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Acute renal failure in pregnancy

Saubhik Sural*, Chandrasekhar Panja†

*Consultant Nephrologist, †Registrar, Department of Nephrology, Peerless Hospital and BK Roy Research Center, Kolkata, India.

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ABSTRACT

Acute renal failure (ARF) is a dreaded complication of pregnancy-associated with significant mortality and morbidity. It is important to know the pregnancy specific causes of ARF. The aim is to write a review on the etiology, differential diagnosis, and management of ARF in women during pregnancy and puerperal period. The principles of management must take into consideration the fetal health. The treating physician must have a good knowledge of physiologic changes that occur in pregnancy. With timely diagnosis and multidisciplinary approach both maternal and fetal outcome improves.

Text incidence

In developed countries, the incidence of acute renal failure (ARF) in pregnancy has come down and is now estimated to be <1 in 20,000 pregnancies. However, in developing countries, renal failure continues to be an important cause of maternal and fetal mortality. In India obstetric ARF constitutes 14.5–4.3% of all ARF.[1–5]

Etiology

Previously septic abortion used to be the commonest cause of ARF in early pregnancy (12–18 weeks). A second peak occurs between gestational week 35 and the puerperium mostly due to various pregnancy specific syndromes. Different causes of ARF in pregnancy are given in the Table 1. A total of 34 patients with pregnancy-related ARF were included in a study period of 3 years between 2004 and 2007 in our hospital.[6] Hemorrhage was the etiology for ARF in 5 (15%). In 12 (34%), puerperal sepsis was the etiological factor, while 2 (6%) patients developed ARF following septic abortion. Pre-eclampsia, eclampsia and hemolysis elevated liver enzyme and low platelet (HELLP) syndrome accounted for 8 (24%). Two (6%) were diagnosed with hemolytic uremic syndrome (HUS) and 5 (15%) were of other miscellaneous etiology like systemic lupus erythematosus (SLE), vasculitis and anti-phospholipid antibody (APLA) syndrome. Four (12%) patients suffered from biopsy-proved cortical necrosis. The differential features of main clinical syndromes leading to ARF specific for pregnancy are given in the Tables 2 and 3.

Table 1
Important etiologies of acute renal failure in pregnancy.

Pregnancy specific	Other causes
Septic abortion	Vomiting, diarrhea
Pre-eclamptic toximea/HELLP	Acute pyelonephritis
Thrombotic thrombocytopenic purpura	Drugs
Hemolytic uremic syndrome	Acute glomerulonephritis
Acute fatty liver of pregnancy	SLE/vasculitis
Puerperal sepsis	Phospholipid antibody syndrome
Hemorrhage	
Amniotic fluid embolism	
Prolonged intrauterine fetal death	
Obstruction due to gravid uterus	

HELLP: hemolysis elevated liver enzyme low platelet, SLE: systemic lupus erythematosus.

Acute pyelonephritis

Acute pyelonephritis, unless complicated, usually does not lead to renal failure in non-pregnant individuals. In pregnancy because of higher sensitivity of the vasculature to bacterial endotoxins and cytokines acute pyelonephritis often causes ARF.

Table 2
Differential features of main clinical syndromes leading to acute renal failure during pregnancy.

	PE	HELLP syndrome	Acute fatty liver of pregnancy	TTP	HUS
Typical onset	3rd trimester	3rd trimester	3rd trimester	2nd–3rd trimester	PP
PE associated		80%	46%	Rare	Possible
Hypertension	100%	80%	25–50%	Rare	50%
Low platelets	+	100%	64%	100%	50%
Fever, neurologic symptoms				+++	+

Modified from Sibai BM.[7] HELLP: hemolysis elevated liver enzyme low platelet, HUS: hemolytic uremic syndrome, PE: pre-eclampsia, PP: post pregnancy, TTP: thrombotic thrombocytopenic purpura.

*Corresponding author.
E-mail address: Saubhik_sural@hotmail.com

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Table 3
Differential laboratory investigations of main clinical syndromes leading to acute renal failure during pregnancy.

