Acute renal failure in pregnancy

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Acute renal failure complicating pregnancy has become an unusual problem with modern medical care, occuring in less than 1 % of all pregnancies[1-14]. In the 1950's, as many as 22 % of all cases of acute renal failure were obstetric in origin with mortality rates as high as 48 %[1-4, 6-9]. Currently less than 10 % of acute renal failure is related to pregnancy[15, 16]. Mortality from this complication has also fallen dramatically with no deaths reported in several recent large series[8, 11, 12].

The improved morbidity and mortality in obstetric acute renal failure may be partially attributed to the dramatic fall in septic abortions which has been noted in data presented from the Necker Hospital in Paris and the National Maternal Hospital in Dublin[8, 17]. Another factor responsible for improved morbidity and mortality in these patients is early detection of complications during pregnancy along with more sophisticated monitoring of high risk pregnancies. Chugh et al. presented a review of 325 cases of acute renal failure from northen India, 22 % of which were obstetric in origin[18]. These women did not have access to appropriate medical care and had an overall mortality rate greater than 50 %. These patients presented acutely ill and renal failure complicating pregnancy was easily identified. The incidence of milder forms of acute renal in more uneventful deliveries may go unrecognized. In a retrospective review of acute renal failure in pregnancy as defined by a serum creatinine of greater than or equal to 1.2 mg/dl, 30 cases were identified at Charity Hospital of New Orleans (an incidence of 1 in 450 deliveries)[19]. Included in this series, however, were patients who probably had underlying renal disease that worsened during pregnancy and did not include only those forms of acute renal failure specific to pregnancy. Despite the falling incidence of acute renal failure in pregnancy this complication can be rather dramatic when it occurs and this review will focus on an organized approach to the evaluation of this unique problem.

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Renal physiologic changes in pregnancy

Understanding of the normal physiologic changes that occur during pregnancy are important in evaluating renal function. Shortly after conception several important renal structural and hemodynamic changes occur. Both the kidneys and ureters may enlarge by as much as 1 cm and the caliceal system, renal pelvis and ureters will appear dilated when evaluated by either intravenous pyelogram or renal ultrasonography[20]. These changes may persist for up to sixteen weeks after delivery and should therefore not be misdiagnosed as hydronephrosis[21]. This should also be recognized as a potential source for stasis within the urinary tract, predisposing to urinary tract infection.

There is an increase in the total body water level by 6-8 liters, 4-6 of which is in the extracellular space[22]. Plasma volume may expand by 50 % and about 900 milliequivalents of sodium may be retained during pregnancy[23]. The renal handling of acute salt and water loads in pregnancy is normal despite an increase in the circulating cortisol, desoxycorticosterone, aldosterone, renin, and angiotensin II levels. Pregnant women who are salt restricted may respond by further increases in renal and aldosterone secretion[24, 25]. However, with severe sodium restriction, natriuresis may occur despite elevated renin and aldosterone levels[25]. There also appears to be a resetting of the osmoreceptors resulting in a fall in the normal plasma osmolality and serum sodium levels without a reduction of antidiuretic hormone levels[26]. The threshold for release of this hormone appears decreased. Atrial natriuretic factor levels are normal except in those patients with pregnancy induced hypertension, in whom it rises[27].

Significant cardiac hemodynamic changes also occur with the cardiac ouput rising while the systemic vascular resistance falls, resulting in a drop in the blood pressure during pregnancy by 10-15 mmHg. A rise of more than 10 mmHg in the diastolic pressure over the baseline or more than a 15 mmHg rise in the systolic pressure may therefore signify hypertension in pregnancy, recognizing that a diagnosis of pregnancy-induced hypertension can be made at blood pressure levels significantly lower than in the non-pregnant female[29-30].

The glomerular filtration rate (GFR) as measured by either inulin or creatinine clearance rises shortly after conception to as much as 50-70 % above baseline[31]. It is therefore important to realize that the serum creatinine level

at term should be no greater than 0.8 mg/dl in normal pregnancy. The hormonal factors for this change in renal hemodynamics are unclear however it does not appear to be prostaglandin or angiotensin related. Renal plasma flow (RPF) also rises early in pregnancy falling close to normal by term so that the filtration fraction (or ratio of GFR/RPF), falls toward the mid-trimester, returning almost to normal at term[31]. In normal pregnancy protein excretion may also be increased up to a level of 0.3 grams per day. Serum uric acid levels fall due to a drop in the net tubular urate reabsorption; glucose excretion is also increased to the extent that glycosuria may occur, due both to the increase in the GFR and the fall in the tubular reabsorption of glucose[31-33].

