Management of Renal Disease in Pregnancy

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• Pregnancy • Renal disease • Glomerulonephritis
• Dialysis • Renal function

In patients with renal disease who become pregnant, the possible harmful effects of pregnancy on kidney function and the impact of renal disease on pregnancy outcome should be considered. In this context, the nephrologist's role is to assess the risk for worsening renal function in pregnancy; ideally nephrologic opinion should be sought before conception. Assessment of maternal hypertension is also crucial, because it contributes significantly to the risk for deteriorating renal function and increases the risk for preeclampsia, preterm delivery, intrauterine growth restriction, and perinatal mortality.

Management of pregnant women with kidney disease may be complicated, and requires an understanding of the physiologic changes associated with pregnancy and close teamwork between obstetricians and nephrologists. Although some areas in obstetric medicine have been extensively studied in randomized controlled trials (eg, prevention of preeclampsia), renal disease in pregnancy has been so less commonly, and the quality of the evidence guiding clinical practice has not been of the highest level. Most evidence consists of case series with modest numbers of subjects. Based on population studies, the prevalence of chronic kidney disease in women of childbearing age is 0.03% to 0.2% of all pregnancies.

RENAL ANATOMY AND PHYSIOLOGY IN PREGNANCY

Anatomic and Functional Changes in Urinary Tract

Normally in pregnancy, increased renal blood flow and glomerular hypertrophy result in an increase in kidney length of approximately 1 cm during normal gestation, and overall kidney volume increases by up to 30%.[1] The major anatomic alterations of the urinary

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tract during pregnancy are seen in the collecting system, where calyces, renal pelvises, and ureters dilate, often giving the erroneous impression of obstructive uropathy.[2] The cause of the ureteral dilation has been attributed to hormonal mechanisms, such as increased progesterone, and mechanical obstruction by the enlarging uterus. These morphologic changes result in stasis in the urinary tract and a higher risk among pregnant women with asymptomatic bacteriuria for progression to pyelonephritis, particularly in those who have a history of prior urinary tract infections.[3] Rarely, ''overdistension syndrome'' may occur, which is a pregnancy-related syndrome characterized by severe hydronephrosis, abdominal pain, decline in renal function, and even hypertension, which may respond to lateral recumbency or require stent placement.

Renal Hemodynamics in Pregnancy

Marked vasodilation is a hallmark of pregnancy and occurs by 6 weeks gestation. Vasodilation is accompanied by a decrease in blood pressure, increase in cardiac output, and increases in renal plasma flow and glomerular filtration, all of which persist until late gestation. Increased progesterone, estrogen, nitric oxide, and relaxin have all been implicated as vasodilatory mediators. Because renal plasma flow increases slightly more than the glomerular filtration rate (GFR), filtration fraction remains constant or slightly lower in pregnancy. Increases in renal hemodynamics reach a maximum during the first trimester, and levels are approximately 50% greater than those of prepregnancy.[4] The increase in GFR (hyperfiltration) during normal pregnancy occurs without increase in intraglomerular pressure, and normal pregnancy is not injurious to the maternal kidney.

Acid–Base Regulation in Pregnancy

Because of the increased circulating level of progesterone, which directly stimulates the medullary respiratory center, tidal volume and alveolar ventilation are increased during pregnancy, resulting in respiratory alkalosis, with reduced arterial P_{CO_2}. To compensate, the kidneys excrete more bicarbonate in pregnancy, which results in a 4- to 5-mEq/L decrease in serum bicarbonate to 20 to 22 mEq/L, changes that are apparent in the first trimester.[5] Compared with nonpregnant patients, the normal anion gap in pregnancy is lower at 8.5 ± 2.9, and normal strong ion difference ($[Na+] + [K+] - [Cl-]$) is 38.3 ± 2.9.[6] Finally, a P_{CO_2} of 40 mm Hg signifies considerable carbon dioxide retention in pregnancy.

Water Metabolism

Pregnancy is associated with a decrease in plasma osmolality of 5 to 10 mOsm/kg lower than that of nongravid women, reaching a nadir at 10 weeks gestation. The decrease in plasma osmolality is associated with appropriate responses to water loading and dehydration, and suggests a resetting of the osmoreceptor system, with thirst occurring at lower serum osmolality. Clinical studies showing decreased osmotic thresholds for thirst and arginine vasopressin (AVP) release in pregnant women support this hypothesis. The lower osmolality and serum sodium represent a new normal set-point. In addition to these changes, pregnant women metabolize AVP more rapidly because of increased production of placental vasopressinases.[7] Pregnant women may develop syndromes of transient diabetes insipidus from the increased metabolism of AVP. These syndromes may be treated with pharmaceutical desmopressin, which remains effective because of a different *N*-terminus that is resistant to the circulating vasopressinases.

