

mortality associated with Pr-AKI has significantly decreased in the developing countries. Recent studies from China and India report maternal mortality rate associated with Pr-AKI of 4.0% and 5.8%, respectively,[3,5] as compared with a rate of 20% during the 1980s.[3] These reports of the decrease incidence in maternal mortality associated with Pr-AKI in the developing countries are very encouraging, but are still unacceptably high in absolute numbers. Aggressive public health initiatives to deliver high-quality obstetric care to the most vulnerable sections of the population are needed to mirror the success achieved in the developed countries.

In the developed world, a significant decrease in Pr-AKI was noted by the end of the 20th century. An Italian study reported a decrease in Pr-AKI from 1 in 3000 pregnancies in the 1960s to 1 in 18,000 pregnancies in the 1990s.[7] However, the landscape of Pr-AKI in the developed world is changing, with recent studies from Canada and the United States reporting an increased incidence of Pr-AKI. The incidence of Pr-AKI increased from 1.66 to 2.68 per 10,000 pregnancies from 2003 to 2010 in Canada,[8] and from 2.4 to 6.3 per 10,000 deliveries in 1999 to 2001 and 2010 to 2011 in the United States.[9] Much of the increase in diagnosis has been attributed to the different coding of AKI (ascertainment bias) and increased surveillance during the study period rather than an absolute increase.[10] This view is supported by data that most Pr-AKI cases reported over a 5-year period were minor and transient (87%).[11] Although ascertainment bias may certainly be a contributing factor, there is also cause for real concern, as evidenced by the increase in severe Pr-AKI requiring dialysis (0.27 to 0.36 per 10,000 deliveries, $P = 0.01$) and maternal mortality associated with Pr-AKI (0.13 to 0.23 per 10,000 deliveries, $P = 0.01$) in the United States.[9] Furthermore, there were increased rates of severe maternal morbidity defined by Pr-AKI, shock, acute myocardial infarction, and respiratory distress syndrome between 2008 and 2009 as compared with 1998 and 1999.[12] The reasons for these hard outcomes were attributed to factors such as older maternal age, pregnancies with hypertensive disorders, and underlying chronic kidney disease.[8,9] In Canada, the incidence of severe Pr-AKI requiring dialysis was low (<1 in 10,000 pregnancies), with most cases occurring in a setting of obstetric catastrophes; however, they exhibited higher maternal mortality than women in the general population (4.3% vs. 0.01%).[12] These reports are indicative of the new challenges facing the developed world, and highlight the need for ongoing studies to parse the differences in the increase of Pr-AKI due to ascertainment bias from the subset of Pr-AKI that are associated with increased maternal risk factors and maternal mortality.

Pr-AKI is also associated with significant fetal mortality and morbidity. The odds of perinatal mortality increases 3.4-fold when compared with pregnancies without Pr-AKI.[1] Studies from India have reported high perinatal mortality of 20% to 45% due to intrauterine death, stillbirth, and prematurity.[2,3] In China, perinatal mortality was 17%, with higher mortality noted with Pr-AKI in the second rather than third trimester.[5] Severe Pr-AKI requiring dialysis in Canada was commonly associated with preterm deliveries, low birth weight, infants small for gestational age, and neonatal death.[12]

Long-term renal outcomes have not been well studied in women with Pr-AKI. In the short term, less severe Pr-AKI demonstrates favorable renal recovery at 40% to 75%.[6] In contrast, 4% to 9% of women with severe Pr-AKI remained dialysis dependent at 4 to 6 months postpartum.[6,13] The rate of progression to end-stage renal disease from Pr-AKI, in general, ranges from 1.5% to 2.5%.[1,3]

Diagnosis of Pr-AKI

The definition of Pr-AKI used in literature is variable, ranging from an increase in serum creatinine to AKI needing dialysis.[14] Hemodynamic and vascular changes in normal pregnancy result in a 40% to 50% increase in glomerular filtration rate. Thus, serum creatinine that is within the normal range for the general population could reflect significant compromise in renal function in a pregnant woman. In the general population, the RIFLE (Risk, Injury, Failure, Loss, and End Stage) and AKIN (Acute Kidney Injury Network) criteria are commonly used to define and classify AKI but are not well validated in pregnancy. Nevertheless, recent studies using the RIFLE and AKIN criteria report that most cases of Pr-AKI are of the AKIN stage 1 category and that a higher RIFLE category was associated with worse outcomes.[11,15] Although more studies to validate these criteria in Pr-AKI are needed, they can provide much needed uniformity.