Interpretation of renal function studies during pregnancy must take into account the above physiologic changes. Renal function studies are frequently not performed in clinically uncomplicated pregnancies and are most frequently determined in patients with proteinuria, hypertension and or edema. Renal failure presenting during pregnancy may be due to any of the many causes of acute renal failure that can occur in the non-pregnant state. Secondly, patients with underlying chronic renal disease will frequently experience worsening hypertension, proteinuria, or deterioration in renal function during pregnancy[34-38]. This may actually be the initial presentation of their renal disease and this should be suspected when proteinuria and hypertension occur during the first trimester of pregnancy. Finally, are causes of renal failure specific to pregnancy on which the remainder of this discussion will focus. As shown in Figure 1, an organized approach to acute renal failure in the first two trimesters of pregnancy relies particularly on urinalysis, while acute renal failure occurring during the third trimester and postpartum period is best evaluated by the clinical presentation including liver function tests, peripheral smear and coagulation factors (Figure 2)[39].

Renal failure in the first and second trimester

Pre-renal azotemia occurring during pregnancy may be secondary to hyperemesis gravidarum. This condition may result in a decreased intravascular volume resulting in a re-

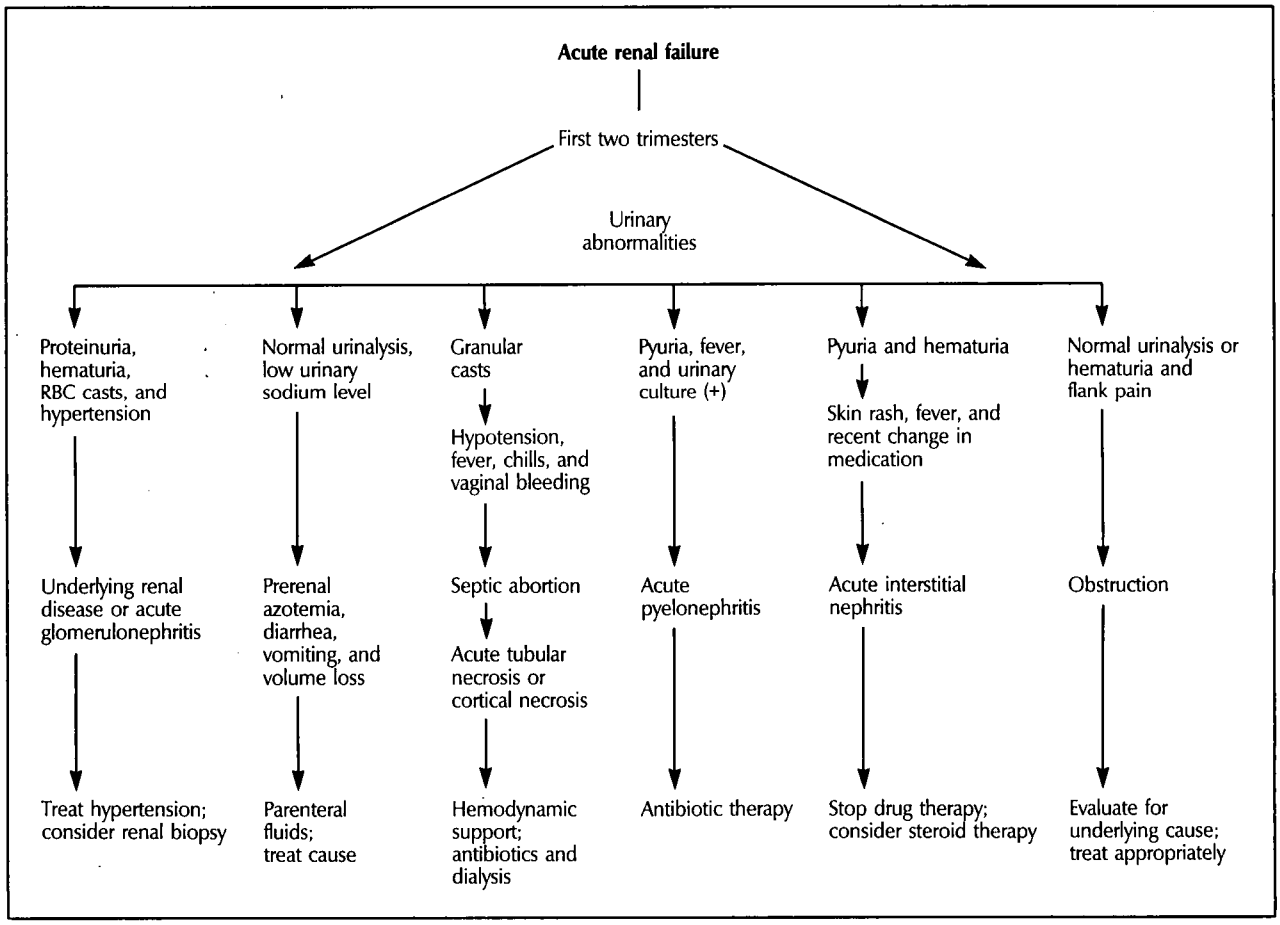

Fig. 1.—Acute renal failure in pregnancy: first two trimesters.