Serum sodium is also lower in pregnancy, which may be caused partly by relaxin, a peptide hormone in the insulin family that is secreted by the corpus luteum and

placenta during human gestation. Relaxin is associated with osmoregulatory changes and increases in GFR and vasodilation in early pregnancy.[8] Human chorionic gonadotropin seems to cause release of relaxin, which then stimulates the subfornical organ in the hypothalamus, resulting in thirst and AVP secretion. Chronic administration of relaxin to rats mimics several of the hemodynamic and osmotic changes of pregnancy, whereas antirelaxin antibodies reverse these changes.

Volume Regulation in Pregnancy

Total body water increases by 6 to 8 L during pregnancy, 4 to 6 L of which is extracellular. Plasma volume increases 50% during gestation, with the largest rate of increment occurring mid-pregnancy. Although serum sodium measurement decreases, a daily positive balance of 2 to 5 mEq and gradual accumulation of approximately 900 mEq of sodium is present during pregnancy (approximately 20 g of sodium chloride), which is distributed between the products of conception and the maternal extracellular space. Despite the increase in plasma volume during pregnancy, no evidence shows a hypervolemic (ie, overfilled circulation) state during pregnancy. Vasodilation, which is observed as early as the first trimester, may be the stimulus for increased sodium retention and increased plasma volume. The observations that blood pressure is significantly lower and the renin–angiotensin system is stimulated during normal pregnancy are consistent with primary vasodilation preceding and causing the increase in plasma volume.

Physiology of Renal Disease in Pregnancy

In patients with abnormal prepregnancy renal function, pregnancy may adversely affect maternal renal function, causing it to deteriorate irreversibly, both during gestation and after delivery. The causes are not altogether clear, although exacerbation of preexisting endothelial dysfunction, alterations in immune function, and increased inflammation associated with pregnancy may contribute. Platelet aggregation, formation of fibrin thrombi, and microvascular coagulation have also been implicated in renal and placental dysfunction. In general, the closer to normal the GFR and blood pressure, the greater the chance of successful pregnancy.

Assessment of Renal Function in Pregnancy

During pregnancy, GFR and creatinine clearance increase by 40% to 65% and creatinine production is unchanged; therefore, the increased clearance results in decreased serum levels. One study reported average values of 0.83 mg/dL (73 μmol/L) in nonpregnant women, and 0.74, 0.58, and 0.53 mg/dL (65, 51, and 46 μmol/L, respectively) in first, second, and third trimester of pregnancy, respectively, with values for the upper limit of normal of 0.96, 0.90, and 1.02 mg/dL (85, 80, and 90 μmol/L, respectively).[9]

In the nonpregnant population, the Cockroft-Gault and MDRD (Modification of Diet in Renal Disease) formulae are most commonly used to assess kidney function. Neither of these have been validated in pregnancy. The Cockroft-Gault formula uses body weight as a surrogate for muscle mass, but because the weight of a gravid women increases without affecting the muscle mass, using pregnancy weight in this formula yields inaccurate results. In one study using prepregnancy weight, the formula better approximated creatinine clearance. The MDRD formula yields results that are corrected for body surface area, but because the body surface area changes in pregnancy, this too yields inaccurate results. In one study, MDRD formula underestimated GFR by more than 40 mL/min.

Measurement of serum cystatin C had been proposed as a more sensitive marker for GFR because it was believed to be independent of age, weight, height, or muscle mass; however this has not been proven when studied in pregnancy.[10] Creatinine clearance measured with 24-hour urine collection remains the best approximate of the gold standard of inulin clearance, and is the most well-validated method for measuring renal function.

Because of the increased GFR in pregnancy, the tubular transport maximum is exceeded and reabsorption is decreased, causing increased excretion of glucose, amino acids, calcium, and urinary protein. The upper limit of normal for urinary protein excretion is 300 mg/d in pregnant patients versus 150 mg/d in nonpregnant patients. Abnormal proteinuria has been evaluated with 24-hour urine collection, urine dipstick, and protein/creatinine ratio, but the gold standard remains the 24-hour urine protein measurement. A 24-hour protein level greater than 300 mg is abnormal in pregnancy and correlates with a urine dipstick 1+ protein measurement. Although commonly used in an obstetrician's office to detect significant proteinuria, urine dipstick testing is susceptible to error because of variations in urine concentration, and may miss up to 1 of 11 hypertensive pregnant women with true proteinuria.[11] Therefore, if the level of suspicion is high, 24-hour urine testing should be performed. Total protein/creatinine ratio has been shown to accurately estimate 24-hour urine protein in nonpregnant patients and, according to a systematic review of 13 studies of pregnant patients, seems to be of value in ruling out proteinuria if less than 0.25 g per 24 hours. Misclassifications tend to occur when the proteinuria is borderline (250–400 mg/d), and therefore the 24-hour collection should be performed to diagnose preeclampsia if the results are equivocal. The protein/creatinine measurement also underestimates severe proteinuria in pregnancy, and therefore cannot be recommended as an alternative to 24-hour measurement.[12]

KIDNEY DISEASE IN PREGNANCY

Kidney disease during pregnancy may be caused by (1) preexisting renal disease that was diagnosed before conception, (2) chronic renal disease that was unappreciated before pregnancy and diagnosed for the first time during pregnancy, or (3) renal disease that develops for the first time during pregnancy. Some overlap exists with respect to the different diseases that are typical of the three categories. For example, lupus nephritis may be a chronic condition, or it may develop for the first time during pregnancy.