Differential Diagnosis

The etiologies for Pr-AKI are numerous and varied (Table 1). Similar to AKI in the nonpregnant population, Pr-AKI can be categorized as prerenal, intrarenal, and postrenal, with prerenal azotemia being the most common. Salient features of major intrarenal and postrenal causes of Pr-AKI are discussed in detail in this review. A rare but potentially irreversible cause of intrarenal Pr-AKI is acute cortical necrosis, which has been reported in cases of severe obstetric emergencies such as abruptio placentae. The exact pathogenesis of acute cortical necrosis is unclear, but the

Table 1. Common causes of acute kidney injury in pregnancy

Prerenal azotemia
- Hyperemesis gravidarum
- Sepsis
  - Postabortal
  - Puerperal
  - Urosepsis
- Heart failure
- Medication
  - Diuretic
  - Nonsteroidal anti-inflammatory drugs

Intrarenal
- Acute tubular necrosis/Acute cortical necrosis
  - Catastrophic obstetric hemorrhage
    - Abruptio placentae
    - Uterine rupture
  - Sepsis
    - Postabortal
    - Puerperal
    - Urosepsis
- Preeclampsia/hemolysis, elevated liver function test, and low platelets (HELLP)
- Thrombotic microangiopathy (TMA)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Atypical hemolytic uremic syndrome (aHUS)
  - Disseminated intravascular coagulation (DIC)
- Acute fatty liver of pregnancy (AFLP)
- Lupus nephritis and/or antiphospholipid antibody syndrome (APS)
- Pyelonephritis
- Medication
  - Nephrotoxicity/Acute interstitial nephritis
- Pulmonary embolism
- Amniotic fluid embolism

Postrenal
- Hydronephrosis due to uterine compression of ureter/bladder
- Obstruction of ureter due to nephrolithiasis
- Iatrogenic injury to the ureter/bladder/urethra during cesarean section or vaginal delivery
- Spontaneous injury to the bladder/urethra during vaginal delivery

hypercoagulable state of pregnancy is believed to play a role with intravascular thromboses noted in interlobular and afferent arterioles, along with diffuse or patchy cortical necrosis on kidney biopsy.[16,17]

Timing of Pr-AKI

The timing of Pr-AKI also gives significant clues for etiology (Figure 1). Pr-AKI in the first trimester usually results from septic abortions (in developing countries) and prerenal azotemia from hyperemesis gravidarum. Most Pr-AKI episodes occur in the third trimester or closer to delivery and offer a larger differential: preeclampsia and hemolysis elevated liver function test and low platelet (HELLP) syndrome; thrombotic microangiopathies, namely thrombotic thrombocytopenic purpura (TTP)/atypical hemolytic uremic syndrome (aHUS); acute fatty liver of pregnancy (AFLP); severe hemorrhage, such as abruptio placentae; or puerperal sepsis. Both preeclampsia/HELLP and aHUS can

extend to the postpartum period, with a higher frequency in the latter.