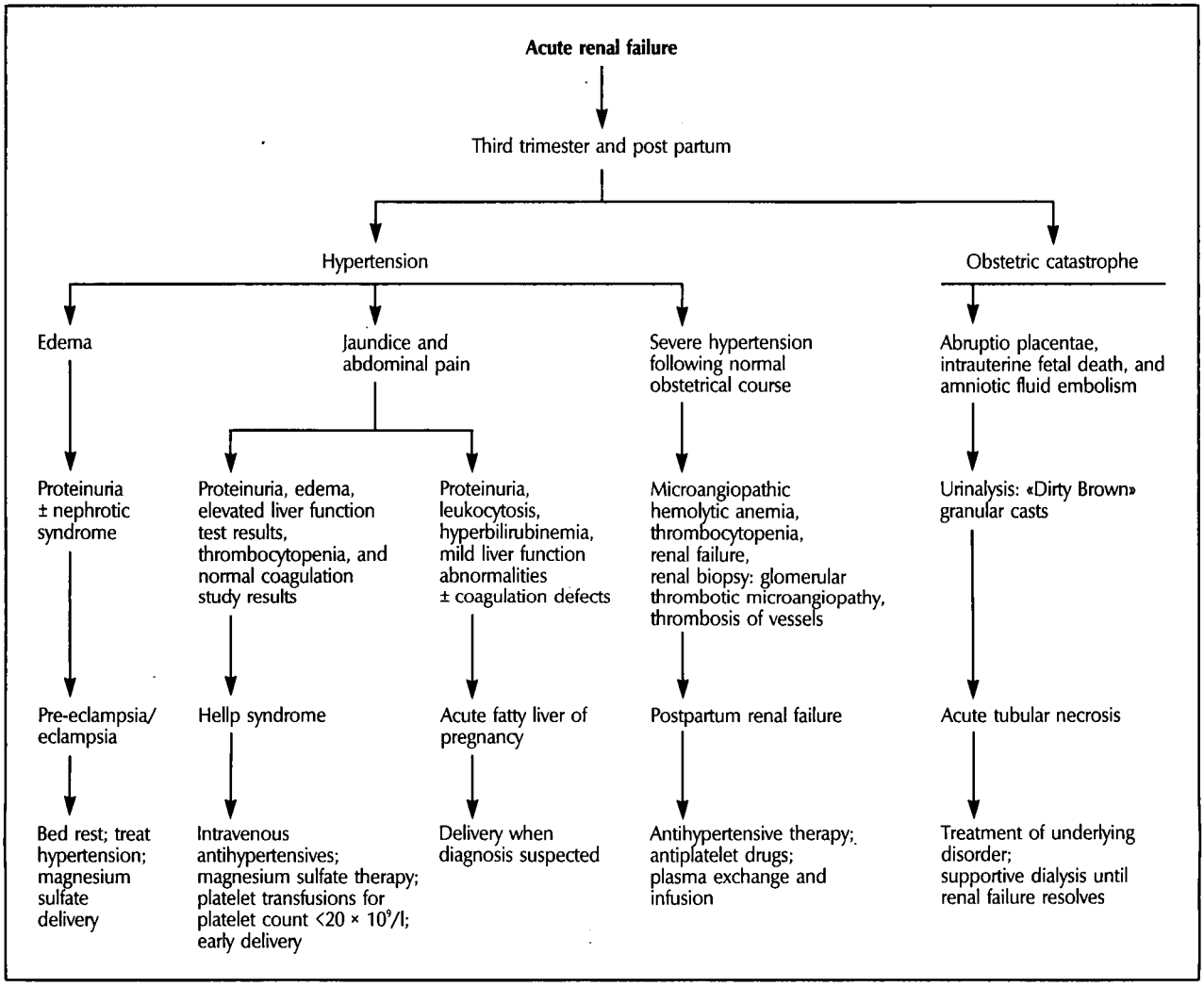

Fig. 2.—Acute renal failure in pregnancy: Third trimester and post partum.

duction in renal perfusion commonly recognized by a rise in the serum urea nitrogen level out of proportion to the rise in serum creatinine. In this setting the patient may demonstrate evidence of volume contraction by physical examination with a hypochloremic metabolic alkalosis, benign urine sediment and an increased specific gravity. The fractional excretion of both sodium and chloride will be reduced. If the patient is actively vomiting the fractional excretion of sodium may actually be high due to the presence of bicarbonate in the urine. Fluid replacement should correct the acid base and electrolyte abnormalities and antiemetic therapy will treat the underlyng problem. Uterine bleeding may also cause pre-renal azotemia and treatment should be aimed at correcting the specific etiology while volume support is maintained.