Chronic Renal Disease: General Principles

Fertility and ability to sustain an uncomplicated pregnancy are related to the degree of renal functional impairment rather than to the specific underlying disorder. The greater the functional impairment and higher the blood pressure, the less likely the pregnancy will be successful (**Table 1**). Patients with preserved renal function and normal or well-controlled blood pressure have favorable maternal and fetal outcomes. Those with mildly elevated creatinine, such as 1.2 to 1.4 mg/dL (106–124 μmol/L) seem to have some risk (16% in one study) for renal function decline. Those with moderate renal insufficiency (serum creatinine 1.4–2.5 mg/dL, or 124–220 μmol/L) are at increased risk for preeclampsia (20%–30%) and preterm delivery. Of these women, approximately 50% have a pregnancy-related decline in creatinine clearance (by 25%), and the renal function decline seems to persist or progress after delivery. Women with severe renal dysfunction, defined by a creatinine level greater than 2.5 mg/dL [220 μmol/L], should be discouraged from conceiving because 70% will experience

Table 1
Effect of pregnancy on renal disease

Author	No. Pregnant Patients	Renal Diagnosis	Clinical Status at Baseline	Outcome
Katz et al[52]	89	glomerulonephritis	Serum Cr $\leq$ 1.4 mg/dL	16% transient worsening of renal function
Abe et al[53]	72	glomerulonephritis	GFR >70 mL/min	No change
Jungers et al[54]	171	glomerulonephritis	Normal GFR	No change
Abe et al[55]	118	IgA nephropathy	GFR mean 70 mL/min	19% had renal function decline, 4% progressed to ESRD or dialysis 1–5 years after delivery
	166	Glomerular disease	GFR >70 mL/min GFR <50 mL/min	Good if GFR >70 and blood pressure <140/90 GFR <50: 33% had decrease in GFR
Jones and Hayslett[13]	67	glomerulonephritis	Cr >1.9 mg/dL	12% on dialysis within 1 year of delivery
Imbasciati et al[14]	49	Nondiabetic renal disease	CrCl 35 mL/min	31% on dialysis at 37 months postpartum
Chopra et al[56]	29	glomerulonephritis	Cr >1.5 mg/dL	29% had progression of disease

Abbreviations: Cr, creatinine; CrCl, creatinine clearance; ESRD, end stage renal disease; GFR, glomerular filtration rate.

preterm delivery, 40% will develop preeclampsia, and 40% will experience pregnancy or postpartum deterioration in renal function, leading to dialysis.[13]

Urine protein excretion may increase markedly in pregnant women with underlying renal disease—perhaps tripling from baseline—which may also adversely affect outcome. In one study of pregnant women with stage 3 to 5 kidney disease, the rate of decline in GFR accelerated in the subgroup with both estimated GFR of less than 40 mL/min and proteinuria greater than 1 g/d before pregnancy.[14] The level of blood pressure at conception is an important variable in pregnancy outcome. In the absence of hypertension, there is significantly less chance of irreversible deterioration in renal function during pregnancy. When hypertension is present, pregnancy outcome is rarely uncomplicated. Preterm delivery and deterioration in renal function are expected. Finally, in patients with renal disease in whom eventual renal transplant is anticipated, pregnancy may result in immune sensitization, leading to difficulty locating a suitable matching donor.

Renal Diseases Associated with Systemic Illness

Diabetes is one of the most common medical disorders of pregnancy, with most cases caused by gestational diabetes. Preexisting diabetes poses significant risks to pregnancy, and many women have type 1 diabetes; if their disease has been present for 10

to 15 years, they may have diabetic nephropathy. Women with diabetes, microalbuminuria, well-preserved renal function, and normal blood pressure have a good prognosis for pregnancy, although they are at increased risk for preeclampsia and urinary infection.[15,16]

One prospective cohort study from Denmark followed-up 240 women who had type 1 diabetes during pregnancy, 11% of whom had microalbuminuria and 5% overt diabetic nephropathy. Of this cohort, 62% of women with microalbuminuria and normal renal function and 91% of women with overt diabetic nephropathy had preterm deliveries (compared with 35% of women with no albuminuria). Preeclampsia developed in 6% of women with no albuminuria compared with 42% and 64% of women with microalbuminuria and overt diabetic nephropathy, respectively.[16] In another study of 72 pregnancies in 58 women with diabetic nephropathy, an elevated serum creatinine at enrollment was associated with preterm delivery, very low birth weight, and neonatal hypoglycemia, and was independent of urinary protein excretion.