Role of Kidney Biopsy

Due to common clinical and laboratory findings in several causes of Pr-AKI, the exact etiology may remain elusive despite extensive laboratory and radiology testing. Even in difficult cases, a kidney biopsy to determine etiology of Pr-AKI is recommended only if the biopsy diagnosis can potentially change treatment; it is contraindicated in the third trimester, as the risk outweighs the benefit of establishing a diagnosis so late in pregnancy.[18]

Preeclampsia/HELLP

Preeclampsia is defined as blood pressure >140/90 mm Hg with proteinuria of $\geq$ 300 mg/d after 20 weeks of gestation in a previously normotensive woman or without proteinuria when there is evidence of end-organ damage.[19] It occurs in 2% to 8% of pregnancies, most commonly in the second and third trimester period, but it can also occur in the postpartum period in up to 5% of cases.[20,21] Interestingly, a history of recovered AKI unrelated to pregnancy is associated with a higher risk of preeclampsia in future pregnancies.[22] Although preeclampsia is associated with a 30% to 40% reduction in renal blood flow and glomerular filtration rate compared with a normal pregnancy, Pr-AKI is an uncommon manifestation (1%), unless preeclampsia is severe or associated with the HELLP syndrome.[23] The HELLP syndrome, associated with Pr-AKI in 7% to 36% of cases, is classified as a preeclampsia/eclampsia continuum, even though 20% of cases do not have antecedent hypertension or proteinuria.[24] In practice, the differentiation of preeclampsia/HELLP from other causes, such as TTP/aHUS and lupus nephritis, is challenging due to overlapping clinical and laboratory parameters. But this distinction is important, as prompt delivery is indicated in severe preeclampsia/HELLP due to the high maternal morbidity and mortality risk with the continuation of pregnancy.[19] Defects in placentation and maternal susceptibility play a central role in the development of preeclampsia, with placental derived angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor, and soluble endoglin as key mediators of the disease.[25] These factors are being explored as biomarkers for preeclampsia diagnosis and its differentiation from other causes of Pr-AKI, as well as targets for therapeutic intervention.[26] An open clinical trial of sFlt-1 removal by dextran sulfate apheresis in 11 women with preeclampsia showed a reduction in proteinuria and prolongation of pregnancy by 2 to 21 days.[27]

| | 1st trimester | 2nd trimester | 3rd trimester | D | Postpartum |

Septic Abortion
Clinical Features
➢Prerenal azotemia or ATN
Treatment
➢Volume resuscitation, antibiotics

Hyperemesis Gravidarum
Clinical Features
➢Prerenal azotemia or ATN
➢Evaluate for molar pregnancy
Treatment
➢Volume resuscitation

Preeclampsia/ HELLP
Clinical Features
➢Hypertension and proteinuria* after 20 weeks of gestation
➢Headache, visual disturbance, seizures, abdominal pain
➢Hemolytic anemia, transaminitis, thrombocytopenia, high LDH
Treatment
➢Delivery, i.v. magnesium for seizure prevention

TTP/aHUS
Clinical Features
➢TTP more common in 2nd/3rd trimester, aHUS more common in postpartum period
➢Neurological involvement is more common in TTP than aHUS
➢Hemolytic anemia, thrombocytopenia, elevated LDH and bilirubin
Laboratory testing
➢TTP: ADAMTS-13 activity <10%
➢aHUS: genetic testing for complement cascade gene mutations
Treatment
➢TTP: plasma exchange
➢aHUS: plasma exchange + eculizumab

Acute Fatty Liver of Pregnancy
Clinical Features
➢Nausea, vomiting, abdominal pain, jaundice, ascites
➢Transaminitis, low platelets, hypoglycemia, lactic acidosis
Laboratory Testing
➢ Maternal and fetal testing for LCHAD gene mutation
Treatment
➢Delivery, plasmapheresis and/or liver transplant in severe cases

Lupus nephritis and/or Antiphospholipid antibody syndrome
Clinical Features
➢Dysmorphic red blood cells on urine sediment, extra-renal lupus manifestations
➢Low complements, positive anti-dsDNA, anti-cardiolipin antibodies, and/or anti-β2 glycoprotein antibodies
➢Kidney biopsy is only recommended if pathology will change management
Treatment
➢Lupus nephritis: steroids + hydroxychloroquine + azathioprine/tacrolimus
➢Antiphospholipid antibody syndrome: aspirin +/- low molecular weight heparin