	PE	HELLP syndrome	Acute fatty liver of pregnancy	TTP	HUS
Ammonia	=	=	+++	=	=
PT and PTT	=	=	>	=	=
Transaminases	=	+++	+	=	=
Bilirubin	=	+	+++	+	++
Hemolytic anemia	=	++	+	++	+++
ADAMTS13				↓↓↓	↓

Modified from Sibai BM.[7] HELLP: hemolysis elevated liver enzyme low platelet, HUS: hemolytic uremic syndrome, PE: pre-eclampsia, PT: prothrombin time, PTT: partial thromboplastin time, TTP: thrombotic thrombocytopenic purpura.

Septic abortion

Septic abortion was the most frequent etiology of septic ARF in pregnancy. The commonest organism was clostridia. The patients used to present with high fever, myalgia, vomiting, diarrhea, and hypotension. Although renal function often recovers completely, bilateral cortical necrosis may occur. This is now much rare after legalization of medical termination of pregnancy.

Pre-eclampsia or eclampsia

Pre-eclampsia may be associated with glomerular endotheliosis and mesangiosis characterized by enlarged glomeruli with empty capillary lumens, endothelial cell swelling, and sub endothelial fibrin deposit.

Pre-eclampsia and its complications are important causes of ARF in pregnancy. This is due to acute tubular necrosis (ATN) though acute cortical necrosis (ACN) may also occur. Glomerular cell swelling along with complete obliteration of the capillary lumen, endothelial dysfunction, vasoconstricton, and hypovolemia contributes to ATN. There are often other precipitating factors like nephrotoxic drug use, antepartum or post-partum hemorrhage, sepsis, and disseminated intravascular coagulation (DIC).

Hemolysis elevated liver enzyme low platelet syndrome

It is often associated with severe pre-eclampsia. However, it can occur in the absence of hypertension and proteinuria (20% cases). The most common presentation is with upper abdominal pain, nausea, and vomiting. Sometimes this is associated with visual symptoms, bleeding, and jaundice. The syndrome can present in post-partum period (up to 30% of cases). Full blood count including platelets and a blood film to look for red blood cells (RBC) fragmentation must be obtained. Diagnostic criteria of Sibai et al is most widely accepted (RBC fragmentation, platelet count $<100\times10^9$/L, lactate dehydrogenase (LDH) >600 U/L, and aspartate aminotransferase (AST) >70 U/L).[7] The platelet count has been found to be moderately predictive of severity: $<50{,}000/mm^3$ is class I (severe), between 50,000 and 100,000 is class II (moderately severe) and >100,000 is class III (mild). This system is termed as the Mississippi classification.[8] Alkaline phosphatase and bilirubin are usually not very high unlike acute fatty liver of pregnancy (AFLP). The liver shows periportal hemorrhage and necrosis.

The ARF occurs in the most severe cases and sometimes with multiple organ dysfunctions. In Sibai series,[7] renal histology showed ATN in all except one (cortical necrosis). One-third of the patients required dialysis and all of them recovered. In a long-term one patient had moderate renal failure and required dialysis 7 years after pregnancy. The HELLP syndrome was the etiology of ACN in one of our patients.[6]

Management usually requires urgent delivery in the maternal interest, although conservative management especially remote from the term has been utilized and associated with improved neonatal outcome. High-dose steroid (10 mg dexamethasone 12 hourly) may improve the hematological and biochemical parameters antenatally and may hasten the resolution of HELLP syndrome. Plasma exchange may be beneficial. In subsequent pregnancies these women are at increased risk of pre-eclampsia and intrauterine growth retardation (IUGR) but risk of HELLP syndrome is low (3–5%).