Uterine beeding may be a greater problem when significant enough to cause hypotension. Smith et al. reported uterine bleeding as an etiologic factor in over half of their cases of acute renal failure in 1968 and Chugh et al. reported 12 of 70 pregnant women having either antepartum or postpartum hemorrhage as the cause of acute renal failure[2, 18]. Seventy-nine percent of their patients had some form of uterine bleeding. The Necker Hospital series reported uterine hemorrhage in 7 % of their cases of renal failure in pregnancy. More recently, Turney et al. reported uterine hemorrhage in 48 of their 142 women with severe acute renal failure[13]. While uterine bleeding may be obvious when it occurs at delivery, abruptio placentae may be a more subtle cause of hemorrhage.

Uterine hemorrhage has also ben associated with both acute tubular necrosis and renal cortical necrosis. It is possible that renal failure in women who develop uterine hemorrhage may be related to a decrease in their intravascular volume, an increased sensitivity to norepinephrine

and angiotensin II, or a relative deficiency of vasodilating prostaglandins[40-43].

Prompt diagnosis and treatment of the underlying cause is the most important factor in managing this complication.

Obstruction associated with compression of the ureters by the gravid uterus has been reported[44]. Uterine incarceration, hydraminios, and nephrolithiasis may also occur and should be suspected particularly when there is a change in urine volume and a benign urine sediment[44-46].

Acute glomerulonephritis and acute interstitial nephritis may also be associated with acute renal failure during pregnancy[47-49]. The presence of red cell casts in the urine should always raise the possibility of acute glomerulonephritis. Diagnosis may require renal biopsy to treat the underlying disorder[50, 51]. Acute interstitial nephritis associated with drugs is another important cause of renal failure, most frequently suspected when it develops in association with fever, skin rash, and arthritis. Renal function usually improves when the offending medication is removed though some patients may require corticosteroid therapy. Sarcoidosis presenting as acute renal failure during pregnancy has also been reported[48]. This patient had dramatic improvement in renal function when treated with corticosteroid therapy. The diagnosis was made by renal biopsy which may be necessary in obscure causes of renal failure including lymphoma[52].

Renal impairment during pregnancy may also be associated with infection. The incidence of urinary tract infection is estimated to be 2 % of all deliveries and during pregnancy the risk of acute pyelonephritis is significantly increased in women who develop urinary tract infections[53]. It has been demonstrated that the creatinine clearance may fall when pyelonephritis occurs during pregnancy, resulting in acute renal failure[54].

Twenty seven percent of 220 women evaluated by Walley et al. were found to have a creatinine clearance of less than 80 ml/min[54]. Eighteen women with clearances less than 70 ml/min who were reevaluated after therapy had improvement of renal function to normal or near-normal levels[54]. Because of the stasis that occurs from compression of the urinary bladder the risk of urinary tract infection during pregnancy appears to be increased. Several factors may explain why renal function deteriorates when pyelonephritis occurs during pregnancy. One possibility is a greater sensitivity of the renal vessels to vasoactive bacterial endotoxins released during these infections, as well as extracellular volume depletion, occult underlying renal disease or even inflammatory edema[54].

Septic abortion is another major cause of renal failure associated with infection in pregnancy. Since the legalization of abortions in many western countries, there has been a dramatic fall in the incidence of procured septic abortion and subsequent acute renal failure[2, 12]. Uterine bleeding associated with septic abortion has been another important associated cause of acute renal failure which also seems to have markedly decreased in incidence. Spontaneous and procured abortions in the series reported by Chugh, however, still accounted for over half the cases of acute renal failure reported by his group in 1976[18].

Septic abortion frequently is dramatic in its presentation with sudden onset of high fever, nausea vomiting, myalgias and only occasional vaginal bleeding[55]. Patients may present with overt septic shock associated with severe peripheral vasoconstriction and marked hemodynamic instability. Hemolytic anemia may cause hyperbilirubinemia; leukocytosis, thrombocytopenia, and disseminated intravascular coagulation may also occur. Several possible explanations for renal failure in patients with septic abortions exist. Severe intravascular volume contraction may be the major cause of renal failure and fluid resuscitation will restore adequate renal perfusion. Septic shock and severe hypotension may also result in acute tubular necrosis or bilateral renal cortical necrosis. Acute hemolysis, and hemoglobinuria may also result in direct tubular injury. Urinalysis may demonstrate proteinuria and red blood cell and pigmented casts. Finally it has been suggested that clostridia may exert a specific nephrotoxic affect though this organism is only occasionally isolated in patients with septic shock[6]. In patients presenting with septic abortion, therapy is primarily aimed at maintaining hemodynamic stability, administering appropriate intravenous antibiotics and frequently arranging for urgent dilatation and curettage. Hysterectomy may be necessary if gas gangrene is present, in which case hyperbaric oxygen may also be of benefit.

One of the more dramatic complications resulting in acute renal failure in pregnancy is bilateral renal cortical necrosis (BRCN) resulting from either septic abortion or complications arising in late pregnancy[56-60]. BRCN is responsible for a very small percentage of acute renal failure outside of pregnancy but accounts for between 10-38 % of obstetric acute renal failure[8, 56, 57]. Typically BRCN results in patchy cortical tissue death with sparing of the medullary portions of the kidney. This may account for the eventual recovery or renal function in many young women with this complication.