With respect to progression of maternal renal disease as a consequence of pregnancy, one study from Denmark reported that 26 women with type 1 diabetes who became pregnant had similar rates of deterioration in renal function over a 16-year follow-up compared with 67 control subjects with comparable disease who had never been pregnant.[17] Thus, when baseline renal function and blood pressure are still normal, pregnancy is not likely to accelerate the progression of early diabetic nephropathy,[17] although urinary protein excretion often increases significantly during pregnancy. Women with non–nephrotic range proteinuria preconception may develop nephrotic range proteinuria during pregnancy, which is usually reversible. Women with overt nephropathy preconception, particularly those with impaired renal function and hypertension, have a high incidence of preterm delivery, preeclampsia, and deterioration in maternal renal function.[15] However, women with type 1 diabetes with microalbuminuria and normal renal function and normotension should be encouraged not to postpone pregnancy, because of the worse prognosis once overt nephropathy develops.

Blood pressure control is important; however, because angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers are contraindicated during all three trimesters of pregnancy, and in the 2nd and 3rd trimesters carry a neonatal mortality rate of 25%, women should be switched to other agents that are safe to use in pregnancy, such as methyldopa, labetolol, or nifedipine, before conception. After delivery, if ACEIs are to be restarted and the patient wishes to breast-feed, enalapril has been deemed safe by the American Pediatrics Association; it is likely a class effect, but safety data are lacking in other ACEIs. No studies of pregnancy and nephropathy associated with type 2 diabetes have been published; however, given the increasing prevalence of this condition, it is an important area for future study.

Lupus nephritis during pregnancy presents unique problems. Although similar considerations apply regarding level of renal function and blood pressure and their relationship to pregnancy outcome, generally lupus is a much more unpredictable illness because of the tendency of the disease to flare. Recent data suggest that pregnancy duration, total disease duration, and disease activity and damage before pregnancy are associated with increased organ damage after pregnancy in women with lupus.[18] Whether pregnancy per se is a risk factor for lupus flares has been disputed. Although some experts report no increase in flares attributable to pregnancy in patients in remission, prospective data suggest that pregnancy is in fact associated with a greater chance of disease exacerbation.[19] Women with lupus nephritis are advised not to conceive unless their disease has been inactive for the preceding

6 months, because active disease is associated with a higher incidence of fetal demise. Disease is considered inactive when the creatinine measurement is less than 0.7 mg/dL or 62 μmol/L, proteinuria is less than 0.5 g/d, and, on spun urine examination, fewer than five red blood cells are present per high-powered field. Fetal loss occurs in 25% to 50% of women who conceive when their disease is active with a creatinine of greater than 1.2 mg/dL, or 106 μmol/L.[20]

Additional complications associated with lupus and pregnancy include placental transfer of maternal autoantibodies, which can cause a neonatal lupus syndrome characterized by heart block, transient cutaneous lesions, or both. Women with lupus are also more likely to have clinically significant titers of antiphospholipid antibodies (anticardiolipin, lupus anticoagulant), which are associated with spontaneous fetal loss of 50% to 75%, hypertensive syndromes indistinguishable from preeclampsia, and thrombotic events, including deep vein thrombosis, pulmonary embolus, myocardial infarction, and strokes.[21] Thus, all women with systemic lupus erythematosus should be screened for antiphospholipid antibodies early in gestation. When titers are elevated (>40 GPL), daily aspirin (80–325 mg) is recommended. If the woman has a history of thrombotic events or pregnancy loss, then heparin in combination with aspirin is recommended.

One difficulty in managing lupus nephritis during pregnancy is that increased activity of lupus may be difficult to distinguish from preeclampsia. Both are characterized by an increase in proteinuria, a decrease in GFR, and hypertension. Thrombocytopenia may also be observed in both conditions. Hypocomplementemia is not a feature of preeclampsia, whereas increases in liver function tests may be observed in preeclampsia but are not characteristic of lupus activity. If disease activity is present before 20 weeks of gestation, then the diagnosis is more likely to be a lupus flare. Spun urine microscopy for red blood cell casts can also signal lupus nephritis activity.

In the latter half of pregnancy, a renal lupus flare may be impossible to distinguish from preeclampsia; frequently both are present simultaneously, and what starts as increased lupus activity seems to trigger preeclampsia. Unfortunately, delivery may be necessary if immunosuppressive therapy and supportive care fail to stabilize the condition.