Acute fatty liver of pregnancy

This is characterized by severe hepatic failure in third trimester, and rarely in puerperium. The usual finding is very high bilirubin with less elevated transaminases. It helps differentiation from the HELLP syndrome. Deficiency of LCHAD (3-hydroxyacyl-CoA dehydrogenase) leads to an accumulation of medium and long chain fatty acid.[9] Some considers it as an adult for of Reye's Syndrome. The features of pre-eclampsia are present in almost 40%. Decrease in anti-thrombin II, DIC and high serum urate are frequently present. Liver histopathology shows microvascular fatty infiltration predominantly in centrilobular area. Ultrasonograph and computed tomography (CT) of liver may give some clue to diagnosis. The incidence of ARF may be up to 60% but often mild and does not require dialysis.

Acute renal factor may be due to hemodynamic factors as is hepatorenal syndrome or as a consequence of DIC and shock.

The mortality rate for mother and fetus, which was once very high[10] is now much better with survival exceeding 80–90%. This is possibly because milder forms of the disease are recognized. The AFLP does not usually recur in subsequent pregnancies.

Uterine hemorrhage

Hemorrhage and hypotension are responsible for ATN in some cases. Most of the time it is an additional factor along with pre-eclampsia, abruptio placentae, and HELLP syndrome.

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) occurs most often during second or third trimester and presentation is microangiopathic hemolytic anemia, thrombocytopenia, neurological abnormalities, fever, and renal dysfunction. Unusually large form of von Willebrand factor is often present and aggregate with platelets to produce thrombosis. The pathophysiological hypothesis is a deficiency of the ADAMTS13 proteinase, which degrades the serum polymers of von Willebrand factor.

Due to the high levels of estrogens during the pregnancy, particularly in the second half ADAMTS activity falls and TTP clinically manifests. As rapid assays for antibodies against ADAMTS13 are not readily available, special consideration must be given to the clinical details in order to make a correct diagnosis.

Plasmapheresis should be initiated soon after the diagnosis is made in TTP. A response manifested by an increase in platelet count and reduction in LDH levels is expected within a few days. Plasma exchanges are performed daily until the platelet count becomes normal and hemolysis resolves as evident by decrease in LDH levels. Maternal mortality with TTP has substantially declined when plasma therapy is utilized. However delay of diagnosis and therapy for initial TTP confounded by pre-eclampsia/(HELLP) syndrome remains a significant maternal-perinatal threat.[11] Some patients with TTP and high antibody titers against ADAMTS may not respond to plasma exchange alone. These patients require immunosuppressive therapy.

Hemolytic uremic syndrome

Hemolytic uremic syndrome typically occurs between a few hours to 8–10 weeks post-partum. Usually the pregnancy is uneventful.

Hence, it is also described as idiopathic post-partum ARF. This is associated with microangiopathic hemolytic anemia. Hypertension may be present along with convulsion and other neurological symptoms. The renal histopathology is either that of HUS in non-pregnant patients or arterial lesion like malignant nephrosclerosis.

The etiology is unknown, but sometimes it is associated with viral infection, retained placental fragments, drugs like ergotamine compounds. Some have hypocomplementemia and anti-thrombin III production deficiency. Complement plays a pivotal role in the pathophysiology of pregnancy. Levels of most complement proteins increase during pregnancy, subsequently falling after delivery precipitating HUS.

This syndrome is characterized by a generalized endothelial dysfunction.

Treatment is supportive, dialysis when necessary, control of hypertension, and dilatation and curettage to remove any retained placental fragment. Fresh plasma infusion or plasma exchange may be beneficial.

The maternal mortality, up to 50% in initial series.[12] has come down with improvement in supportive measures. Complete or partial recovery occurs in 30% cases and some may require chronic dialysis. In a recent article, Fakhouri et al showed that atypical HUS associates with pregnancy in 20% of patients, and most of them occur post-partum.[13] Complement abnormalities were found in 86% of these patients. In their study 76% of patients develop end-stage renal disease despite receiving plasma exchange. The incidence of pregnancy-related HUS was maximum in second pregnancy.