Pathogenesis of renal cortical necrosis during pregnancy may be related to alterations of clotting factors. Sepsis, hypotension or hemorrhage may induce a hypercoagulable state and explain why extensive fibrinogen deposition can occur in the glomeruli and small arteries in histopathologic studies[61-64]. Other studies have demonstrated spasm of the renal arteries when catecholamine infusion has been used to induce shock and intravascular coagulation[65]. An explanation for the glomerular thrombi that results from increased intravascular deposition in these patients will require further investigation.

BRCN should always be suspected in acute renal failure during pregnancy when associated with prolonged anuria or oliguria. In Chugh's series of acute renal failure, septic abortion was frequently associated with disseminated intravascular coagulation resulting in the frequent occur-

rence of BRCN in early pregnancy[18]. Kleinknecht et al. reported 26 patients in whom BRCN more frequently occurred in late pregnancy[58]. When comparing this complication with acute tubular necrosis the former was more likely to be associated with lower fibrinogen levels and fewer toxemic symptoms. Several investigators have reported acute cortical necrosis complicating pre-eclampsia particularly associated with abruptio placentae[13, 14, 56, 57, 59]. It is clear therefore that BRCN may occur either in the setting of septic abortion in early pregnancy and pre-eclampsia particularly with abruptio placentae in late pregnancy.

In acute oliguric renal failure in the obstetric settings described above selective renal angiography may be used to make an early diagnosis of renal cortical necrosis by demonstrating either an absent or non-homogeneous roentgenographic appearance[66, 67]. Renal biopsy may histopathologically confirm the diagnosis, however this may not be practical in these acutely ill women in the setting of coagulopathy[8]. The diagnosis may be suggested by renal ultrasonography, or computed tomography of the kidney and presumably by magnetic resonance imaging if they demonstrate areas of cortical lucency reflecting the extent of necrosis[68].

The prognosis of cortical necrosis has varied among different investigators. Turney et al. reported no survivors after 6 years in all women who suffered cortical necrosis whereas eventual recovery of renal function occurred in most patients reported by Klineknecht[13, 58]. Even in this latter series some women who recovered enough function to discontinue dialysis eventually developed end-stage renal disease. Recognition of this severe form of acute renal failure by newer imaging techniques should allow earlier diagnosis and with current supportive therapy, morbidity and mortality may fall.

Acute tubular necrosis may present in a very similar manner to bilateral renal cortical necrosis. Expected recovery of renal function from this syndrome is typically 1 to 3 weeks, clearly differentiating it from the prolonged oliguria or even anuria of cortical necrosis. This complication may occur during pregnancy from the same ischemic or toxic injuries to the kidney that occur in the non-gravid state. It has also been reported to occur as a complication of a number of obstetric catastrophes including abruptio placentae, uterine hemorrhage, septic shock, intrauterine fetal death and amniotic fluid embolism[16, 57]. Either severe pre-eclampsia or microangiopathic hemolytic anemia may be complicated by hemoglobinuria leading to acute tubular necrosis. As in all phases of acute renal failure, the clinical setting and the urinalysis, which in this case will demonstrate the characteristic «dirty brown» granular casts, and elevated functional excretion of sodium will help confirm the diagnosis. With appropriate supportive care, recovery of renal function is expected. In an acute oliguric patient, dialysis therapy is likely to be required. However, non-oliguric acute tubular necrosis may be managed conservatively.

Renal failure in the third trimester

Pre-eclampsia is probably the most frequent clinical syndrome that may result in acute renal failure during pregnancy[14, 19]. It is usually diagnosed in late pregnancy when hypertension, proteinuria and or edema occur in the primigravid patient. There are no specific placental pathologic findings. However, reduction of uteroplacental blood flow may result in placental ischemia or even infarction[69-71]. To the nephrologist, the «gold standard» in the diagnosis of pre-eclampsia is the histopathologic finding of swelling of the glomerular endothelial cells, termed glomeruloendotheliosis[72-74]. Some investigators however, have made the diagnosis without this characteristic lesion. In a review of 176 hypertensive pregnant patients at the University of Chicago from 1958 through 1976, Fisher et al. made a diagnosis of pre-eclampsia in 79 primigravidas and in only 17 of the multiparous women, based on the renal pathologic finding of glomeruloendotheliosis[75]. The remainder of the patients in this series had either normal histologic features, nephrosclerosis or some other primary renal histopathologic lesion, either alone or in combination with glomeruloendotheliosis.

Fisher's study demonstrates that most primigravidas presenting with hypertension, proteinuria, and edema in the latter portion of pregnancy will have pre-eclampsia confirmed using the renal biopsy definition. However, a variety of other underlying disorders, particularly nephrosclerosis of previously undiagnosed primary renal disease may be present, particularly in the multiparous women. This is in agreement with many other reviews demonstrating that women with underlying glomerular disease are expected to develop worsening of their proteinuria, hypertension and renal functional deterioration[35-38]. Some of these complications may be irreversible.

