29 Renal diseases in pregnancy

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INTRODUCTION

Caring for pregnant women with renal disease is usually a difficult task for both the obstetrician and the nephrologist. These pregnancies are viewed as high risk, due to concerns of increased maternal and perinatal morbidity and mortality. It is estimated that at least 4% of the women in the childbearing age carry a diagnosis of chronic kidney disease (CKD) (1) of different etiologies: diabetic nephropathy, lupus nephritis, polycystic kidney disease, reflux nephropathy, or different forms of glomerulonephritis. Although the frequency of conception decreases as the impairment in kidney function progresses, with levels as low as 0.5% per year in dialysis patients (2), it is not unheard of patients on either hemodialysis or peritoneal dialysis (PD) to get pregnant. When end-stage renal disease patients get a kidney transplant, the return of fertility is usually the rule and caring for these pregnancies is even more challenging due to the continued need for immunosuppression, with its associated fetal risks for congenital anomalies, and small-for-gestational-age babies (2).

This chapter is intended to provide information needed to take care of these patients, and will start by reviewing normal renal anatomy and physiology during pregnancy. The interplay between CKD, acute renal failure (ARF) or acute kidney injury, hypertension (HTN) and pregnancy will be further explored.

RENAL ANATOMY AND PHYSIOLOGY DURING PREGNANCY

There are marked changes in the renal hemodynamics and function during normal pregnancy, associated with significant anatomical changes such as increased renal size and dilatation of the collecting system. They occur in concert with multiple other physiologic alterations that take place during pregnancy, including significant expansion of the blood volume, increased cardiac output, and enhanced blood flow in several regions of the body (3) (Table 1).

Blood volume can increase almost 50% in a normal pregnancy, compared with the nonpregnant state. This represents roughly 1500 mL increase, of which about 500 mL is in red blood cell volume. Volume expansion starts in the first trimester, but is more marked in the second trimester and the rise is much less in late pregnancy. It is believed to be caused by the increased metabolic demands of the enlarged uterus with its increased vascularity, placenta and fetus, the need to protect the fetus against the harmful effects of decreased venous return when in supine and upright position, and the need to protect the mother against blood loss during delivery (3). Aldosterone levels are elevated, but it is not known whether this contributes to hypervolemia. It is accompanied by vasodilatation, especially in the pelvis. There are no clinical signs of volume overload in a normal

pregnancy (3). Expansion of the blood volume may be greater in multiple gestations or smaller in pre-eclampsia (4).

Other cardiovascular changes include increase in cardiac output and significant decrease in systemic vascular resistance with resultant decrease in blood pressure in normal pregnancy (4).

Dilatation of the Collecting System

Dilatation of the collecting system seems to be the result of a combined progesterone-induced ureteral smooth muscle relaxation and compression of the ureter by the enlarged uterus and iliac vessels. A pelvicaliceal diameter of up to 2 cm is usually allowed as “physiologic hydronephrosis” of pregnancy. Hydronephrosis is most commonly seen on the right, due to anatomical reasons (5,6). By ultrasound criteria, hydronephrosis is defined as at least 5 mm (5) dilatation of the calyceal diameter. This dilatation of the urinary collecting system starts developing during the second trimester, is seen only above the linea terminalis, and resolves in few weeks after delivery (6). Symptomatic hydronephrosis is not a frequent event, occurring in about 0.2% to 3% of pregnant women (7), but those who are symptomatic frequently have associated urinary tract infections (6).

The dilated collecting system can retain some of the urine meant to be saved for the twenty-four hour urine collections. As a result, creatinine clearance may be underestimated, unless the collection is done carefully and the patient is volume repleted before the test. If in the last few hours of the collection the patient is maintained in the left lateral recumbent position, the chances of obtaining a full collection are also increased.

Increase in Renal Volume

During pregnancy, the kidneys increase in volume, probably due to increase in blood flow and interstitial volume. A study of humans that excluded dilatation of the renal pelvicaliceal system demonstrated that renal volume can increase by 30% in normal pregnancy (8).

GFR

Renal hemodynamics undergo significant changes: renal plasma flow (RPF) increases by 50% to 80%, while GFR increases by 50% (9). Systemic and renal hemodynamics adaptations occur early in pregnancy, before complete placentation takes place, demonstrating that they are dependent mainly on maternal factors for their development (10). They are also present in pseudopregnancy, a condition where the fetoplacental unit is absent (11), and different studies have suggested roles for relaxin, an ovarian hormone, and also for nitric oxide synthase, prostaglandins, and endothelin (9).

The physiologic increase in GFR is the result of expansion in the renal plasma blood flow, associated with characteristic

renal vasodilatation resulting from both afferent and efferent arteriolar relaxation (11). The parallel reduction in preglomerular (afferent) and postglomerular (efferent) arteriolar resistance explains why single nephron GFR increases without an increase in the glomerular capillary pressure (11), which is an important phenomenon, and explains further why normal pregnancy is not followed by loss of kidney function. This last aspect was demonstrated in animal studies on rats (12), where it was shown that repetitive pregnancies were not associated with increased risk of deterioration of kidney function. Rats provide a good animal model to study this particular problem since they have a gestation of only 22 days. After six repetitive pregnancies,

the study rats had no renal changes compared with never-pregnant controls (12).