The approach to treating lupus nephritis during pregnancy is based largely on anecdotal experience, principles of treatment used in nonpregnant patients, and knowledge of fetal toxicity of immunosuppressants. Steroids and azathioprine are the mainstays of treatment. Hydroxychloroquine during pregnancy seems to be associated with improved outcomes and does not seem to be toxic to the fetus.[22] Cyclophosphamide is generally not recommended during pregnancy because of potential fetal toxicity, and should only be used when the mother's life is in jeopardy. Mycophenolate mofetil should not be used during pregnancy to treat lupus nephritis because it is embryotoxic in animal studies, has been associated with fetal malformations in humans, and recent reports have characterized it as a teratogen.[23]

Chronic Glomerulonephritis

Childbearing women may be afflicted with any of the forms of chronic glomerulonephritis, including immunoglobulin A nephropathy, focal and segmental glomerulosclerosis, membranoproliferative glomerulonephritis, minimal change nephritis, and membranous nephropathy. The authors are unaware of data that would support the notion that histologic subtype confers a specific prognosis for pregnancy. Rather, the previously mentioned principles are applicable to women with chronic glomerulonephritis; baseline renal function and blood pressure are what dictate outcomes.

Polycystic Kidney Disease

Young women with autosomal dominant polycystic kidney disease (ADPKD) are frequently asymptomatic, with normal renal function and normal blood pressure, and may be unaware of their diagnosis. Little has been written about polycystic kidney disease and pregnancy because many patients with this condition have well-preserved renal function until after childbearing.

A series involving 235 women with autosomal dominant polycystic kidney disease and 108 unaffected family members evaluated pregnancy outcomes reported an increased incidence of maternal complications in affected compared with unaffected women.[24] Preexisting hypertension was the most common risk factor for maternal complications during pregnancy, because hypertension is a well-known risk factor for preeclampsia.[24]

Pregnant women with polycystic kidney disease should also be considered at increased risk for urinary tract infection. Estrogen is reported to cause liver cysts to enlarge, and repeated pregnancies may result in symptomatic enlargement of liver cysts. Given the association between cerebral aneurysms and ADPKD in some families, screening for these aneurysms should be considered before natural labor. All patients should undergo genetic counseling before pregnancy to ensure they are aware that their offspring have a 50% chance of being affected.

Chronic Pyelonephritis

Chronic pyelonephritis is defined as nephropathies associated with recurrent urinary tract infection, often in association with urinary tract abnormalities (eg, vesicoureteral reflux). Chronic pyelonephritis caused by dilation and stasis in the urinary tract may exacerbate in pregnancy. Women with reflux nephropathy have been reported to have an adverse prognosis during pregnancy.

A prospective study of 54 pregnancies in 46 women with reflux nephropathy found that preeclampsia was present in 24%, most commonly in women with preexisting hypertension.[25] Deterioration in renal function during pregnancy occurred in 18%, and those with preexisting reduced renal function were at greater risk. One third of the infants were delivered preterm, and 43% had vesicoureteral reflux. These women should have a high fluid intake and be screened with urine cultures at least monthly for bacteriuria, and should be treated promptly when infections are present. In some cases, after a first infection, suppressive antibiotic therapy for the duration of pregnancy may be warranted.

Chronic Renal Diseases That May be First Diagnosed During Pregnancy

The presence of chronic renal disease may first be appreciated during pregnancy partly because pregnant women are scrutinized more closely, and also because the renal hemodynamic alterations during pregnancy may cause proteinuria to increase and be clinically detectable for the first time. Frequent measurement of blood pressure may also lead to diagnosis of renal diseases accompanied by hypertension. Furthermore, the presence of even mild preexisting renal disease is associated with an increased risk for preeclampsia, and therefore underlying renal disease may first become apparent after preeclampsia has developed.

Renal diseases that may have been silent preconception and may ‘‘present’’ during pregnancy include IgA nephropathy, focal and segmental glomerulosclerosis, polycystic kidney disease, and reflux nephropathy. Renal diagnostic testing during pregnancy can include blood and urine testing and ultrasonography. Renal biopsy is

usually deferred until after delivery unless acute deterioration in renal function occurs[26] or morbid nephrotic syndrome is present.

Although experienced operators have reported few complications of renal biopsy during pregnancy, increased renal blood flow, hypertension, and difficulty positioning the patient are concerns.[27–29] The timing of renal biopsy after delivery depends on the clinical circumstances. If renal function is normal, and only proteinuria is present, it is reasonable to delay biopsy up to 6 months postpartum, because proteinuria may improve once the pregnancy-associated hemodynamic alterations have resolved. However, if renal function is impaired, then biopsy may be considered within a few weeks of delivery.

Renal Diseases That Develop for the First Time During Pregnancy

Pregnant women are at risk for any of the renal diseases that occur in women of childbearing age, including pyelonephritis, glomerulonephritis GN, interstitial nephritis, and acute renal failure. Pyelonephritis is more likely to be associated with significant azotemia in pregnant women than nonpregnant women, and should be treated aggressively. Glomerulonephritis and interstitial nephritis are not more likely to develop during pregnancy, although they do occur.

