Chapter 18
Chronic Kidney Disease and Pregnancy

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Introduction

During normal pregnancy, maternal anatomic and physiologic adaptations alter systemic and renal hemodynamics [1, 2] (Table 18.1). Awareness of these adaptive pregnancy-associated renal physiologic changes is necessary in order to identify and interpret the unique disorders that may result in de novo or worsening of existing renal disease [3]. Moreover, pregnancy in patients with underlying renal disease has important implications for maternal and fetal morbidity and mortality [4]. It is important to understand these adaptive changes for appropriate risk assessment before conception and to provide close monitoring during pregnancy to identify early the maternal and fetal compromise. Similarly, availability of pre-pregnancy baseline renal function, urinalysis, and blood pressure recordings can avoid misclassification of any abnormalities encountered during pregnancy.

Anatomic and Physiologic Adaptations

During pregnancy, kidneys increase in size by about 1–1.5 cm in length secondary to an increase in renal volume by up to 30%. A physiologic hydronephrosis occurs due to the influence of progesterone hormone inhibiting ureteral peristalsis and to the mechanical obstruction of the ureter (right > left) due to dextrorotation of the uterus by the sigmoid colon. These physiologic changes typically peak by the 20th week of gestation and resolve within 48 hours after delivery, but they may persist for up to 12 weeks postpartum [5].

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Table 18.1 Anatomic and physiologic renal adaptations in pregnancy

Anatomic changes	**Clinical implications**
Dilatation of the collecting system and increase in renal size	Increases risk of pyelonephritis in asymptomatic bacteriuria Makes diagnosis of true obstruction difficult
Physiologic changes	**Clinical implications**
Systemic and renal vasodilatation	Decreases blood pressure
Increases blood volume	Physiologic edema and anemia
Increases renal blood flow rate and glomerular filtration rate	Decreases serum creatinine, BUN
	Mildly increases proteinuria
Altered tubular function	Causes glucosuria, hypercalciuria, hypouricosuria

Blood pressure (BP) falls shortly after conception and returns to normal at term. This decrease is due to peripheral vasodilatation and insensitivity to angiotensin II secondary to high prostacyclin and prolactin levels, increased nitric oxide synthesis, and relaxin produced by the placenta and corpus luteum [6]. The hemodynamic changes that result in a rapid fall in preload and afterload lead to a compensatory increase in heart rate and activation of volume-restoring mechanisms, including the renin-angiotensin-aldosterone system (RAAS). The circulating blood volume increases by 50% in part due to cumulative sodium retention (500–900 mEq) in the proximal tubule stimulated by angiotensin II and in the distal portion of nephrons secondary to elevated aldosterone levels. The resultant rise in stroke volume increases cardiac output (CO) by about 40% above the non-pregnant level at mid-gestation. This could lead further to increased extracellular fluid volume, weight gain, and "benign" edema of lower extremities. The increased CO and renal vasodilatation increases renal blood flow by as much as 85% in the second trimester. This results in renal hyperfiltration and increased glomerular filtration rate (GFR) of about 50% and, respectively, blood urea nitrogen (BUN) and creatinine levels fall [7]. Therefore, as GFR equations commonly overestimate or underestimate the true renal function, trends in serum creatinine levels, even small increases, provide better assessment of kidney function deterioration [8]. These changes return to prepartum levels within 3 months of delivery. Interestingly, despite highly RAAS activity, in part secondary to increased angiotensinogen production by estrogen, there is resistance to hypertensive action of angiotensin II due to increased synthesis of prostaglandins by the placenta. Similarly, aldosterone-associated kaliuresis is blunted by progesterone, which competes for mineralocorticoid receptor [9].

A range of other physiologic changes occurs with pregnancy. Hypo-osmolar hyponatremia occur due to a downward resetting of the osmotic threshold for both AVP secretion and thirst. Transient diabetes insipidus occurs due to high placental vasopressinase activity. It usually occurs at term and is short lived, and it responds to synthetic AVP analog desmopressin (DDAVP), which is not metabolized by vasopressinase [10]. Physiologic anemia of pregnancy is secondary to lower red blood cell mass rise of 30% compared to 50% rise in plasma volume. There is an increased calciuria secondary to high 1,25 $(OH)_2$ vitamin D_3 production without increased risk of nephrolithiasis.