GFR increases to a maximum of about 50% by mid-pregnancy (13), remains elevated during the pregnancy, and returns to baseline values 3 months after delivery (1), while RPF starts to fall toward the end of pregnancy (13) (Fig. 1). The increase in GFR is not accompanied by an increase in the production of urea and creatinine: their serum concentration will decrease in pregnancy. Serum creatinine concentration falls by about 0.4 mg/dL, so the normal pregnancy range is 0.4 to 0.8 mg/dL (14).

Estimation of GFR using the modification of diet in renal disease (MDRD) formula has been recently evaluated in pregnant women. In a study that looked at three groups of pregnant women—healthy pregnant volunteers, women with pre-eclampsia, and pregnant women with previously known CKD—the MDRD formula significantly underestimated kidney function although performed better in pre-eclampsia and CKD group (15). Alper et al. found that the MDRD formula, along with the Cockcroft–Gault formula, was inaccurate in predicting GFR in pre-eclamptic patients (16).

Cystatin C is a low-molecular weight (MW) protein, which has been recently studied in the general population in an attempt to find a better endogenous marker that could be used for more accurate estimation of GFR (17). Studies have found that while serum creatinine levels decrease in pregnancy, cystatin C levels were higher for pregnant women as compared with healthy nonpregnant women (18) and also significantly higher in twin as compared with singleton pregnancies (18). Cystatin C levels increase during pregnancy in relationship to gestational age, being highest in the third trimester (19). Its actual role in pregnancy is very interesting, as cystatin C is a member of the cystatin superfamily of cysteine protease inhibitors. Proteinases and their inhibitors regulate the trophoblast invasion, and the serum concentration of cystatin C has been found in several studies to be increased not only in late pregnancy but also in pre-eclampsia (18–20). Based on the available data, it is unlikely that cystatin C will have any utility in monitoring kidney function in pregnancy but might prove useful in the early detection of patients who will develop pre-eclampsia (21).

Table 1 Physiologic and Anatomic Changes in Normal Pregnancy	
Blood volume	Increased 50% (1500 cc)
Cardiac output	Mild increase
Net sodium retention	900 mmol
Systemic vascular resistance	Decreased
Systemic blood pressure	Decreased
Systolic	15 mmHg
Diastolic	10 mmHg
RPF	Increased 50–80%
GFR	Increased 50%
Glomerular capillary pressure	Unchanged
Serum osmolality	Decreased 10 mmOsm
Urine concentration and dilution	No change
Proteinuria	200–300 mg/day
Glucosuria	Present in the absence of diabetes
Serum creatinine, uric acid, BUN	Decreased
Serum cystatin C	Increased
Acid–base	Compensated respiratory alkalosis
Kidney volume	Increased 30%
Urinary collecting system	Dilated
Abbreviations: RPF, renal plasma flow; GFR, glomerular filtration rate; BUN, blood urea nitrogen.

Figure 1 Renal hemodynamics during normal pregnancy. Source: From Ref. 13. Abbreviations: GFR, glomerular filtration rate; RPF, renal plasma flow.

Renal Tubular Function in Pregnancy

Uric Acid

Uric acid after being freely filtered at the glomerular level is extensively reabsorbed, mainly in the proximal tubule, so that only 10% of the filtered load is excreted (13). Plasma concentration decreases early on in pregnancy by at least 25%, largely due to the significant rise in GFR, but also due to decrease in tubular reabsorption (13). In late pregnancy, the fractional excretion of uric acid decreases and the plasma levels trend toward nonpregnant levels (13).

Glucose

The presence of glucose in the urine may rather be a sign of tubular dysfunction than diabetes mellitus. Proximal and distal tubules have a decreased capacity to reabsorb filtered glucose due to an unknown mechanism. The increase in GFR causes an increase in filtered load of glucose on one hand. On the other hand, the increase in plasma volume may inhibit the tubular reabsorption of sodium and hence glucose (13).

Sodium

There is a gradual retention of sodium during pregnancy, reaching 900 mmol, due to a positive sodium balance and an increase in tubular reabsorption of sodium (22).

Water Metabolism

Although the kidneys' abilities to maximally dilute and concentrate urine are intact, the serum sodium concentration and serum osmolality concentration are about 5 mEq/L and 10 mOsm/kg, respectively, lower throughout most of gestation than in the nonpregnant state. This is mainly due to a decrease in osmotic threshold for thirst and arginine vasopressin (AVP) release (23). In addition, a transient increase in AVP clearance during mid-gestation may produce a diuresis, the so-called transient diabetes insipidus of pregnancy.

Proteins

Proteins present in the urine are a combination of plasma proteins that are normally filtered at the glomerular capillary level, and escape reabsorption in the proximal tubule, and proteins produced by the urogenital tract: 40% are represented by albumin, 15% to 20% are immunoglobulins, and 55% to 60% is Tamm-Horsfall glycoprotein, the latter being of tubular origin (24).

