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Challenges in Diagnosis and Treatment of Acute Kidney Injury During Pregnancy

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ABSTRACT

Pregnant women with acute kidney injury (AKI) represent a unique challenge for health care providers. In approaching AKI in pregnant women, emphasis should be placed on making an early and accurate diagnosis to allow prompt intervention and to facilitate recovery from AKI. In this article, I review the prevalence of AKI in pregnancy and the impact it has on morbidity and mortality. I then review diagnostic criteria and discuss fetal monitoring methods. The utility of various renal replacement methods available for pregnant women with AKI is discussed, as well as the specific adjustments to hemodialysis prescriptions for pregnant women. This review summarizes the existing data on the management of AKI during pregnancy, however, most of these studies were observational. Future research with longitudinal study designs are needed to allow examination of the effect of AKI during pregnancy on adverse maternal and fetal outcomes.

Implication for health policy/practice/research/medical education:
This review summarizes the existing data on the management of AKI during pregnancy, however, most of these studies were observational. Future research with longitudinal study designs are needed to allow examination of the effect of AKI during pregnancy on adverse maternal and fetal outcomes.

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1. Introduction

An acute kidney injury (AKI) in pregnant patients poses unique challenges for clinicians involved in the care of these patients. The renal system undergoes anatomical and physiological changes during a normal pregnancy. Clinicians need to be familiar with these changes because they may affect the diagnosis and management of AKI. Renal plasma flow increases by 50% to 70% during pregnancy in the first 2 trimesters (1). Additionally, the glomerular filtration rate (GFR) increases from an average of 97 mL/min to 128 mL/mm by the end of the first trimester. Consequently, both blood urea nitrogen (BUN) and creatinine concentrations are lower than the normal range, and thus a normal BUN or creatinine level in a pregnant female may actually indicate underlying renal disease (2). Serum sodium decreases by 3 mEq/L and both ionized and unionized calcium concentrations also show a small decrease (3). Magnesium concentrations decrease by approximately 10% to 20% during the first trimester (4). Hyperventilation that occurs during pregnancy is probably due, in part, to progesterone stimulating the respiratory center (5). The effect is chronic respiratory alkalosis, which is compensated for by the renal excretion of bicarbonate. A typical plasma bicarbonate level is 21 mmol/L (6).

The presence of AKI increases the mortality associated with any primary disease (7). The overall mortality rate associated with AKI is 20%, and those requiring renal replacement therapy (RRT) have a mortality rate approaching 50%. It has traditionally been thought that patients who do survive ultimately recover renal function; however, recent population-based studies suggest that a strikingly large percentage of patients who have AKI require perma-

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nent RRT or do not fully recover renal function (8, 9).

2. Epidemiology of AKI in Pregnancy

AKI is a common medical problem, affecting approximately 5% of all hospitalized patients and 30% of critically ill patients (10-12). However, the incidence of AKI in pregnancy is not as common, decreasing from 1 per 2000 pregnancies to 1 in 20,000 pregnancies in developed countries (13, 14). This low incidence is probably attributed to improved obstetric care. Conversely, the incidence is higher and continues to be a major problem in developing countries, resulting in high maternal mortality (15).

3. Etiology of AKI in Pregnancy

The initial assessment of patients with AKI classically includes the differentiation among prerenal, intrinsic renal, and postrenal causes when the patient is in a nonpregnant state (16-19). However, certain conditions are associated with pregnancy that varies between the first and second halves of gestation. In most women, careful clinical assessment will identify the underlying etiology (*Table 1, Algorithm 1*). In early pregnancy, the most common problems are prerenal disease, due to hyperemesis gravidarum, or acute tubular necrosis, resulting from a septic abortion (20).

Pre-eclampsia and HELLP (hemolysis, elevated liver enzymes, and low platelet count) are some of the most important causes of AKI in pregnancy, but most of the patients suffering from any of these conditions do not have AKI (21-23). The estimated incidence of AKI occurring with pre-eclampsia is 1.5% to 2% (21). Other pregnancy-specific causes include acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, amniotic fluid embolism, infection, sepsis, intravascular volume depletion and obstruction, or idiopathic etiologies (21-23). At the end of pregnancy, uterine hemorrhage and hypotension occur in 7% to 39% of patients with AKI (21-24). Postpartum hemorrhage is one of the leading causes of maternal death (23-25). Bilateral renal cortical necrosis (in less severe cases acute tubular necrosis) may be induced during pregnancy by abruptio placentae or other severe complications such as placenta previa, prolonged intrauterine fetal death, or amniotic fluid embolism (26, 27).