Hyperfiltration can result in microalbuminuria due to an increase in fractional excretion of albumin, but significant proteinuria of over 300 mg in a 24-hour period or hematuria always indicates unmasked kidney disease and worsening of pre-existing or de novo development of renal disease. Uric acid levels decrease secondary to increased GFR. Glycosuria secondary to inefficient tubular reabsorption in the setting of increased filtered load of glucose is a common normal finding. The early-morning urine is more alkaline due to mild chronic respiratory alkalosis secondary to progesterone-induced hyperventilation. Respectively, serum bicarbonate levels are generally lower. Asymptomatic bacteriuria warrants treatment due to dilatation of the renal collecting system that can result in pyelonephritis, bacteremia, septic shock, renal failure, or mid-trimester abortions.

Acute Kidney Injury in Normal Pregnancy

Pregnancy-associated acute kidney injury (AKI) is a rare but serious complication and has significant adverse outcomes for both maternal and fetal well-being [11, 12]. Unfortunately, there is no standardized definition of pregnancy-associated AKI. Unfortunately, early and accurate diagnosis and classification of pregnancy-associated AKI are difficult due to the increase in GFR related to renal hyperfiltration and the reduction of the serum creatinine. Although AKI could be reversible, affected women are at increased risk of developing CKD [13]. Acute kidney injury could occur during pregnancy in early pregnancy, late pregnancy, or postpartum period or result from other causes [14] (Table 18.2).

Pregnancy in Women with Underlying Chronic Kidney Disease

Chronic kidney disease represents a heterogeneous group of disorders characterized by changes in the structure or function of the kidney. Low GFR, hypertension, and proteinuria are the typical clinical manifestations, with the severity depending on underlying cause of renal disease. Progression of CKD results in diminished fertility, and women on long-term dialysis get pregnant rarely. Moreover, human chorionic gonadotropin levels are inversely related to GFR and therefore results must be interpreted with caution. Pregnancy in women with underlying CKD is associated with a significant risk factor for adverse outcome [15]. Women with CKD planning pregnancy should ideally have pre-conception baseline renal function testing, including serum creatinine, BUN, creatinine clearance, and proteinuria; complete blood cell count; uric acid; and liver enzymes in view of being potentially at high risk for progression of underlying kidney disease or development of preeclampsia later in pregnancy. The degree of renal insufficiency, even in the early stages, is a critical determinant of pregnancy outcome. There is a stepwise increase in risks

Table 18.2 Acute kidney injury in pregnancy

Early pregnancy	Late pregnancy	Postpartum	Other causes
Pre-renal azotemia due to hyperemesis gravidarum or hemorrhage of spontaneous abortion. In severe cases, this could lead to ATN	Acute fatty liver of pregnancy that typically presents with jaundice and abdominal pain and possible fulminant hepatic failure in severe cases	Days to weeks after normal pregnancy, secondary to thrombotic thrombocytopenic purpura/hemolytic uremic syndrome	Obstructive uropathy secondary to gravid uterus, polyhydramnios, nephrolithiasis, or enlarged uterine fibroids
ATN secondary to septic abortion in the first trimester or pigment induced secondary to myoglobulinuria in the setting of Clostridium induced myonecrosis of the uterus	Preeclampsia, eclampsia, and HELLP syndrome		
Renal cortical necrosis secondary to obstetric catastrophes: abruption placentae, septic abortion, severe preeclampsia, amniotic fluid embolism, and retained fetus			

ATN acute tubular necrosis, *HELLP* hemolysis, elevated liver enzymes, low platelets

both for maternal and fetal outcomes from stage 1 to stage 5 with the highest risk in patients on dialysis [16, 17]. Respectively, women with stage 1 CKD and hypertension and/or proteinuria should be followed closely during pregnancy due to an increased risk of preeclampsia, intrauterine growth retardation, preterm delivery, prematurity, small for gestation age, fetal loss, or neonatal death compared to women with normal renal function. Moreover, pregnancy can accelerate the renal disease progression, such as development of hypertension, increase in proteinuria, and decrease in GFR, either reversible or irreversible, leading to the so-called CKD shift and the need to start dialysis earlier than anticipated. The likelihood of disease progression depends on the severity of underlying kidney disease rather than the type. In addition to the degree of renal dysfunction, the risk of disease progression increases in the setting of coexisting hypertension, chronic diseases like diabetes or lupus, and nephrotic syndrome. Currently, there are no means to predict which women will experience renal deterioration during or immediately after pregnancy. Similarly, pregnancy termination does not reliably reverse the decline in renal function [18–23]. Finally, optimization of pre-existing diseases significantly affects the pregnancy outcome [24, 25].