Albumin, MW 69,000 daltons (D), is a plasma protein usually filtered to a limited degree due to its MW and anionic charge. Below MW 60,000 D, there is a progressive increase in filtration at the glomerular level so that in healthy, nonpregnant subjects, low-MW proteins and only small amounts of albumin are normally filtered, then almost entirely reabsorbed and catabolized in the proximal tubule.

Normal urinary protein excretion averages 20 to 80 mg/day in normal nonpregnant women, with an accepted upper limit of normal of 150 mg/day. Albuminuria is considered to be a more sensitive marker for glomerular damage and CKDs than

total proteinuria (25), and the upper limit of normal for daily albuminuria is considered to be 30 mg (26).

In pregnancy, proteinuria is considered to be abnormal if exceeds 300 mg/day (27). Studies that have looked at proteinuria and albuminuria in normal pregnancy have found a maximum total daily urinary protein excretion of 260 mg/day (28), or even a little lower, at 200 mg/day (29), with an absolute amount of albumin, which does not seem to be higher than that in normal, nonpregnant state (30). Higby (28) found that total daily albumin excretion in normal pregnancy was 29 mg and Beetham (30) showed that there is a tendency for albuminuria to increase as the normal pregnancy progresses, being significantly higher in the third trimester compared with the first, but the absolute amount will remain less than 30 mg/day. The available evidence suggests that the diminished tubular reabsorption of low-MW proteins play a significant role for the increase in proteinuria during normal pregnancy (30,31).

The gold standard for total protein quantification is the 24-hour urine collection with its well-known limitations: can be inaccurate due to undercollection, is cumbersome for the patient, and the results are delayed pending collection. Screening for proteinuria using the dipstick (most sensitive to albumin) is fast and convenient in the clinic, where a random urine sample can be used. Unfortunately, the accuracy of the dipstick urinalysis in predicting significant proteinuria is poor (32), but the use of a protein to creatinine ratio in a spot urine seems to be a practical and reasonable choice (14).

Acid-Base Regulation

Plasma bicarbonate decreases during pregnancy, ranging from 18 to 22 mEq/L. It is believed that progesterone-induced hyperventilation occurs during pregnancy, leading to respiratory alkalosis with decrease in PCO₂ close to 27 mmHg and increase in pH to about 7.44. There is no apparent defect in renal handling of acid (33).

PREGNANCY IN WOMEN WITH CKD

The influence of pregnancy on the course of renal disease and the effect of renal disease on the outcome of pregnancy are important concerns in treating and advising patients with renal disease. The available published data on pregnancy in women with CKD have limitations due to small sample size, single-center and retrospective studies, using varied definitions of kidney disease, and adverse maternal and fetal outcomes (1,14,34). Given the low prevalence of CKD in women of childbearing age and difficulties related to randomization, it is easy to understand the complexity of conducting good quality trials in this population. In spite of these imperfections, factors that have consistently emerged, and are widely agreed upon, as important in influencing both maternal and fetal outcomes are advanced CKD, preexistent HTN, and proteinuria. Pregnant women who have normal or only mildly impaired kidney function, normal blood pressure, and little or no proteinuria before conception are expected to have an uneventful pregnancy, without maternal complications (worsening kidney function, HTN, and pre-eclampsia) and without fetal complications (prematurity,

small-for-gestational-age, fetal loss, etc.). On the other hand, those who have significantly impaired kidney function and/or HTN and proteinuria before conception are at increased risk for maternal and fetal complications. With respect to the type of the renal disease, the current consensus is that in primary nephropathies (IgA nephropathy, focal and segmental glomerulosclerosis, membranous glomerulonephritis, etc.), the above-mentioned factors dictate the maternal and fetal outcomes irrespective of the type of the disease; in systemic diseases with renal involvement such as diabetes mellitus (DM) and systemic lupus erythematosus (SLE), there are additional disease-specific features that will affect prognosis (1,14,34).

Effects of Pregnancy on Kidney Disease

In a study (35) involving CKD patients with serum creatinine levels lower than 1.4 mg/dL, it was shown that GFR, creatinine clearance, and effective RPF increase during gestation, similar to the response observed in women without underlying renal disease. It is then expected to see a decline in serum creatinine levels in these patients during pregnancy and a return to baseline values after delivery. Women with more advanced renal dysfunction will not always have the physiologic increase in GFR seen in women without or only with mild renal insufficiency, and their pregnancies are more frequently complicated with worsening kidney function (2,11,36). A potential mechanism for inducing permanent kidney damage during pregnancy could be an increase in intraglomerular pressure, but animal studies (11) have showed that even in the presence of preexistent renal damage, pregnancy does not lead to glomerular HTN.

Proteinuria usually increases during pregnancy, then declines after delivery (11). Among others, Katz et al. (35) analyzed 121 pregnancies in 89 women with previously known CKD. De novo or increased proteinuria was noted in almost 50% of the pregnancies, and 60% of those who were proteinuric during pregnancy had regression of proteinuria at follow-up.

When counseling patients regarding the effects of pregnancy on their kidney disease, prognosis is based, in general, on three categories of renal function, which have been described in the literature as mild, moderate, and severe (1).