Acute kidney injury in association with pregnancy is a rare complication in developed countries, and is also decreasing in incidence in the developing world, with only 190 cases observed in a 20-year period in Eastern India.[30] Recent estimates suggest that the incidence of acute kidney injury from obstetric causes is less than 1 in 20,000 pregnancies.[31]

Treatment of acute glomerulonephritis presenting during pregnancy is challenging because immunosuppressants are toxic to the fetus, and high-dose steroids have not been studied during pregnancy. Acute glomerulonephritis presenting in pregnancy should be treated in close collaboration with the obstetrician and nephrologist. If acute renal deterioration is seen after 28 to 32 weeks gestation, the patient should probably be delivered and renal biopsy performed postpartum.

When acute kidney injury occurs early in pregnancy (12–18 weeks), it is usually associated with septic abortion or prerenal azotemia caused by hyperemesis gravidarium. Most cases of acute kidney injury in pregnancy occur between gestational week 35 and the puerperium, and are primarily caused by preeclampsia and bleeding complications. Preeclampsia, particularly the HELLP variant (hemolysis, elevated liver enzymes, low platelet count), is an important cause of acute kidney injury in pregnancy.[15] Although most cases of preeclampsia are not usually associated with renal failure, the HELLP syndrome may be associated with significant renal dysfunction, especially if not treated promptly with delivery. In rare instances, dialysis may be necessary, but most women without preexisting renal or hypertensive disease do not require long-term dialysis therapy. Additional important clinical entities causing acute kidney injury during pregnancy are discussed.

Thrombotic Microangiopathy

Although rare, thrombotic microangiopathies (thrombotic thrombocytopenic purpura [TTP] and hemolytic uremic syndrome [HUS]) are an important cause of pregnancy-associated acute renal failure because they are associated with considerable morbidity. They also share several clinical and laboratory features of pregnancy-specific disorders, such as the HELLP variant of preeclampsia and acute fatty liver of pregnancy. Therefore, distinction of these syndromes is important for therapeutic and prognostic reasons.

Features that may be helpful in making the correct diagnosis include timing of onset and the pattern of laboratory abnormalities. Preeclampsia typically develops in the

third trimester, with only a few cases developing in the postpartum period, usually within a few days of delivery. TTP usually occurs antepartum, with many cases developing in the second and third trimesters. HUS is usually a postpartum disease; symptoms may begin antepartum, but most cases are diagnosed postpartum.

Preeclampsia is much more common than TTP/HUS and is usually preceded by hypertension and proteinuria. Renal failure is unusual in women with preeclampsia, even in severe cases, unless significant bleeding or hemodynamic instability or marked disseminated intravascular coagulation occurs. In some cases, preeclampsia develops in the immediate postpartum period and, when thrombocytopenia is severe, it may be indistinguishable from HUS. However, preeclampsia spontaneously recovers, whereas TTP/HUS is often associated with persistent renal insufficiency and hypertension, with many requiring dialysis or transplantation long-term.[32]

In contrast to TTP/HUS, preeclampsia may be associated with mild disseminated intravascular coagulation and prolongation of prothrombin and partial thromboplastin times. Another laboratory feature of preeclampsia/HELLP syndrome that is not usually associated with TTP/HUS is marked elevations in liver enzymes. The presence of fever is more consistent with a diagnosis of TTP than preeclampsia or HUS. The main distinctive features of HUS are its tendency to occur in the postpartum period and the severity of the associated renal failure.

Treatment of TTP/HUS includes plasma infusion/exchange and other modalities used in nonpregnant patients with these disorders. Treatment of preeclampsia/HELLP syndrome involves delivery and supportive care. More aggressive treatment is rarely indicated. Some centers have reported the use of steroids in cases of severe HELLP syndrome, although this therapy has not been rigorously evaluated in placebo-controlled clinical trials.[33]

Acute Tubular Necrosis

Acute tubular necrosis induced by volume depletion or exposure to nephrotoxins may occur during pregnancy, although the incidence is low. In the first trimester, acute tubular necrosis is usually associated with hyperemesis gravidarium, whereas later in pregnancy and in the peripartum period it is usually associated with abruptio placenta or other causes of obstetric hemorrhage. Occasionally, nonsteroidal anti-inflammatory agents, used for postpartum analgesia, may precipitate acute kidney injury in patients who are volume-depleted from hemorrhage, decreased fluid intake, or both. In severe cases of obstetric hemorrhage, acute cortical necrosis with associated disseminated intravascular coagulation may be present, and ultrasonography or computed tomography may demonstrate hyperechoic or hypodense areas in the renal cortex. These patients usually require dialysis, but 20% to 40% may have partial recovery of renal function.

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) is a rare complication of late pregnancy characterized by rapidly progressive liver failure. Women usually present with nausea, vomiting, and anorexia, and many have clinical and laboratory features that overlap with preeclampsia or HELLP syndrome.[34] Other laboratory abnormalities (in addition to marked elevations in alanine aminotransferase and aspartate aminotransferase) frequently observed include elevated bilirubin, hypofibrinogenemia, prolonged partial thromboplastin time, hypoglycemia, anemia, and low platelet count.[35] Many cases are associated with significant azotemia, and one series comparing AFLP with HELLP syndrome observed that acute renal failure was significantly more common with AFLP.[36]

Because AFLP is believed to be a disease of mitochondrial dysfunction,[37] the kidney dysfunction associated with AFLP may reflect inhibition of β-oxidation of fats in the

kidney. This disease occurs in women heterozygous for long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency and whose fetus has the disorder. Abnormal fatty-acid metabolites produced by the fetus seem to enter the maternal circulation and overwhelm the mitochondrial-oxidation machinery of the heterozygous mother. Autopsy data have shown microvesicular fat in the kidneys of women with AFLP. Delivery is urgently required, and most patients improve shortly afterwards.