In many young women, evaluation of renal function or urinalysis occurs for the first time during pregnancy. It is clear from both Fishers' data and other studies investigated renal function during pregnancy that it may be difficult to distinguish pre-eclampsia from underlying glomerular diseases clinically. When evaluating a woman with hypertension, proteinuria and/or edema during pregnancy, one should always consider the possibility of the patient having some form of underlying renal disease if the proteinuria and hypertension began early in pregnancy. This distinction is important in that one will expect, worsening proteinuria and hypertension in these women and, secondly, long-term follow up must be provided to subsequently diagnose the etiology of the underlying renal disease.

In those women with mild to moderate pre-eclampsia, the clinical syndrome is expected to resolve with delivery and the long-term outlook is excellent[76]. Supportive management consists of strict bed rest for blood pressures greater than 140/90 mmHg, with antihypertensive therapy for persistent significant elevations of the blood pressure[77]. Magnesium sulfate may be used prophylactically to

prevent seizures but this should be used with caution if the patient has impaired renal function. Delivery provides definitive therapy and this may be expedited when there is evidence of either deteriorating maternal or fetal well-being.

Multi-system involvement may occur in more severe cases of pre-eclampsia-eclampsia. This may include central nervous system involvement, cardiovascular deterioration, hepatocellular changes, or hematologic abnormalities. Pritchard, in 1954, described 3 women with pre-eclampsia complicated by thrombocytopenia, hemolysis, and abnormal livers function tests[78]. Other investigators have reported similar patients[79-83]. Weinstein in 1982 reviewed 29 patients with hemolysis, elevated liver function tests, and a low platelet count using the term HELLP syndrome[81]. This syndrome is a severe form of pre-eclampsia associated with systolic blood pressures greater than 160 mmHg or diastolic pressures greater than 110 mmHg, proteinuria greather than 5 grams per day, oliguria, visual field disturbances and pulmonary edema. Weinstein in 1985 reviewed 57 patients with the HELLP syndrome all of whom had platelet counts less than 100,000 with liver function test abnormalities[83]. In all patients but one, proteinuria greater than 2+ was present with abnormal renal function tests in over half of the women. Prothrombin and partial thromboplastin times and the plasma fibrinogen levels were normal in all but one patient, differentiating this disorder from those associated with disseminated intravascular coagulation. Sibai et al. have described this syndrome in 112 pregnancies. Thirty-eight percent of these women had evidence of disseminated intravascular coagulation, frequently associated with either abruptio placentae or intrauterine fetal death. Acute renal failure with a mean creatinine clearance of 7.6 ml/min occurred in nine patients[83].

Maternal and fetal prognosis depends on early recognition of this syndrome and prompt institution of therapy. Following delivery, renal function usually returns to normal. Establishing the diagnosis of HELLP syndrome leads to expedited delivery with appropriate supportive therapy including hospitalization, magnesium sulfate and antihypertensive medications. Based on the similaries between severe pre-eclampsia, thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, plasmapheresis has been suggested for women with progressive renal failure associated with hemolysis and thrombocytopenia[84]. To date no control studies have been performed demonstrating the efficacy of plasmapheresis.

Whether or not the HELLP syndrome is truly a unique form of severe pre-eclampsia or not may best be answered by looking at renal biopsy results reported by Beller et al.[85]. Four patients with this syndrome had only glomeruloendotheliosis. Two had nephrosclerosis, one had hemolytic uremic syndrome and three patients had other forms of undelying glomerulonephritis. These data are quite similar to those reported by Fisher, supporting the notion that this is more of a clinical syndrome rather than a well defined clinical entity. Particularly in those multiparous patients presenting with HELLP syndrome, one must always consider the possibility that the patient has some other form of underlying renal disease.

More recent investigations into the pathophysiology of pre-eclampsia have centered on the balance between thromboxane A_2 ($Tx A_2$), a potent vasoconstrictor and prostacyclin (PGI_2), a potent vasodilating prostaglandin that decreases platelet aggregation, increases ureteroplacental blood flow and decreases uterine activity[86, 87]. The reduction in the ratio of PGI_2:$Tx A_2$ may play a role in reducing placental blood flow and in causing the attendant complications of pre-eclampsia[87-94]. Attempts have been made to identify those women most at risk for the development of pre-eclampsia. It is known that normal pregnancy is characterized by a resistance to the hypertensive action of angiotension II infusion[88]. This response is attenuated in women developing pregnancy induced hypertension and therefore may serve as a marker for those women likely to develop pre-eclampsia[88]. It has been suggested from these controlled studies that pre-eclampsia may be prevented in women at risk, but application of this therapy for widespread clinical use will require further investigation.