Mild Decrease in Kidney Function (Serum Creatinine Lower Than 1.4 mg/dL) Before Conception

There is a general consensus that pregnancy usually does not modify the natural course of kidney disease in this setting. However, some patients with normal kidney function can have a temporary decline in renal function during pregnancy (35,37). Rarely, there can be an unexpected and irreversible loss of kidney function during pregnancy (38,39), which usually happens in more aggressive histologic forms of glomerular and/or tubulointerstitial disease (34). Jungers et al. (37) have shown that in women with reflux nephropathy, pregnancy had no negative impact on their kidney disease if they had normal kidney function at conception. Multiple other authors report similar positive results of pregnancies in women with serum creatinine less than 1.4 mg/dL (35,40,41).

The presence of HTN and proteinuria becomes major predictive factors for worsening kidney function in this clinical scenario.

Preexistent or untreated HTN has been found to be an independent risk factor for loss of renal function in few studies (41,42). The role of proteinuria was convincingly demonstrated by Hemmelder (43) in a retrospective analysis of 30 pregnancies in 19 patients with primary glomerular disease and normal kidney function and blood pressure at conception. This group was compared with a control group of 31 patients who did not become pregnant after the diagnosis of kidney disease. Patients were followed for 11 years, and at the end of follow-up, patients who became pregnant had higher serum creatinine levels than controls. Pregnancy and initial proteinuria were found to be independently related with the rate of loss of kidney function. Of the 30 pregnancies that were preceded and complicated with nephrotic-range proteinuria, 10 were followed by an accelerated rate of loss of kidney function compared with the other 20 pregnancies.

Jungers (41) also found that in patients with primary chronic glomerulonephritis and normal kidney function, proteinuria had a predictive role for the progression of kidney disease on pregnancy, although not as strong as HTN.

Moderate Decrease in Kidney Function (Serum Creatinine 1.4–1.8 mg/dL)

Moderate decrease in kidney function (serum creatinine 1.4–1.8 mg/dL) is associated with a higher risk of further decline during pregnancy. In a retrospective review (37), 19% of the patients with moderate decline in kidney function had irreversible further loss of maternal renal function. Proteinuria and HTN are more frequent in this population and additive risk factors for further decline in renal function (1,44).

Severe Decrease in Kidney Function (Serum Creatinine Greater Than 1.9 mg/dL)

Severe decrease in kidney function (serum creatinine greater than 1.9 mg/dL) has been shown to be a higher risk factor for renal function loss during pregnancy. The landmark study by Jones and Hayslett (44), published in 1996, showed that the risk of accelerated progression to end-stage renal disease was the highest when the serum creatinine concentration was above 2 mg/dL at the beginning of the pregnancy. With an initial serum creatinine of at least 1.4 mg/dL in 67 women and 82 pregnancies, they reported a pregnancy-related loss in renal function in 43% of the cases. The risk is even higher when uncontrolled HTN is present (34).

The only prospective study that analyzed the outcomes of pregnancies in patients with serum creatinine levels greater than 1.4 mg/dL (36) found an accelerated loss of kidney function only in the subgroup of patients with both estimated GFR <40 mL/min/1.73 m² and proteinuria >1 g/day before pregnancy.

Women with serum creatinine levels >3 mg/dL are usually infertile (45) due to amenorrhea or anovulatory menstrual cycles.

Based on the available information, women with CKD who contemplate to become pregnant should be advised about the possible risk of accelerated loss of kidney function if serum creatinine level is greater than 1.4 mg/dL before pregnancy. Proteinuria exceeding 1 g/day portends a higher risk for accelerated loss of kidney function and, in some cases, even a twofold higher incidence of end-stage renal

disease (1). HTN control should be a major goal of pregnancy. Even if they are normotensive before pregnancy, these patients are at higher risk of becoming hypertensive during pregnancy (1,35).

Pregnancy should probably be discouraged in patients with multiple risk factors: moderate to severe kidney disease, proteinuria, and HTN.

Effect of Kidney Disease on Fetal Outcomes

Mild Decrease in Kidney Function (Serum Creatinine Lower Than 1.4 mg/dL) Before Conception

Katz (35) observed in a retrospective study that there were more fetal complications in patients with serum creatinine lower than 1.4 mg/dL than in general population, but at acceptable levels. Ninety-four percent of the pregnancies resulted in live births. Abe (40) has also noted same positive results in women with GFR >70 mL/min and blood pressure less than 140/90 mmHg. In women with autosomal dominant polycystic kidney disease (42) and normal kidney function before conception (serum creatinine less than 1.2 mg/dL), preexistent HTN was the most important risk factor for the development of poor fetal outcomes, including prematurity and fetal loss.

Munkhaugen (46) found in a very recent study that women with estimated GFR 60 to 89 mL/min/1.73 m² were not at increased risk of pre-eclampsia, small-for-gestational-age, or preterm delivery unless they were also hypertensive.

Moderate and Severe Decrease in Kidney Function (Serum Creatinine >1.4 mg/dL)

Moderate and severe decrease in kidney function (serum creatinine >1.4 mg/dL) translates in higher risk for fetal loss, prematurity, and small birth weight. Jones and Hayslett (44) reported moderately reduced fetal loss (93% survival rate), but significantly increased preterm delivery (59% compared with the expected rate of 10% in general population) and growth retardation (37% of infants were below the 10th percentile for birth weight).