Figure 1. Main causes of pregnancy-related acute kidney injury with overlapping clinical features. ADAMTS-13, ADAM metallopeptidase with thrombospondin type 1 motif 13; aHUS, atypical hemolytic-uremic syndrome; ATN, acute tubular necrosis; D, delivery; HELLP, hemolysis, elevated liver function test, and low platelets; LCHAD, long-chain 3-hydroxyl coenzyme A dehydrogenase; LDH, low-density lipoprotein; TTP, thrombotic thrombocytopenic purpura. *Updated diagnostic criteria of preeclampsia[19]: New onset hypertension after 20 weeks of gestation (defined by blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic on 2 occasions at least 4 hours apart or blood pressure ≥ 160 mm Hg or ≥ 110 mm Hg confirmed within a short period [minutes] to facilitate timely antihypertensive therapy) AND proteinuria (defined by ≥ 300 mg/24 h urinary collection, protein/creatinine ratio of ≥ 0.3, or urine dipstick reading of 1+) OR in the absence of proteinuria with thrombocytopenia (platelet count of <100,000/μl), renal insufficiency (serum creatinine ≥ 1.1 mg/dl or doubling of serum creatinine), impaired liver function (transaminases elevated to twice the normal concentration), pulmonary edema, or cerebral or visual symptoms.

Complement system dysregulation has emerged as another possible underlying cause of maternal susceptibly and a mechanistic pathway for organ injury in preeclampsia/HELLP.[28] Mutations in complement regulatory genes have been reported in 8.5% to 18.0% of women who developed preeclampsia in the setting of systemic lupus erythematosus (SLE) and/or antiphospholipid antibodies.[29] Single nucleotide polymorphisms in complement gene C3 can modify susceptibility to severe preeclampsia with both predisposing and protective effects based on the allele combination.[30] Mouse models susceptible to preeclampsia with high sFlt-1 levels during pregnancies were able to have pregnancies without preeclampsia when treated with a C3 inhibitor during the early phase of placental development.[31] Complement activation, which occurs in normal pregnancy, is exacerbated in preeclampsia, as detected by systemic and placental markers of activation.[32,33] An *in vitro* study demonstrated that serum from women with preeclampsia/HELLP is cytotoxic due to complement activation and that administration of eculizumab, a complement inhibitor, ameliorates this finding.[34] A case report of the use of eculizumab for the treatment of severe preeclampsia/HELLP has found favorable maternal and fetal outcomes.[35] Although in nascent stages and not yet considered standard of care, these novel mechanisms and therapeutic modalities provide a glimmer of hope for improving maternal and fetal outcomes.