In 1934 Stander and Cadden first described a case of acute fatty liver associated with pregnancy[95]. This disorder of late pregnancy usually occurs after the 35th week of gestation, with recurrent nausea and vomiting associated with variable degrees of liver failure, sometimes associated with jaundice, encephalopathy, disseminated intravascular coagulation or renal failure. One review of this disorder suggested an estimated incidence of less than 1 case per 13,000 deliveries. However, it is possible that a number of recent reviews may bring more attention to this problem, increasing its recognition[96, 98, 99]. This diagnosis must be considered in all patients presenting, in the last trimester of pregnancy with abdominal pain and jaundice, However, more subtle, non-specific complaints may also occur, including malaise, headache, nausea and vomiting. Because most patients with acute fatty liver of pregnancy also develop hypertension edema and proteinuria, pre-eclampsia, with or without the HELLP syndrome, is an important consideration in the differential diagnosis. Almost all cases of acute fatty liver of pregnancy have described some degree of renal failure. In those cases with severe renal failure complicating liver failure the maternal mortality rate is significantly higher. The diagnosis is confirmed when a liver biopsy specimen demonstrates the pathognomonic findings of microvesicular fat and swollen hepatocytes with central nuclei and in a centrolobular distribution. Histopathologically, these findings resemble both Reye's syndrome and tetracycline toxicity. However, these disorders can all be differentiated based on clinical presentation.

Prompt delivery when the diagnosis is suspected, is usually associated with improvement. Therefore, a strong index of suspicion for this disorder in all women presenting with liver function abnormalities and/or nausea vomit-

ing and abdominal pain in late pregnancy is important. Early reports of this syndrome were associated with high maternal and fetal mortality. However, early diagnosis and treatment has resulted in almost 100 % maternal and fetal survival. Wheter or not it is important to separate this syndrome from pre-eclampsia is unclear, and some investigators even consider this part of the clinical spectrum seen with pre-eclampsia. Fatty liver of pregnancy should also be distinguished from acute viral hepatitis because of the markedly abnormal transaminase levels that occur in the latter. Appropriate serologic studies will also confirm the diagnosis. Benign jaundice of pregnancy may also present similarly, however liver and renal function tests should be normal with this condition. Acute alcoholic liver disease with alcoholic hepatitis may also present with nausea, vomiting, abdominal pain and leukocytosis but the appropriate clinical history should be obtained to help distinguish this entity from acute fatty liver of pregnancy.

Termination of pregnancy is the treatment of choice in acuty fatty liver of pregnancy. When this disease presents in very late pregnancy this is usually achieved without difficulty. If the patient presents however, at a time when fetal viability may be an issue and the diagnosis is unclear, computed tomography of the liver or biopsy may be necessary to help decide management issues. Patients who develop overt hepatic or renal failure will require supportive therapy which may include dialysis until recovery occurs. Delivery usually results in prompt recovery unless the preceeding events have already occurred. Safe pregnancies have been reported following recovery from acute fatty liver of pregnancy[97].

In all of the preceeding disorders renal failure begins during pregnancy. However, the syndrome of idiopathic postpartum renal failure typically occurs after delivery in uneventful pregnancies. This syndrome was first described by Robson et al. in 1968 with many reports of overlapping syndromes including postpartum hemolytic uremic syndrome, thrombotic thrombocytopenic, purpura and idiopathic postpartum renal failure[100-111]. The typical features of this disorder include severe hypertension, microangiopathic hemolytic anemia, and thropmbocytopenia associated with acute renal failure developing 48 hours to 1 month following a normal delivery unrelated to any obstetric complications.

In most reviews of this subject the most consistent clinical finding associated with post-partal renal failure has been microangiopathic hemolytic anemia. In their series of patients with postpartum renal failure, Sun reported about one-third of their patients as having spontaneous bleeding, also associated with hypertension, congestive heart failure or seizures[106]. In Segonds review, thrombocytopenia and hypertension were common but not invariable findings[108]. Histopathologic descriptions of renal tissue have included intimal proliferation, fibrinoid necrosis and fibrosis of smaller renal arteries with thrombotic microangiopathy as well as focal cellular proliferation and basement membrane thickening. Immunofluorescent studies have demonstrated fibrin-fibrinogen present in the mesangium, arterioles and glomerular capillary wall[112]. Segonds also reported subendothelial lucencies in the glomeruli and blood vessels in all electron microscopic studies. The extent of the glomerular lesions appears to correlate with the renal prognosis.

Though the pathogenesis of this disorder is unknown many features are similar to the generalized Shwartzman reaction which is induced in laboratory animals by two successive injections of endotoxin[113]. Factor XII is activated, resulting in thrombin generation with subsequent fibrin deposition in the terminal arterioles and capillaries, with production of fibrin degradation products and intravascular coagulation[114]. Cytotoxin producing *Escherichia coli* have also been associated with this clinical syndrome, particularly in children[115]. It has therefore been suggested that bacterial endotoxins or vasoactive animes, in the circulation of affected women, may stimulate the coagulation cascade or initiate thrombosis by causing endothelial damage[116]. The absence of consumptive coagulopathy and failure to improve survival with heparin argues against this theory[116]. Deposition of platelet thrombi in the micro-vasculature may also play a central role in postpartum renal failure[114]. Bacterial toxins, vasoactive amines or immune complexes may cause endothelial damage resulting in platelet aggregation or a circulating factor which inhibits prostacyclin may be present[118-122].