Abe (40) also found that in women with moderately decreased kidney function, the rate of live births was relatively high, except for cases where HTN was present before pregnancy and/or was not controlled during pregnancy.

Imbasciati (36) found that in women with GFR <40 mL/min/1.73 m² and proteinuria >1 g/day, pregnancy was associated with poor fetal outcomes: increased perinatal death and low birth weight.

Jungers (34) also found a high risk of fetal death when serum creatinine was 1.8 to 2.0 mg/dL. HTN and nephrotic-range proteinuria, when present early in pregnancy, were found to be additive risk factors for poor fetal prognosis.

In summary, when counseling women with CKD regarding fetal outcomes, the following recommendations could be made:

- Fetal survival rate seems to be higher than 90%, but decreases when uncontrolled HTN and/or proteinuria are also present.
- Preterm delivery and growth retardation are more commonly found in women with at least moderate impairment in kidney function.

- HTN and proteinuria are additional risk for poor outcomes in this category, too.

MANAGEMENT

Over the years, the benefits of progress in obstetrics in neonatal care, including improved access to medical care, improved technology for fetal surveillance and antihypertensive medications available to treat high blood pressure in pregnant women, have translated in improved maternal and fetal outcomes in pregnancies that occur in women afflicted with CKD and HTN (37,42).

Pregnant women with CKD should be followed in collaboration with a nephrologist and with an obstetrician familiar with the effects of renal disease on pregnancy. Their prenatal visits should occur more frequently, ideally every 2 weeks until the third trimester and then weekly. Maternal renal function should be followed very closely, at least at monthly intervals, and asymptomatic bacteriuria should be promptly treated. Likewise, fetal surveillance with ultrasound and fetal heart monitoring should be done very closely. Maternal HTN requires special attention and needs to be treated efficiently. Preterm delivery needs to be offered when maternal renal function deteriorated rapidly, if fetal distress occurs, or pre-eclampsia is severe.

LUPUS NEPHRITIS

It remains questionable whether pregnancy exacerbates lupus. Earlier studies suggest that pregnant women with SLE clinically flare their disease three times more frequently during pregnancy and seven times more frequently postpartum compared with nonpregnant controls (47). More recently, it became apparent that the incidence of a lupus flare during pregnancy is more likely correlated with the disease activity before conception. Hayslett (48) showed that exacerbations or relapse occur in a wide range of patients during pregnancy or in the immediate period after delivery, namely in 25% to 60% of pregnancies. Relapses or exacerbations occur only in one-third of the patients if they had no signs of clinical activity 6 months before conception, as opposed to two-thirds of the patients when they had signs of clinical activity at onset of pregnancy. Activity of the disease also influenced fetal survival, which was 85% to 95% in patients with inactive disease and 50% to 80% in patients with active disease at conception. The presence of circulating anticardiolipin antibodies and lupus anticoagulant factors appears to worsen the perinatal outcomes. Fetal loss rate increases from 25% to about 60%, and the risk of maternal thromboembolism increases to about 50% (49,50).

The risk of prematurity and pre-eclampsia is increased even if patients have stable, but established renal disease and controlled HTN in the 6 months prior to conception (51). The risk of pre-eclampsia is high especially if the women have a history of antiphospholipid syndrome (52).

Flares cannot be prevented with routine increase in dose or prophylactic use of steroids, which are not recommended for this purpose either before pregnancy or after delivery (53). Therefore, women with lupus nephritis should be encouraged to postpone pregnancy for at least 6 months after the last flare.

The diagnosis of a lupus flare in pregnancy is not always straightforward, and the most challenging scenario is to make a distinction between pre-eclampsia and lupus flare, as they can both present with HTN, proteinuria, thrombocytopenia, and kidney injury (53). A renal biopsy is rarely needed, because a rising anti-dsDNA titer, and low complement levels are in favor of lupus flare, as opposed to hyperuricemia and abnormal liver function tests that favor pre-eclampsia. Flares are more common in women who had more than three flares before pregnancy, and the type of flare follows the previous known pattern of disease specific to the individual patient (51,53).

In pregnant women with active lupus nephritis, the maternal and perinatal outcomes are improved if a remission is achieved. Corticosteroids are the drugs of choice (51,53), given either as an increased oral form or intravenous methylprednisolone 500 mg daily for 3 days. Azathioprine can be used safely in pregnancy and during lactation (51,53). Hydroxychloroquine, often used to prevent flares, seems to be safe for use in pregnancy and should not be stopped in early pregnancy (51–53). Antiphospholipid-positive patients should be started on at least low-dose heparin to prevent thrombosis (52). The use of low-dose aspirin has been advocated for prevention of pre-eclampsia in patients at risk.