4. Diagnosis of AKI in Pregnancy

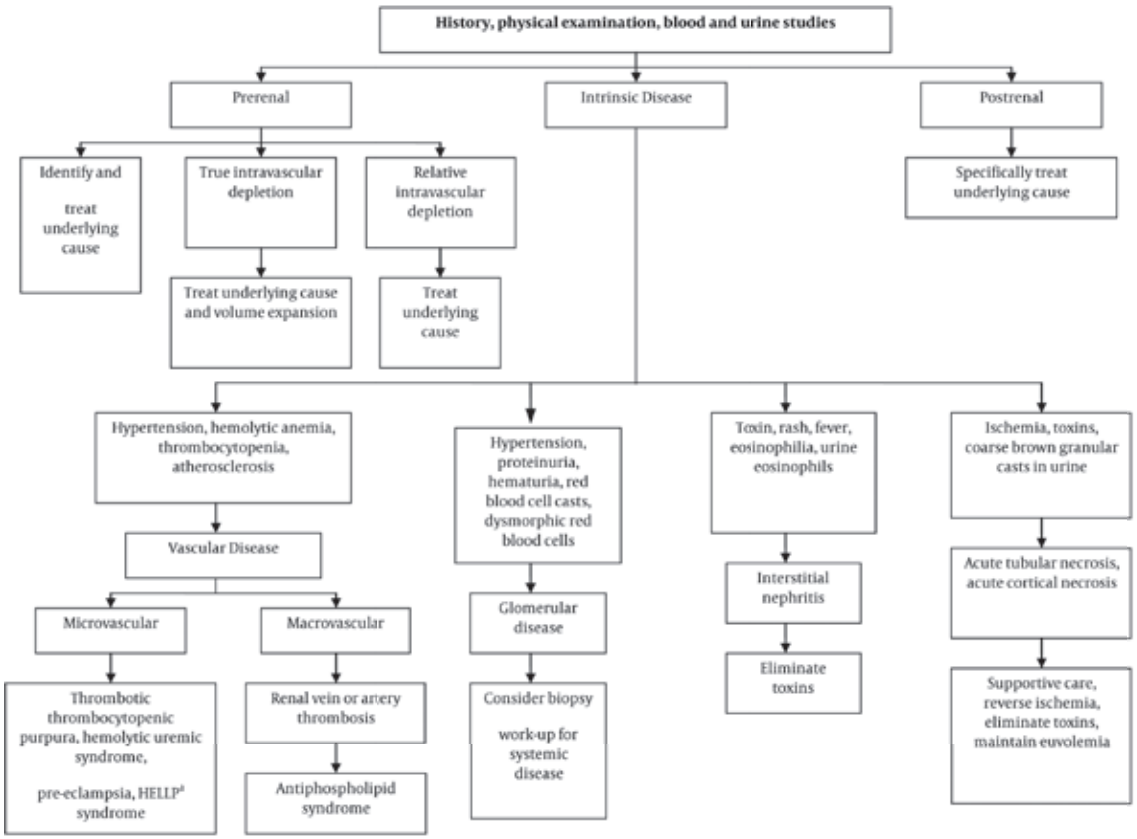
Acute kidney injury is defined as an abrupt absolute increment in the serum creatinine concentration of ≥ 0.3 mg/dL (26.4 μmol/L) from the baseline concentration within 48 hours, a percentage increase in the serum creatinine concentration of ≥ 50%, or oliguria of less than 0.5 mL/kg per hour for more than 6 hours (10, 11). The absolute change in serum creatinine of ≥ 0.3 mg/dL is based on epidemiologic data that demonstrated an 80% increase in mortality risk associated with changes in the serum creatinine concentration of only 0.3 to 0.5 mg/dL (10, 11, 17). However, the clinical utility of these criteria during pregnancy still needs to be assessed. The utility of the creatinine increment cutoff of 0.3 mg/dL may need to be studied to determine its applicability in testing for AKI in pregnant women, although the urine output criterion will continue to be the most reliable criterion for early diagnosis. Therefore, clinicians should have a low threshold for triggering laboratory assessment for AKI once a drop in urine output is observed in a pregnant woman. Fractional excretion of sodium and fractional excretion of urea nitrogen have been used to distinguish between the two main causes of AKI: prerenal state and acute tubular necrosis (28). However, these formulas have not been validated in pregnancy. Several biomarkers for AKI have been evaluated in nonpregnant patients; however, none of the biomarkers have been used for daily practice. These biomarkers will hopefully facilitate early diagnosis and stratify the cases of AKI (28, 29).