Thrombotic Microangiopathies: TTP/aHUS

The renal thrombotic microangiopathies comprise disorders such as TTP and aHUS. Their common characteristics are that of disseminated occlusion of arterioles and capillaries with fibrin and possibly agglutinated platelets resulting in mechanical destruction of red blood cells and decreased platelet count. Although their occurrence in pregnancy is rare, they are associated with high maternal and fetal morbidity and mortality.[36] Deficiency of ADAMTS-13, a von Willebrand factor–cleaving protease, is responsible for most cases of TTP, occurring mostly in the second and third trimesters of pregnancies.[37–39] Pregnancy, itself a procoagulant state, is a trigger for TTP, especially in the setting of ADAMTS-13 deficiency. Hence, treatment of TTP requires plasma exchanges or fresh frozen plasma infusions for clearance of autoantibodies and restoration of enzymatic activity.[40] aHUS, on the other hand, is due to the excessive activation of the alternative complement pathway. Genetic mutations in the complement regulatory proteins, such as complement factor H, complement factor I, C3, membrane cofactor protein, or a combination, can result in an unchecked activation of alternative complement pathway.[41] A large European study recently showed that of 87 women who developed pregnancy-associated HUS, 56% exhibited novel or rare variants in complement genes, the most common mutations being in genes for complement factor H and complement factor I.[42] Those with complement gene variants fared worse: they required dialysis at presentation more frequently than those without (81% vs. 58%, $P = 0.02$), progressed to end-stage renal disease more frequently (64% vs. 36%, $P = 0.01$), and had a higher risk of relapse (38% vs. 16%, $P = 0.04$).[42] They also demonstrated worse pregnancy outcomes as compared with women without detectable genetic defects: fetal loss at 4.8% vs. 0% and preeclampsia at 7.7% versus 0%, respectively.[43] Similar to TTP, empiric plasma exchange has been the cornerstone of aHUS treatment: removal of auto-antibodies to alternative complement pathway and replacement of deficient gene products with plasma. This is a reasonable approach given the extreme difficulty in differentiating cases with new-onset aHUS from TTP initially and the long turnaround time for genetic testing. However, it is not a definitive treatment, and it has shown to be effective in about 50% of adults.[43] The advent of eculizumab, a humanized monoclonal anti-C5 antibody that binds with high affinity to C5, thereby inhibiting the C5 cleavage and generation of the membrane attack complex, has revolutionized the treatment of aHUS.[44] Its use appears to be safe in pregnancy, as eculizumab has not been detected in umbilical cord or blood samples of neonates.[45] In an observational study of 22 women with pregnancy-associated HUS in which 10 patients or 45% of patients were treated with eculizumab, all treated patients showed a favorable clinical response.[46] At this time, the duration of treatment is unclear and the decision is generally individualized. In a case series of 10 patients with aHUS in the general population who had achieved stable remission on eculizumab therapy, 7 patients were able to successfully discontinue the therapy, whereas 3 patients relapsed within 6 weeks of discontinuation but achieved remission again with resumption of eculizumab.[47] In our limited personal experience, we have had favorable clinical outcomes on discontinuation of eculizumab after achieving clinical remission in cases of pregnancy-triggered aHUS in the absence of known genetic mutations. Another unanswered question is whether eculizumab should be prophylactically administered in subsequent pregnancies in women with prior episodes of pregnancy-associated HUS. Again, there is no specific recommendation to do so, as the pregnancy history is not predictive of recurrence. However, it is recommended to follow these women very closely throughout their pregnancies until up to 3 months postpartum and to administer eculizumab immediately in case of recurrence. These are not official recommendations, as evidence is lacking, but rather expert opinions that may evolve as we improve our understanding of this disease.

Acute Fatty Liver of Pregnancy

AFLP is a rare (1:20,000 pregnancies) but potentially fatal obstetric emergency, with maternal and neonatal mortality of 2% and 10%, respectively.[48] Mutations in maternal and fetal long-chain 3-hydroxyacyl-CoA dehydrogenase enzyme result in accumulation of long-chain fatty acids, which causes hepatotoxicity in the mother.[49] When it is severe, liver dysfunction results in elevated bilirubin, transaminitis, coagulopathy, hypoglycemia, lactic acidosis, ascites, and encephalopathy.[50] Liver biopsy, often impractical due to coagulopathy and not mandatory for diagnosis, reveals a hallmark histology finding of microvesicular fatty infiltration of hepatocytes.[51] Pr-AKI associated with AFLP is common, occurring with varying degrees of severity in 50% to 75% of patients with AFLP.[48,52] Similar to liver pathology findings, an autopsy series reported free fatty acid deposition in the renal tubular epithelium in some cases.[53] Distinguishing AFLP from preeclampsia/HELLP is challenging, and in fact 20% to 40% patients with AFLP have a concomitant diagnosis of preeclampsia/HELLP.[52,54] Both diseases are most prevalent in the third trimester, with nausea, vomiting, epigastric pain, and jaundice being common presenting

symptoms. Hypertension and proteinuria, quintessential manifestations of preeclampsia/HELLP, occur commonly in AFLP (70%). Fortunately, the initial management of both diseases is similar: expedited delivery and aggressive supportive care. Practice guidelines from the American College of Gastroenterology recommend prompt delivery in women with AFLP, molecular testing for long-chain 3-hydroxyacyl-CoA dehydrogenase in mothers and offspring, and monitoring the offspring for clinical manifestation of long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, such as hypoketotic hypoglycemia and fatty liver.[55] Although most cases have spontaneous liver recovery after delivery, in severe cases, plasma exchange and liver transplantation have been successfully used.[56,57] Short-term renal outcome is also favorable, with normalization of laboratory findings after delivery, but long-term effects of AFLP are not well understood.[56,58]