DIABETIC NEPHROPATHY

About 5% of pregnant women with type 1 DM can have diabetic nephropathy (54). Fortunately, most of them have preserved kidney function and the progression of their diabetic nephropathy does not seem to be affected by pregnancy in this situation. As is true with all patients with moderate to severe CKD, diabetic patients also will have higher risk of irreversible deterioration of kidney function during pregnancy, which has been estimated in some series to be as high as 40% (55); the risk of HTN and pre-eclampsia are also increased in diabetics. Proteinuria increases during pregnancy, an effect that could also be attributed to the cessation of ACE inhibition therapy due to potential teratogenic effects (54).

Women with diabetic nephropathy often have diabetic retinopathy, which should not go untreated during pregnancy. Diabetic retinopathy can progress during pregnancy and laser treatments are sometimes needed to prevent vision loss (54).

Perinatal outcomes are generally good with tight glycemic and blood pressure control.

Perinatal survival exceeds 95% (56,57), but there is a high risk of preterm delivery (50%) and small babies (15%) (56, 58–60). There is concern that prematurity can predispose the infants of diabetic mothers to long-term morbidity: severe psychomotor retardation and mild developmental retardation have been described in this setting (61).

ARF

The definition of ARF in pregnancy varies across studies. ARF has been defined as a creatinine level above 0.8 mg/dL, >25% decrement in GFR over the level documented before the beginning of pregnancy, or the need for dialysis (62–64). Since the 1960s, there has been a consistent decrease in the incidence of the ARF in pregnancy, which has been attributed to a steady decrease in the septic abortions in most developed countries

due to legalization of abortions and due to better access to care (63,64). The incidence of ARF in pregnancy has decreased from 20% to 40% in the 1960s to 2% to 10% in the 1980s (63).

Despite the decreased incidence, the development of ARF in pregnancy remains associated with significant morbidity and mortality.

ARF in pregnancy can be induced by any of the disorders leading to renal failure in the nonpregnant women: volume depletion, nephrotoxins, obstruction, interstitial nephritis, and so on. Pregnancy complications characteristic of each trimester can result in ARF. It is believed that the most common cause of ARF in pregnancy is pregnancy-related HTN (62,64,65).

Pre-eclampsia

Pre-eclampsia is a disorder specific of pregnancy, complicates around 5% of all pregnancies (66), and is characterized by new-onset HTN and proteinuria in excess of 300 mg/day, usually after 20 weeks of gestation. Blood vessels throughout the body are affected, and recently identified antiangiogenic substances of placental origin seem to be the cause of the diffuse endothelial dysfunction. The characteristic glomerular lesion, “endotheliosis,” appears histologically as endothelial swelling and occlusion of the capillary lumens, and although it is a variant of thrombotic microangiopathy, intraglomerular thrombosis is unusual (66). ARF is rare, and only 1.5% to 2% of the pre-eclamptic patients will have impairment of the kidney function (62). Patients with pre-eclampsia have an overall decrease in GFR and RPF, but not significant enough to cause ARF (62,63). They also have vasoconstriction and intravascular volume depletion, this way being at increased risk for the development of ARF when another obstetrical complication like hemorrhage or abruptio placentae is present. Superimposed volume depletion in these clinical scenarios will commonly lead to acute tubular necrosis and in the most severe cases to cortical necrosis (63). Treatment of pre-eclampsia-related ARF requires delivery of the fetus and placenta (63).

HELLP Syndrome

HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome occurs in 10% to 20% of the cases of severe pre-eclampsia (67). It has been reported that ARF can occur in 7% to 36% of the cases (67). Renal biopsy studies most commonly reported acute tubular necrosis or acute cortical necrosis in more severe cases (68) same as in less severe pre-eclampsia. Associated thrombotic microangiopathy has also been described, but with acute tubular necrosis as the dominant lesion (69).

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) is not a common complication of pregnancy, but represents an obstetric emergency of the third trimester (70,71). The patients present with abdominal pain, nausea, vomiting, headache, malaise, anorexia, jaundice, and rarely with hepatic encephalopathy. The etiology could be related to a familial genetic defect in fatty acid metabolism (70). Up to 90% of the women with AFLP can develop ARF (70). Disseminated intravascular coagulopathy is usually present. Serum transaminases are generally not as

severely elevated as they are in hepatitis. Most patients with renal failure have evidence of decreased renal perfusion similar to hepatorenal syndrome or acute tubular necrosis. Treatment again involves delivery of the baby.