Therapeutic application of theories on pathogenesis of this disorder have resulted in trials with either heparin anticoagulation or platelet inhibiting therapy. No studies have clearly demonstrated improved mortality or renal function with the use of heparin sodium[123-124]. The simultaneous use of platelet inhibitors to prevent thrombi formation and plasma exchange to remove potential plasma factors that promote platelet aggregation have been used[125-127]. Infusion of intravenous prostacyclin, fresh frozen plasma and oral aspirin in one patient did result in resolution of both thrombocytopoenia and renal failure[120]. O'Regan et al. failed to demonstrate a benefit in children with hemolytic uremic syndrome in a controlled study using aspirin and dipyridamole[128]. Currently, antiplatelet therapy with plasma infusion exchange appear to be the mainstay of therapy, based on the suspected pathogenesis of this disorder. Prostacyclin therapy may eventually play a larger role in treatment, but the role of heparin as an anticoagulant is unclear.

Early recognition of this clinical syndrome with better supportive therapy has lead to improved survival. In Segonds review of the literature in 1979, 76 % of the untreated patients died and 12 % developed end-stage renal disease[108]. Mortality was 41 % for those patients who were treated with 15 % of them developing progressive renal failure[108]. In their 1988 review of 67 patients with postpartum hemolytic uremic syndrome, Li et al. reported complete recovery in 13 patients, persistent renal impairment in 10 patients and an overall mortality of 46 %. The use of therapy aimed at preventing platelet aggregation

and thrombosis, which seems to play a central role in the complications of this disorder, may improve the outcome. Clinical trials will be necessary to demonstrate the efficacy of this form of therapy.

Management of renal failure in pregnancy

Understanding the physiologic changes of renal function, and the unique clinical syndromes that may occur are essential in the management of renal failure in pregnancy. One must first try to separate the many causes of acute renal failure unrelated to pregnancy from those that are specific to pregnancy and finally, it is particularly important to try and distinguish those women in whom underlying undiagnosed chronic renal failure may exist. In this latter group of women, the progressive development of proteinuria, hypertension and frequent worsening of renal function may mimic acute renal failure during pregnancy and therapy aimed at a specific underlying disease may be required. One should suspect underlying renal disease when proteinuria or hypertension develop in the first half of gestation, particularly in the multigravid patient. In most patients the correct diagnosis can usually be suspected from the clinical presentation. However, when it is unclear whether the patient has acute glomerulonephritis that may require specific therapy, renal biopsy may be necessary during pregnancy[51]. If the information obtained by renal biopsy will either alter therapy or make therapeutic termination of pregnancy an option, it should be considered as early as possible.

Treatment is clearly aimed at treating the underlying disease state. In HELLP syndrome, pre-eclampsia, or acute fatty liver pregnancy, prompt delivery usually results in recovery. Once delivery occurs then therapy can obviously be instituted without concern for compromise of the uteroplacental blood flow. When severe renal failure occurs prior to fetal maturation, then supportive dialysis therapy may be necessary until delivery can be safely accomplished[129-135]. Significant problems that must be considered in treating the pregnant woman requiring dialysis include management of anemia, blood pressure control, and appropriate vitamin support and calcium metabolism. Early intensive dialysis has been recommended with careful attention to avoid hypotension. The safety of erythopoietin to correct the anemia of renal failure is unclear though it has been used safely during pregnancy[132]. In his review of dialysis and pregnancy, Elliott reports that polyhydraminos, premature labor, intrauterine growth retardation, and hypertension were common complications in women in whom hemodialysis was initiated during pregnancy[134]. However, fetal survival was still 94 %. Earlier reports have almost universally used hemodialysis in those women requiring dialysis therapy during pregnancy. Redrow et al., however, have described the experience of 9 chronic peritoneal dialysis patients in whom pregnancy occurred[135]. The potential advantages of more constant intravascular volume and better blood pressure control make this a potentially better treatment modality in women in whom dialysis may be required for extended periods of time to achieve fetal maturity. This provides one more option in the management of this complex clinical problem.

Acute renal failure in pregnancy therefore, represents a constellation of many clinical syndromes that must be distinguished by the nephrologist and obstetrician to assure a successful delivery and prevent maternal complications. These may include either progressive renal failure or even death. Close cooperation between the obstetrician and nephrologist is an integral part of the care that the woman must receive. Understanding the many causes of renal functional deterioration of pregnancy will lead to an appropriate diagnostic evaluation, with the appropriate therapeutic decisions improving the likelihood of a successful maternal and fetal outcome.

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