Women with CKD are likely to have concomitant hypertension, as the relationship is bidirectional. Hypertension during pregnancy with characteristic dilated afferent arteriole of glomerulus may play a detrimental role in underlying disease due to high intraglomerular capillary pressure induced by transmission of systemic BP into glomerulus. Women with CKD and hypertension are at an increased risk for

preeclampsia. The maternal and fetal outcomes depend on maternal renal function/GFR at the beginning of pregnancy, underlying hypertension, and proteinuria. Any persistent renal damage, even in the setting of preserved GFR and in the absence of uncontrolled hypertension or significant proteinuria, increases the risk for adverse pregnancy outcomes. High maternal BUN levels can act as osmotic diuresis within the fetal renal system resulting in polyhydramnios, early labor, and or even fetal loss.

In summary, pregnancy in the setting of underlying CKD does not only increase the risk of pregnancy-associated complications, but also influences the quality of life of the mother and child. In general, women with preserved kidney function before pregnancy are unlikely to have significant renal function loss as long as BP and proteinuria are managed prior to conception. Respectively, strategies to optimize outcomes need to begin preconception and continue through delivery and the postpartum period.

Shared decision-making in a multi-disciplinary setting is of paramount importance. Pre-pregnancy counseling and risk stratification are crucial for optimal maternal and fetal outcomes and should be provided by a multi-disciplinary care provider team, including a nephrologist, high-risk obstetrician, and maternal–fetal medicine specialist for pregnancy-associated complications. Special care includes management of hypertension and any proteinuria or CKD deterioration, prevention of preeclampsia, avoidance of nephrotoxic or teratogenic medications, and renal dosing of all medications. Ideally, one should discuss the pregnancy planning while the patient is still in the lower stages of CKD or postpone pregnancy until after kidney transplantation secondary to relatively lower risk [26–28].

Proteinuria Treatment

Proteinuria should be addressed and minimized preconception, because the degree of proteinuria is associated with adverse pregnancy outcomes. Renal biopsy should preferably be performed before conception or, in case of new-onset nephrotic syndrome, in early gestation if definitive diagnosis will affect treatment options [29]. Use of RAAS blockers to suppress proteinuria is contraindicated, but diuretics can be used cautiously for peripheral edema [30]. Safe immunosuppression regimen during pregnancy and breastfeeding include prednisone, azathioprine, and calcineurin inhibitors. In contrast, mycophenolate mofetil and cyclophosphamide are contraindicated during pregnancy and breast-feeding.

Hypertension Management

Chronic hypertension is a risk factor for maternal and fetal outcomes [31]. Respectively, preconception intensive BP control decreases the risk of adverse pregnancy outcomes. Patients should ideally be switched to antihypertensive

medications compatible with pregnancy, such as nifedipine, labetalol, hydralazine, or methyldopa before conception. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are teratogenic in the second and third trimesters and ideally should be discontinued preconception or no later than the eighth week of gestation with careful fetal imaging and monitoring [32].

There is no definite consensus on the diagnosis and definition of hypertension in pregnancy. Hypertensive disorders of pregnancy are classified as outlined in (Tables 18.3 and 18.4) [33]. In general, hypertension is defined as systolic BP > 140 mm Hg and diastolic BP > 90 mm Hg [34]. Moreover, currently there is no optimal BP target for pregnant patients with or without CKD. Data from the CHIPS (Control of Hypertension in Pregnancy Study) trial, which randomized women to a target diastolic BP of 85 mm Hg (tight control) or 100 mm Hg (less tight control) found no significant difference in risks of adverse pregnancy outcomes between the groups. However, more individuals developed severe hypertension (>160/110 mm Hg) in the less tight group [35]. Further, the International Society for the Study of

Table 18.3 ISSHP classification for hypertensive disorders in pregnancy

1. Chronic hypertension	Hypertension that predates the pregnancy or is recognized at <20 weeks' gestation
2. Transient gestational hypertension	De novo hypertension that develops at any gestation and that resolves without treatment during the pregnancy
3. Gestational hypertension	De novo hypertension that develops at or after 20 weeks' gestation without any features of pre-eclampsia
4. Preeclampsia	Gestational hypertension developed at or after 20 weeks' gestation and the coexistence of one or more of the new onset conditions listed in Table 18.4
5. Preeclampsia superimposed upon chronic hypertension	Chronic hypertension with signs and symptoms of preeclampsia as defined above
6. White coat hypertension	Elevated BP in the office/clinic, but normal BP in the out-of-office setting
7. Masked hypertension	Elevated BP in the out-of-office setting, but normal BP in the office/clinic