Thrombotic Microangiopathies

Thrombotic microangiopathies are thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS), pathologies that are very rarely seen in pregnancy, occurring in less than 1 in 100,000 pregnancies (71). HUS was initially described as occurring in the postpartum period, between 1 day and 3 months after delivery, but it has become clear that it can occur during pregnancy also (70). In patients with a severe form of familial deficiency of ADAMTS13, TTP can also present during pregnancy (72). ADAMTS13 is a metalloprotease, which normally binds the von Willebrand factors secreted by the endothelial cells. When ADAMTS13 is deficient, abnormally large multimers of von Willebrand factors accumulate and trigger platelet adhesion and aggregation inside the blood vessels with microthrombi formation (72). Familial forms of HUS have been also described, with both autosomal dominant and recessive form of inheritance and pregnancy as an eliciting event. A functionally abnormal factor H protein could be the cause of HUS in the autosomal dominant transmitted familial cases (72,73). Normally functional factor H protects endothelial cells from the damaging effects of the activated complement (72). The primary pathologic disorder in both TTP and HUS will be systemic or intrarenal microvascular aggregation of platelets, causing microangiopathic hemolytic anemia. These changes will be manifested by decrease in hemoglobin and platelets, presence of fragmented red blood cells on the peripheral blood smear (schistocytes), increase in lactic dehydrogenase (LDH), and decrease in haptoglobin. Liver enzymes may be normal or elevated, and coagulation studies are frequently normal (71). The classic clinical pentad of TTP consists of thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fevers, and renal dysfunction. In HUS, renal failure is the predominant feature and sometimes it is difficult to make a clear distinction between the two entities (72). Renal involvement is associated with hematuria and proteinuria (71). Management involves plasma exchanges (plasmapheresis) until platelet counts and LDH levels normalize. Sometimes immunosuppressive therapy is required. Platelet transfusions should be discouraged, due to risk of microvascular thrombosis. Maternal morbidity and mortality are high in pregnancies complicated with TTP/HUS (71).

Obstructive Uropathy

Obstructive uropathy is uncommon in pregnancy. "Physiologic hydronephrosis" of pregnancy is an expected phenomenon, present in 80% to 90% of the normal pregnancies (5,6). Right-sided hydronephrosis occurs more commonly than left-sided one. The diagnosis of pathologic urinary tract obstruction during pregnancy can be difficult and can be recognized in some cases by the normalization of renal function in the lateral recumbent position, which relieves pressure on the ureters by the uterus, and its recurrence when supine (6). In some cases, however, either insertion of a ureteral catheter or delivery of the fetus is required.

Renal Cortical Necrosis

Renal cortical necrosis can be considered a severe form of ATN, often associated with disseminated coagulopathy and usually occurring in a setting of septic shock, septic abortion, or severe abruptio placentae. Bilateral renal cortical necrosis (BRCN) is estimated to occur in about 2% of the adult patients with ARF, but the incidence is the highest in obstetric patients, especially in the last part of pregnancy and postpartum (74). The risk of BRCN seems to be higher with prolonged anuria, usually longer than 2 weeks. Patients require dialysis and some will become dialysis dependent. Kidney biopsy provides the definitive diagnosis and prognostic information. Imaging techniques could be employed to show decreased cortical blood flow. CT angiogram or renal angiography shows decreased cortical nephrogram.

DIALYSIS AND TRANSPLANTATION

Multiple mechanisms that interfere with the hypothalamic-pituitary-ovarian axis cause marked decrease in fertility in young women with advanced CKD and those requiring dialysis (75). Recent publications report fertility rates ranging between 1% and 7%, which is much improved compared with older literature (76–78). These improved trends could be due to improved CKD management translated in increased dialysis population, better dialysis techniques, and improved care of the high-risk pregnancies.

Pregnancy in dialysis patients remains a very challenging clinical situation, where even the diagnosis of pregnancy itself may be a difficult task. Serum markers like β -HCG may be falsely elevated in dialysis patients due to poor renal excretion, and ultrasound evaluation is needed to confirm and date the pregnancy (79). Spontaneous abortion remains common, occurring in 21% of pregnancies reaching second trimester (80). Overall, it has been reported that only 50% of the pregnancies result in surviving infants (77). Premature delivery is very common, occurring in 80% of pregnant dialysis women (77). Other common fetal complications include polyhydramnios and low birth weight (77,81,82). Maternal risks include acid-base abnormalities, HTN, volume overload, and pre-eclampsia. Due to these increased complication rates, most centers do recommend contraception in women of childbearing age on dialysis. When pregnancy does occur, it should be managed by a multidisciplinary team comprising nephrologists, obstetricians, dialysis staff, and neonatologists.

Although in most reported cases pregnant patients have been on hemodialysis, successful pregnancies have also been reported in PD (77,82–84). Whether one dialysis modality is superior to other in pregnant patients is unclear due to lack of randomized controlled studies. Feasibility of intensifying hemodialysis, limitations of PD volumes due to the gravid uterus, and prevalent practices among nephrologists may play a role in the choice of a particular renal replacement therapy over another.

The precise details of the dialysis management in pregnant patients are beyond the scope of this textbook, but some of the principles suggested by experts in this field are enumerated in Table 2.

Prolonged or intensive dialysis during pregnancy results in longer gestational periods, higher fetal birth weights, and

Table 2 Recommendations for Dialysis Management in a Pregnant Patient

Treatment factor	Recommendation
Frequency of treatments	Intensifying HD four to six times/wk after first trimester (goal >20 hr/wk) Increasing no. of PD dwells (8–12 L/day)
Predialysis BUN	<45–50 mg/dL
Dialysate	Bicarbonate—25 mEq/L Potassium 3–4 mEq/L (adjust based on HD frequency and serum values)
Anemia	Hgb target 10–11 g/dL May need increase in Erythropoietin dose Iron saturation >30%, use IV iron to maintain levels Folate 1 mg/day
Blood pressure/hemodynamics	No clear guidelines. Diastolic BPs below 80–90 Avoid maternal volume depletion and hypotension during dialysis Avoid ACEI, ARBs Ultrafiltration goals to be adjusted as pregnancy progresses accommodating placental and fetal growth (approx. 1 lb/wk) Fetal monitoring during HD once fetus viable