Table 1. Pregnancy-Related Causes of Acute Kidney Injury

Prerenal	Renal	Postrenal
Hypovolemia	Acute tubular necrosis	Gravid uterus
Vomiting	Acute interstitial nephritis	Papillary necrosis
Hyperemesis gravidarum	Acute fatty liver	Polyhydramnios
Blood loss	Pre-eclampsi	
Abortion	HELLP [a] syndrome	
Placenta previa	TTP [a] or HUS [a]	
Placenta abruption	Acute cortical necrosis	
Hypoperfusion	Glomerulonephritis	
Sepsis	Amniotic fluid embolism	
Pyelonephritis	Antiphospholipid syndrome	
Infected abortion	Arterial thrombosis	
Heart failure	Renal vein thrombosis	

[a] Abbreviations: HELLP, hemolysis elevated liver enzymes and a low platelet count; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura

Algorithm 1. Algorithmic Approach to the Diagnosis of Acute Kidney Injury in Pregnancy.



[a] Abbreviation: HELLP, hemolysis elevated liver enzymes and a low platelet count

5. Management of AKI in Pregnancy

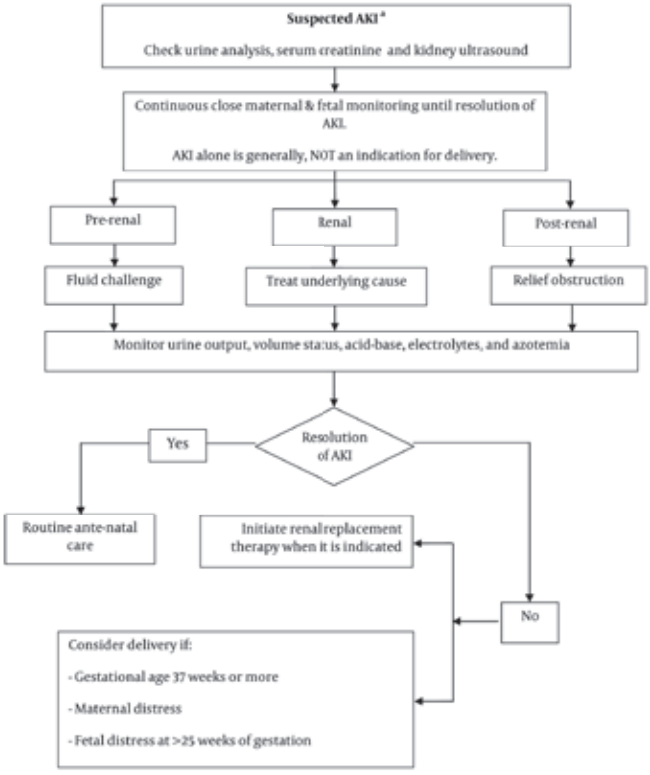
The optimal care of pregnant women with AKI requires a multidisciplinary team, including a maternal-fetal medicine specialist, who should be involved early in the care (*Algorithm 2*). Early treatment for AKI typically includes optimization of the hemodynamic status and correction of any volume deficit. This will have a salutary effect on kidney function, helping to minimize progression of further kidney injury, and potentially facilitating recovery from AKI with a minimization of any residual chronic impairment of kidney function (30). The intravascular volume and mean arterial pressure should be maintained, and acidosis and electrolyte abnormalities should be corrected. Further damage should be prevented by avoiding nephrotoxic agents. All medications need to be adjusted for the level of renal function. Pregnant women with AKI need to be monitored for any other organ dysfunction.

Fetal monitoring is needed for all pregnant women with AKI. In cases where the gestational age is 25 weeks or less, assessment is usually limited to Doppler auscultation to document the fetal heart (31, 32). At 26 weeks or more, other more sensitive methods can be used, including a fetal movement assessment, contraction stress test, nonstress test, biophysical profile, or umbilical artery Doppler velocimetry (31, 32). Regular fetal monitoring with contingency planning for a possible emergency cesarean delivery is conducted if fetal distress is observed for fetuses that have reached an adequate level of maturity.