This disorder was formerly associated with a more ominous outcome, which may have been a consequence of late diagnosis, although in a recent case series maternal mortality occurred in 2 of 6 women.[35] When diagnosed early, long-term morbidity is reduced.

Urinary Tract Obstruction

Pregnancy is associated with dilation of the collecting system, which is not usually accompanied by renal dysfunction. Rarely, complications such as large uterine fibroids that enlarge in the setting of pregnancy can lead to obstructive uropathy. Occasionally, acute urinary tract obstruction in pregnancy is caused by a kidney stone. Diagnosis can usually be made with ultrasonography. Often the stone will pass spontaneously, but occasionally cystoscopy is needed to insert a stent to remove a fragment of stone and relieve obstruction, particularly if sepsis or a solitary kidney is present. Extracorporeal shock wave lithotripsy is contraindicated during pregnancy because of the possibility of adverse effects on the fetus.

Treatment of Acute Kidney Injury

Treatment of acute kidney injury occurring in pregnancy or immediately postpartum is similar to that in nongravid subjects, although several important considerations are unique to pregnancy. Uterine hemorrhage near term may be concealed and blood loss underestimated; thus, any overt blood loss should be replaced early. When dialysis is required, peritoneal dialysis and hemodialysis have been used successfully in patients with obstetric acute kidney injury. Neither pelvic peritonitis nor the enlarged uterus is a contraindication to the former method. In fact, this treatment is more gradual than hemodialysis and may be less likely to precipitate labor.

Because urea, creatinine, and other metabolites that accumulate in uremia traverse the placenta, dialysis should be undertaken early, with the goal of maintaining the blood urea nitrogen at approximately 50 mg/dL (8 mmol/L). Excessive fluid removal should be avoided, because it may contribute to hemodynamic compromise, reduction of uteroplacental perfusion, and premature labor. However, polyhydramnios is a complication of a high maternal urea, leading to high urea and solute diuresis by the fetus, and is also believed to contribute to premature labor. When large volumes of ultrafiltration are required, continuous fetal monitoring during dialysis may be advisable, particularly after mid-pregnancy.

THERAPY FOR END-STAGE RENAL DISEASE DURING PREGNANCY

Dialysis

Fertility is reduced in patients undergoing dialysis because of abnormalities of pituitary luteinizing hormone release leading to anovulation. Pregnancy that occurs in women undergoing maintenance dialysis is extremely high risk for the fetus, and conception should not be encouraged because of very high fetal mortality. Large surveys have shown that only 42% to 60% of these pregnancies result in a live-born infant. Preterm birth, very low birth weight, and intrauterine growth restriction are common, and more than 85% of infants born to women who conceive after starting dialysis are born before 36 weeks gestation.

Management of pregnant patients on dialysis includes several considerations, but the single most important factor influencing fetal outcome is the maternal plasma urea level.[38] In patients undergoing hemodialysis, the number of dialysis sessions per week must be increased and the session duration prolonged to a minimum of 20 h/wk, aiming for a predialysis urea of 30 to 50 mg/dL (5–8 mmol/L).[38–40]

In small series, daily nocturnal hemodialysis has also been used with success to this end.[41] Heparinization should be minimal to prevent obstetric bleeding. Dialysate bicarbonate should be decreased to 25 mEq/L to target a predialysis bicarbonate level of approximately 22 mEq/L. If peritoneal dialysis is used, decreasing exchange volumes through increasing exchange frequency or cycler use is recommended.[42]

Adequate calorie and protein intake is required; 1 g per kilogram body weight per day of protein intake plus an additional 20 g/d has been suggested.[43] After the first trimester, maternal "dry" weight should be increased by approximately 1 lb/wk (400 g/wk) to adjust for the expected progressive weight increase in pregnancy.