Lupus Nephritis

Because SLE affects mostly women of childbearing age, the risk of developing lupus nephritis and subsequent Pr-AKI is a concern. Complications of lupus during pregnancy include lupus flares, preeclampsia, thrombotic events, and/or fetal complications, such as miscarriage, preterm birth, intrauterine growth restriction, and neonatal lupus.[59] Women with SLE/lupus nephritis are advised to undergo preconception counseling in a multidisciplinary approach. It is difficult to predict the course of lupus during pregnancy, as it is unclear if pregnancy predisposes to lupus flares or worsening of lupus nephritis[60]; however, the risk of flares does correlate with preconception lupus activity,[61] low C3,[62] and a history of lupus nephritis.[62] Furthermore, merely diagnosing lupus nephritis, especially for the first time in pregnancy, is difficult as it shares clinical features with other thrombotic microangiopathies (anemia, thrombocytopenia, proteinuria, AKI). The presence of decreased complements, antibodies of the antinuclear antibody panel (anti–double-stranded DNA, anti-Smith antibodies), active urine sediment, and extrarenal lupus manifestations is helpful. It may be possible to predict adverse pregnancy outcomes in SLE with angiogenic markers in the future: the PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) study demonstrated that women with the highest levels of sFlt-1 or a high sFlt-1:placental growth factor ratio in the late first trimester/second trimester exhibited an increased risk of an adverse outcome.[63] Lupus patients with concomitant antiphospholipid syndrome, in addition, have an increased risk of maternal complications (preeclampsia/HELLP) and fetal outcomes (fetal loss, intrauterine growth restriction, preterm labor).[64] Patients with SLE should be given low-dose aspirin preconceptionally or no later than gestational week 16 to prevent the development of preeclampsia and fetal growth restriction.[65,66] In patients with antiphospholipid syndrome, the addition of enoxaparin to low-dose aspirin is recommended to decrease rates of recurrent pregnancy loss.[67] If lupus nephritis is diagnosed during pregnancy, the mainstay of treatment includes steroids, calcineurin inhibitors, or azathioprine; on the other hand, mycophenolate mofetil and cyclophosphamide are avoided due to their known teratogenicity.[68] Hydroxychloroquine should be maintained throughout the pregnancy, as discontinuation has been associated with lupus flares.[69]

Pyelonephritis

The occurrence of urinary tract infections is common in pregnancy due to functional, hormonal, and anatomical changes.[70] Untreated bacteriuria itself leads to low birth weight and preterm delivery, whereas its eradication reduces the incidence of pyelonephritis and improves fetal outcomes.[71,72] Thus, it is recommended by the American College of Obstetrics and Gynecology to conduct routine screening for bacteriuria at the first prenatal visit.[73] Risk factors of urinary tract infection include diabetes mellitus, HIV, urologic anomalies, sickle cell hemoglobinopathy, and history of *Chlamydia trachomatis*.[74] The most common culprit remains *Escherichia coli*, at an incidence of 76% to 81%,[75,76] whereas other gram-negative organisms, such as *Klebsiella, Enterobacter*, and *Proteus* species, occur at less than 10%[75,76]; gram-positive organisms (group B *Streptococcus*) can occur at 10%.[77] An untreated urinary tract infection can progress to pyelonephritis, which is a severe entity in pregnancy[78] because approximately 1 in 5 women with pyelonephritis will develop some criteria of the sepsis syndrome.[77,79–82] Thus, early aggressive treatment with appropriate antibiotics is crucial and has significantly decreased the incidence of Pr-AKI from 20% to 2%.[77] Hydration, on the other hand, must be carefully administered, as the risk of developing respiratory distress syndrome is high given the altered alveolar capillary membrane permeability due to endotoxin-mediated endothelial injury.