The prognosis for renal transplantation in these atypical HUS patients is also bad, especially in those who have a factor H mutation, 80% of whom will lose an allograft to recurrent disease within 2 years of transplantation.[14] Few reports suggest that the C5 mAb eculizumab may be an effective form of treatment for atypical HUS but its role in pregnancy-related HUS is yet to be ascertained.[15]

Miscellaneous causes

Drugs, acute glomerulonephritis, vasculitis, lupus nephritis, antiphospholipid antibody syndrome are other causes of ARF in pregnancy.

Cortical necrosis

Acute cortical necrosis can occur sometimes in pregnancy-related ARF. Persistent anuria is almost constant in contrast to ATN.

The histopathology shows either diffuse or patchy cortical necrosis. Renal biopsy may give an incomplete idea when the process is patchy. Selective renal angiography can quantify the lesion. Interlobular arteries show delayed filling and poor arborization. The cortical nephrogram appears heterogeneous in patchy and absent in diffuse. Computer tomography scan and magnetic resonance imaging (MRI) may be beneficial. Lacks of enhancement of the renal cortex, and poor or absent renal excretion on CT scan suggest ACN. Cortical tram track or egg shell calcification can be seen later on plain X-ray or CT scan.

Anuria may be permanent requiring chronic dialysis. Usually many patients recover some renal function and improvement has been reported to occur up to 3 years after onset.

The reasons why pregnant women are vulnerable to develop ACN are:

1. The vasculature is more prone to vasoconstrictors like angiotensin II.
2. Thromboxane excess and prostacyclin deficiency.
3. Increased concentration of endothelin I and diminished nitric oxide production.
4. Activation of coagulation cascade with early platelet activation, decreased concentration of anti-thrombin III. This is all because of generalized endothelial dysfunction.
5. Acute cortical necrosis also shares many similarities with generalized Schwartzmann reaction-induced in rabbits by endotoxin. In non-pregnant animals two small doses administered 24 hour apart cause this phenomenon whereas only one injection is sufficient in pregnant rabbits.

Many women are older multipara with pre-existing diffuse arteriolar nephrosclerosis.

Prognosis and specific treatment of acute renal failure in pregnancy

Though overall prognosis has improved, still there is significant mortality and morbidity. In our study,[6] maternal mortality was 14.8% ($n=5$). Of the 29 (85.2%) surviving patients, 26 (76.4%) had recovery of renal function and 3 (8.8%) required chronic dialysis. Management is mostly same as in non-pregnant ARF. The following points are important:

1. One must look for concealed uterine hemorrhage.
2. Dialysis should be done early to prevent toxic metabolites to cross placenta to harm the fetus.
3. Both hemodialysis and peritoneal dialysis (PD) can be done in pregnancy.
4. Prompt delivery must be done if gestational age is sufficient (28–32 weeks).
5. In case of severe pre-eclampsia, HELLP or AFLP to prevent maternal death delivery may have to be done whatever be the gestational age or fetal status.
6. In case of TTP or HUS special measures like plasma exchange needs to be done. One should try to make accurate diagnosis. However, the distinction between pre-eclampsia–eclampsia, HELLP and TTP may not always be possible due to the various overlapping clinical and laboratory findings. The therapeutic plasma exchange therapy should be considered in persistent, life-threatening microangiopathy that is refractory to conservative measures.
7. Precautions to be taken in hemodialysis are to avoid hypotension, fluid fluctuation, and volume change. Fetal contractions should be scrutinized closely for pre-term contractions and pre-term labor during dialysis.

Conclusion

Acute renal failure in pregnancy continues to be a challenge to the physicians of the developing world. It is important to know the physiologic changes and various pregnancy specific disorders that cause obstetric renal failure. The management of these life-threatening disorders differs; therefore, an accurate diagnosis is required. Better understanding of complement dysregulation in pregnancy complications is essential, especially to guide development of pharmacologic agents to modulate this system. By understanding the etiology, a logical differential diagnosis can be established, allowing appropriate therapeutic decisions to preserve both maternal and fetal well-being.

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