Antihypertensive therapy should be adjusted for pregnancy by discontinuing ACEIs and angiotensin receptor blockers, and aiming to maintain maternal diastolic pressure at 80 to 90 mm Hg using methyldopa, labetolol, and sustained release nifedipine in standard doses to achieve target. Anemia should be treated with supplemental iron, folic acid, and erythropoietin. Erythropoietin is safe in pregnancy, and pregnancy-related erythropoietin resistance requires a dose increase of approximately 50% to maintain hemoglobin target levels of 10 to 11 g/dL.[39] Frequent monitoring of iron stores and treatment with intravenous iron should be prescribed as necessary.[43]

Because of placental 25-hydroxyvitamin D3 conversion, decreased supplemental vitamin D may be required and should be guided by levels of vitamin D, parathyroid hormone, calcium, and phosphorus. Sevelamer should not be used in pregnancy because animal studies have shown reduced or irregular ossification of fetal bones. Oral magnesium supplementation may be needed to maintain the serum magnesium level at 5 to 7 mg/dL (2–3 mmol/L), particularly because magnesium is a tocolytic, and low serum levels could theoretically promote uterine contractions. Based on a large meta-analysis, low-dose aspirin to prevent preeclampsia in women at risk for this complication may be advisable in those also on dialysis.[44] Babies born to mothers on dialysis may require monitoring for osmotic diuresis in the immediate postpartum period if maternal urea was high at delivery.

Anticonvulsant Therapy

The presence of dialysis or significant renal dysfunction, loading dose, and infusion rate of magnesium sulfate must be modified and monitored with serial magnesium levels, because doses will accumulate.

Renal Transplantation

Josephson and McKay provide a more detailed discussion of renal transplantation in pregnancy elsewhere in this issue. However, a brief summary follows.

Menstruation and fertility resumes in most women at 1 to 12 months post–renal transplant. Several thousand women have undergone pregnancy after renal transplantation, and pregnancy in this population seems to involve much lower risk to mother and baby than pregnancy in patients on dialysis. Although pregnancy has become common after transplantation, little other than case reports, series, and voluntary databases are available to guide practice. A Consensus Conference generated a report in 2005 summarizing the literature, produced practice guidelines, and identified gaps in knowledge.[45] Most pregnancies (>90%) succeed that proceed beyond

the first trimester; however, immunosuppressant effects, preexisting hypertension, and renal dysfunction cause maternal and fetal complications. Maternal complications of steroid therapy include impaired glucose tolerance, hypertension (47%–73%), preeclampsia (30%), and increased infection. Fetal complications include a 45% to 60% incidence of premature delivery (mean gestational age is 36 weeks) and intrauterine growth restriction with lower birth weight (average 2.3–2.6 kg). Best practice guidelines outline criteria for considering pregnancy in renal transplant recipients,[45–47] and suggest that those contemplating pregnancy should meet the following:

- Good health and stable renal function for 1 to 2 years after transplantation with no recent acute or ongoing rejection or infections
- Absent or minimal proteinuria (<0.5 g/d)
- Normal blood pressure or easily managed hypertension
- No evidence of pelvicalcyceal distention on ultrasonography before conception
- Serum creatinine less than 1.5 mg/dL (133 μmol/L)
- Drug therapy: prednisone 15 mg/d or less; azathioprine 2 mg/kg or less; cyclosporine less than 5 mg/kg per day.

Because of risk for intrauterine growth restriction and preeclampsia, all pregnant transplant recipients should be managed by a high-risk obstetrician.

Future studies are required to address optimal immunosuppression in pregnancy. Although cyclosporine levels tend to decrease during pregnancy, no information is available on whether drug dosage should be increased. Experience with tacrolimus is increasing; although it has not been used as widely in pregnancy as cyclosporine, growing experience suggests that it is safe and has a similar side effect profile to cyclosporine.[48] Considerations regarding hypertension and growth restriction are important; no established blood pressure target exists, although 130/80 mm Hg or less is suggested by the authors and Josephson and McKay in their article found elsewhere in this issue.

Antihypertensives should be switched to those safe in pregnancy.[49] Mycophenolate mofetil and sirolimus are not considered safe in pregnancy.[50] Mycophenolate mofetil has been reported to be embryotoxic in animals, is associated with ear and other deformities in humans, and was recently characterized as a teratogen.[23] This drug should be discontinued 6 weeks before conception, and women should be switched to azathioprine if indicated. Sirolimus causes delayed ossification in animal studies, and although successful live-born human outcomes have been reported, its use is contraindicated until more data are available.

Finally, data from the National Transplantation Pregnancy Registry and European Dialysis and Transplant Association suggest that pregnancy rarely negatively affects the graft, although minor increases in serum creatinine may be seen postpartum compared with prepregnancy levels.[46,50] A long-term analysis of parous compared with nulliparous women who underwent transplantation followed up for 20 years suggests that a live birth in women with a functioning graft does not have an adverse impact on graft and patient survival.[51] Rejection is difficult to diagnose in pregnancy, and renal biopsy may be required; the consensus opinion is that steroids are safe treatment as is intravenous immunoglobulin, but the safety of antilymphocyte globulins and rituximab in pregnancy are unknown.[45]

SUMMARY

Although kidney disease in pregnancy is uncommon, it poses considerable risk to maternal and fetal health. Based on case series published over the past several decades, pregnancy outcome seems to be directly related to level of baseline renal

function and degree of hypertension. Because these disorders are uncommon, multicenter efforts are needed to better identify risks and determine optimal therapeutic strategies.

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