Antibiotic therapy should be directed by the microbiology and sensitivity analysis (Table 2). Oral antibiotics, such as nitrofurantoin and beta-lactams, are preferred for uncomplicated urinary tract infections or cystitis. However, nitrofurantoin should be avoided in women with glucose-6-phosphate dehydrogenase deficiency and in the third trimester of all pregnancies due to the theoretical risk of hemolytic anemia in the fetus or

newborn.[83] Another class of drugs to be cautious about is trimethoprim/sulfonamides: trimethoprim harbors concerns of neurotube and cardiovascular defects in the first trimester, whereas sulfonamides carry the risk of increasing unbound bilirubin due to competitive binding causing fetal jaundice.[84] Hence, the use of trimethoprim/sulfamethoxazole should be avoided in both the first and third trimesters.

Treatment of pyelonephritis, on the other hand, requires the use of parenteral antibiotics (Table 2). We recommend avoidance of fluoroquinolones and aminoglycosides if possible, given concerns over animal reports of arthropathy of the fetus in the former class[85] and the risk of nephrotoxicity of the mother in the latter. Successful treatment should be confirmed with a negative urine culture 1 to 2 weeks after completion of antibiotics to demonstrate "test of cure."

Postrenal Pr-AKI

Obstructive causes of Pr-AKI are unusual in pregnancy. Physiologic hydronephrosis, which occurs in up to 90% of pregnant women, is a normal occurrence in pregnancy due to the compression of the ureter at the pelvic brim by the growing uterus and smooth muscle relaxation induced by increased progesterone levels.[86,87] The combination of urinary stasis and lithogenic factors of pregnancy (increased urinary calcium, oxalate, uric acid, and sodium) may contribute to renal calculi formation.[88,89] Bilateral renal calculi, although a rare cause of Pr-AKI, will almost always require a surgical intervention, such as ureteroscopy,[90] placement of ureteral stents, or nephrostomy tubes.[91] Iatrogenic injuries to the bladder and ureters are exceptionally rare causes of Pr-AKI and are usually a result of emergent cesarean deliveries, especially in women with altered urologic anatomy, such as ectopic kidneys or duplication of ureters.[92] Obstructive uropathy, by uterine compression of the ureters, is another rare event that has shown to result in a high fetal mortality of 33% in one study.[91] The etiologies ranged from multiple gestations, solitary kidney, polyhydramnios, and nephrolithiasis, and treatment was directed at the underlying cause.[91] Ultimately, despite the infrequent

Table 2. Preferred antibiotics for treatment of urinary tract infection and pyelonephritis in pregnancy[95]

Drug	Mode of administration	Dosage	Comments	FDA category[a]
Penicillins				
• Amoxicillin	Oral	500 mg every 8 hours or 875 mg every 12 hours	Give 3–7 days May have limited utility against gram-negative organisms	B
• Ampicillin	Oral	250 mg to 500 mg every 6 hours	Give 3–7 days Commonly used	B
• Piperacillin-tazobactam	i.v.	3.375 g every 6 hours	Give 7–14 days For severe infection	B
Cephalosporins				
• Cephalexin	Oral	500 mg every 6 hours	Give 3–7 days Commonly used	B
• Cefpodoxime	Oral	100 mg every 12 hours	Give 3–7 days	B
• Ceftriaxone	i.v.	1 gm every 24 hours	Give 7–14 days Commonly used	B
• Cefepime	i.v.	1 gm every 12 hours	Give 7–14 days Covers *Pseudomonas*	B
Monobactam				
• Aztreonam	i.v.	1 g every 8 hours	Give 7–14 days In setting of beta lactam allergy	B
Carbapenems				
• Imipenem/cilastatin	i.v.	500 mg every 6 hours or 1 g every 8 hours	Give 7–14 days Limited data; for severe infection	C
• Meropenem	i.v.	1 g every 8 hours	Give 7–14 days Limited data; for severe infection	B
Nitrofurans				
• Nitrofurantoin	Oral	100 mg every 12 hours	Give 5–7 days Common prophylactic agent; avoid in G6PD deficiency and third trimester for risk of hemolytic anemia	B

FDA, Food and Drug Administration; G6PD deficiency, glucose-6-phosphate dehydrogenase deficiency.
[a]FDA Pregnancy Categories: Category A, adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters); Category B, animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women; Category C, animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; Category D, there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; Category X, studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

occurrence, obstructive uropathy can result in high morbidity.

