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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 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 Traditional causes of Pr-AKI, such as septic abortions and puerperal sepsis, have been replaced by hypertensive diseases, such as preeclampsia and thrombotic microangiopathies comprising thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic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.

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Pregnancy-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 postabortal 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

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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] The increase of Pr-AKI was associated with older maternal age, pregnancies with hypertensive disorders, and underlying chronic kidney disease.[8,9] 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 still 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 cGould 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 obstetrics emergencies such as abruptio placentae. The exact pathogenesis of

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