No controlled trial data are available, but clinicians should be prepared to start dialysis early in pregnant patients and maintain effective doses as the pregnancy continues (33). Acute indications for dialysis are the same for pregnant patients as for nonpregnant patients in terms of fluids, electrolytes, and complications of uremia. However, the replacement therapy should be initiated early and not postponed until the onset of advanced uremic manifestations (33, 34). Information from registries suggests that aggressive control of azotemia results in better fetal and maternal outcomes; therefore, we should target a BUN within the normal range (33, 34).

The options for renal replacement therapy in patients with AKI include peritoneal dialysis (PD), intermittent hemodialysis, and continuous renal replacement therapy (CRRT). PD is less efficient than hemodialysis in providing adequate clearance in an acute state, and it is more difficult to insert a PD catheter (35). The gravid uterus will also limit the volume of fluid used in each exchange (36). Despite these limitations, this treatment may be the only option available in many rural areas in developing countries. Adequate control of azotemia with a lower

Algorithm 2. Algorithmic Approach to the Management of AKI in Pregnancy.



[a] Abbreviations: AKI, acute kidney injury; HELLP, hemolysis elevated liver enzymes and a low platelet count; HUS, hemolytic uremic syndrome, TTP, thrombotic thrombocytopenic purpura

blood flow rate to avoid hemodynamic instability can be performed by either slower solute removal (over 6 to 12 hours by sustained low-efficiency dialysis) or by CRRT. Before acute hemodialysis is initiated, vascular access must be established. Placement of the venous dialysis catheter must be considered carefully, particularly in critically ill pregnant women. The location depends upon whether the patient has a clinical and ambulatory status (37). The internal jugular vein is most often the preferred site. The femoral vein is another site that is used but is less preferred because of the increased risk of deep vein thrombosis during pregnancy.

Determining the ultrafiltration (5) goals in pregnant women can be challenging. The intravascular volume in a normal pregnancy is expanded; therefore, a guided UF that avoids intradialytic hypotension is critical. Monitoring uteroplacental perfusion, fetal blood flow, and amniotic fluid volume may assist in maintaining adequate fetal perfusion and titrating ultrafiltration (38, 39). This ultrafiltration can be achieved by minimizing the UF rate requirements by increasing the frequency and duration of treatments, as well as by ultrafiltration profiling. Vasoconstriction due to a lower body temperature has been used to increase vascular resistance and improve hemodynamic stability during dialysis. Hypothermia, however, may be an undesirable consequence in critically ill pregnant patients due to the adverse effects of vasoconstriction and possible decline in uterine perfusion (40). Similarly, sodium profiling should be avoided because the serum sodium concentration in pregnant women is physiologically decreased, and the impact of sodium profiling on a fetus is not known. The dialysate calcium and potassium concentration should be adjusted to avoid electrolyte disturbances.

Coagulation factors are also altered during pregnancy. Fibrinogen (factor I) is markedly increased by approximately 2 g/L at term (41). Factors VII, VIII, and X are also increased. Furthermore, the activity of factors IX and XII increase, and factors XI and XIII decrease by 30% or more at term (42, 43). Antithrombin II probably decreases (43). A progressive increase occurs in fibrin and fibrinogen degradation products throughout pregnancy. The agent of choice is heparin because it does not cross the placental barrier, has no teratogenicity, and is easy to dose (44, 45). Heparinization of the extracorporeal circuit (regional heparinization) with the use of its protamine sulfate is another method that is recommended to correct the excess anticoagulant effect of heparin, particularly in women with active bleeding (46). Trisodium citrate safety in pregnancy is not known; therefore, its use should be avoided. The dialysate bicarbonate concentration should vary based upon the acid-base status of the patient; however, overcorrection should be avoided, and the physiologic metabolic acidosis should be targeted. For postpartum patients, no evidence exists regarding dosing dialysis any differently to that for other patients with AKI.

6. Conclusion

AKI during pregnancy poses a challenge for physicians. In view of the multifaceted problems that potentially complicate pregnancies in women with AKI, multidisciplinary involvement comprising nephrologists, obstetricians, and neonatologists is extremely important. To date, there have been no randomized or prospective trials that have examined the impact of AKI on maternal and fetal outcome or therapeutic interventions. Therefore, epidemiologic studies are a crucial first step in achieving early detection and intervention, as well as for improving outcomes in pregnant women with AKI.

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