Abbreviations: HD, hemodialysis; BUN, blood urea nitrogen; PD, peritoneal dialysis; Hgb, hemoglobin; BP, blood pressure; ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers. *Source:* From Ref. 76,77,81–84.

greater fetal survivability (76,77,80). Home hemodialysis and nocturnal hemodialysis are emerging modes of intensive HD that have shown to offer multiple clinical advantages in terms of HTN, volume status, and mineral metabolism. A retrospective study from Canada prescribing nocturnal HD (>36 hr dialysis) for women in childbearing age group showed not only improved fertility rates (15%) but also more successful live births and fewer maternal–fetal complications (85).

With successful kidney transplantation, fertility seems to be restored to near normal within a few months. The U.S. National Transplant Pregnancy Registry (NTPR) reported a total of 1208 pregnancies in 781 kidney transplant recipients (86). Live births occurred in approx. 75% of the patients based on NTPR and the U.K. registry data (87,88).

Despite improved outcomes following transplantation, a different set of complexities entail kidney transplant recipients who become pregnant. Impact of pregnancy on the kidney allograft, premature delivery, pre-eclampsia, and the long-term effects of immunosuppressive medications on the offspring remains some challenges in this group. Counseling about pregnancy should start in the pre-transplant period, continued following transplantation, and reliable contraception is recommended until patient is ready to embark on a planned pregnancy (89–91). The optimal timing of pregnancy after transplantation is considered to be 1 to 2 years. Analyses of the NTPR data have suggested greater percentage of nonviable outcomes in female transplant recipients who became pregnant less than 6 months after transplantation (86). Several individual factors should be considered when offering advice for the timing of pregnancy including adequacy of allograft function (serum creatinine <1.5 mg/dL), recent episodes of acute rejection, and risk of opportunistic infections (86).

These pregnancies should also be considered high risk and preferably managed by both transplant physicians and specialists in high-risk pregnancies. Major goals during pregnancy are to optimize maternal health, including allograft function, maintain a normal metabolic environment (normoglycemia), minimize complications associated with preterm births, detect and manage hypertensive complications

especially pre-eclampsia, and ensure adequate fetal growth. Pre-eclampsia occurs in approximately one-third of pregnant women with kidney transplant, and diagnosing it can be challenging as many transplant patients can have preexisting proteinuria and an increasing trend in blood pressures after 20 weeks of gestation (92).

Urinary tract infections are the most common complication in pregnancies following kidney transplantation probably due to an immunosuppressed state and the increased likelihood of reflux. Most investigators recommend screening in all pregnant women and treating any positive cultures (93).

Rejection of the kidney allograft is unusual and the risk is considered to be no higher than in the nonpregnant transplant patients if pregnancy is properly planned (90). Anemia can frequently complicate pregnancy post-transplantation even in the absence of kidney function deterioration (90). Compared with normal pregnancies, transplant recipients have lower erythropoietin levels (94).

The anatomic location of the allograft in the iliac fossa does not interfere with vaginal delivery and most transplant patients can deliver vaginally unless there are some obstetric indications (90). One of the challenges in pregnancies post-transplantation is the choice and dosing of immunosuppressive medications. Transplant recipients should be maintained on immunosuppressive medications during pregnancy with some modifications to avoid allograft rejection and consequently fetal loss (90). Cell counts, renal parameters, liver function tests, and drug levels should be frequently monitored to avoid significant toxicity.

Most immunosuppressive medications are considered risky by the Food and Drug Administration; however, the U.S. registry data do not show any consistent pattern of congenital anomalies associated with the use of calcineurin inhibitors (cyclosporine and tacrolimus), azathioprine, or steroids (89). These are still considered as mainstay therapy for pregnant transplant patients by most centers given their relatively safer profile. Cyclosporine can be associated with low birth weight and also may exacerbate HTN during pregnancy (90). Tacrolimus has been associated with an increased incidence of DM and hyperkalemia in the newborns (95). Azathioprine has been shown to be teratogenic

in higher doses in animals; however, these effects were not reproduced in humans (96). Case reports have described fetal adrenal insufficiency and thymic hypoplasia when corticosteroids are used in higher doses but these rarely occurred in doses of 15 mg/day or less (97–99).

Mycophenolate mofetil and sirolimus are contraindicated and should be stopped 6 to 12 weeks prior to conception due to risks of teratogenicity (86,100).

Most transplant immunosuppressive medications are excreted in the breast milk although in small amounts and no adverse effects have been reported (86). Although recommendations are evolving in this area, most transplant centers currently advise against breast-feeding (101).

In the absence of any guidelines for the management of pregnant dialysis patients and increased fetal complications, it may be prudent to advise effective contraception and delaying pregnancy until after transplantation. Improved outcomes have been reported in the transplant literature; however, the use of immunosuppressive medications adds another dimension and makes pregnancies more difficult to deal with in the post-transplant period.

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