Management of Pr-AKI

Successful management of Pr-AKI requires a multi-disciplinary approach with close collaboration among nephrologists, obstetricians, intensivists, and other team members. The identification of the underlying etiology of Pr-AKI is crucial in its proper management. For biopsy-proven glomerulonephritis, steroid and immunosuppressive therapy will be necessary. For cases of severe preeclampsia/HELLP syndrome or AFLP, prompt delivery of the fetus is warranted. The use of i.v. magnesium remains a cornerstone in the prevention of seizures in a patient with preeclampsia, but as magnesium is renally excreted, women with moderate to severe Pr-AKI are at risk of magnesium toxicity. In women with preserved renal function, the usual loading dose of magnesium is 4 to 6 g followed by a maintenance dose of 1 to 2 g per hour for 24 hours after the last seizure.[93] For moderate reduction in renal function, the standard loading dose with a reduction in maintenance dose has been suggested, with monitoring of serum magnesium level (therapeutic levels of 5–8 mg/dl) and clinical toxicity (hypotension, hyporeflexia, and somnolence). In cases of severe renal impairment requiring dialysis, the lower range of loading dose (4 g) is recommended, with further administration based on frequent surveillance of serum magnesium levels as outlined previously.[93] For most cases of TTP, plasma exchange is recommended, whereas a diagnosis of aHUS will require the addition of eculizumab. Additional measures, such as volume resuscitation, prevention of further injury, timely initiation of renal replacement therapy, and prompt delivery of fetus may be needed. If volume repletion is necessary, resuscitation efforts should be carefully monitored, as women with either endotoxin-mediated injury or preeclampsia are prone to developing pulmonary edema. Most complications of Pr-AKI can be medically treated similar to nonpregnant patients: volume overload can be treated with loop diuretics, hyperkalemia managed with cation exchange resins, metabolic acidosis with alkali therapy, and anemia with blood transfusion and/or erythropoietin-stimulating agents. If despite these interventions, the kidney injury progresses or the patient develops signs of uremia, initiation of renal replacement therapy will be necessary. There are limited data on the timing of initiation, duration of therapy, or choice of modality of renal replacement therapy in Pr-AKI, thus the dialysis prescription needs to be individualized. Like dialysis management in pregnant women with end-stage renal disease,

longer and more frequent dialysis sessions should be considered to avoid hypotension, to restore electrolyte homeostasis, and to adequately remove uremic toxins. Along with management of the mother, fetal monitoring for well-being and appropriate growth is an integral part of the care plan. If the gestation is less than 34 weeks and delivery is imminent, administration of glucocorticoids is indicated to reduce the risk of neonatal respiratory distress syndrome.[94]

Conclusion

At first glance, the overall incidence of Pr-AKI is declining in most parts of the world; however, there is a disturbing trend of an increased incidence in developed nations such as the United States and Canada, although the absolute numbers are still low. A concerted effort is needed to standardize the definition and classification of Pr-AKI. Identification of underlying etiology of intrarenal Pr-AKI is not always straightforward and very much depends on timing, risk factors, and sometimes a therapeutic trial (i.e., steroids for lupus nephritis). The availability of biomarkers, such as angiogenic factors, may prove to be pivotal in the diagnosis of preeclampsia and prediction of adverse pregnancy outcomes. Genetic testing is important to diagnose etiologies of AFLP and aHUS; however, they are expensive, time-consuming, and not immediately available to help guide clinical practice at presentation. The use of eculizumab for aHUS and potentially for preeclampsia/HELLP may be groundbreaking and life-saving. More research is sorely needed to develop novel preventive and treatment modalities, especially as pregnancies in women with pre-existing comorbidities and risk factors for Pr-AKI are increasing.

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