BP blood pressure, *ISSHP* International Society for the Study of Hypertension in Pregnancy

Table 18.4 ISSHP definition of preeclampsia

1. Proteinuria: spot urine protein/creatinine > 30 mg/g or >300 mg/day
2. Other maternal organ dysfunction:
   Renal insufficiency (creatinine > 1 mg/dL)
   Liver involvement (elevated transaminases with or without right upper quadrant or epigastric pain)
   Neurological complications (eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches, persistent visual scotomata)
   Hematological complications (thrombocytopenia, DIC, hemolysis)
3. Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, stillbirth)

Hypertension in Pregnancy (ISSHP) recommends maintaining BP in the range 110–140/80–85 mm Hg. Regardless of the hypertensive disorder of pregnancy, BP requires urgent treatment in a monitored setting when ≥160/110 mm Hg.

Because uncontrolled hypertension increases the risk of preeclampsia in pregnant women with CKD, home BP monitoring and adequate BP control are even more critical for these patients. They should be monitored for developing signs of preeclampsia using urinalysis at each visit along with clinical assessment, and blood tests should include hemoglobin, platelet count, liver transaminases, uric acid, and creatinine levels. Other recommended measures to prevent preeclampsia include supplementation with low-dose aspirin (preferably 150 mg/day started before 16th week of gestation) and calcium of 1.2 g/day in the setting of low calcium intake (<600 mg/day) [36, 37]. Delivery should be dependent on gestational age and maternal and fetal status. All women with chronic hypertension, gestational hypertension, or preeclampsia require lifelong follow-up because of their increased cardiovascular risk.

Pre-conception Medication and Contraception Use in Chronic Kidney Disease

Use of commonly prescribed teratogenic medications (e.g., RAAS blockers, statins, and certain immunosuppressors [mycophenolate mofetil, cyclophosphamide, rituximab]) should be preceded by a negative pregnancy test or discontinued ideally preconception in patients with CKD. It is also important to review effective contraceptive options. The choice of contraceptive may have an effect on underlying hypertension and proteinuria as the potential associated side effects of the drug. Both estrogen/progesterone combinations and exogenous progesterone upregulate RAAS, causing an increase in BP and development of albuminuria. Therefore, patient should be closely monitored for worsening hypertension and proteinuria. Progestin-only options do not significantly affect BP, and they do not worsen proteinuria. Due to the anti-mineralocorticoid activity of drosipernone, women with advanced CKD should be monitored for risk of hyperkalemia [38, 39].

Management of Chronic Kidney Disease in Pregnancy

Patients need regular monitoring of their renal function including BUN, creatinine, bicarbonate and electrolyte levels, complete blood cell count, urinalysis with spot urine protein to creatinine ratio, and parathyroid hormone as indicated. In general, nephrotoxic medications, including NSAIDs, and tocolytic agents, such as indomethacin, should be avoided. Teratogenic medications should be discontinued ideally preconception or as soon as a pregnancy test is confirmed positive. All other medications are to be dose-adjusted appropriately for estimated GFR.

Anemia associated with CKD should be treated early with appropriate iron replacement and/or initiation of erythropoietin-stimulating agent (ESA) as indicated. Due to relative erythropoietin deficiency secondary to high demand for red blood cell production as well as erythropoietin resistance from inflammatory cytokine production associated with the pregnant state, higher doses of ESA are usually required. Secondary hyperparathyroidism and the associated hyperphosphatemia can be treated with calcium-based phosphate binders and vitamin-D analogs despite limited safety data. Sodium bicarbonate therapy may be required in case of significant metabolic acidosis (pH < 7.2).

In the setting of advanced CKD or disease progression without evidence of fetal deterioration, dialysis should be initiated earlier to prevent significant metabolic disorder and elevated BUN levels. Inadequate clearance of uremic toxins (elevated BUN) results in fetal osmotic diuresis and polyhydramnios, requiring frequent assessment for intensification of dialysis dose or an increase in ultrafiltration volume with close monitoring of intra hemodialysis BP [40–42]. In general, outcomes are significantly improved with an intensified dialysis regimen. Hemodialysis should be performed almost daily to prevent significant fluid and metabolic shifts. There is a positive relationship between the number of hours on dialysis and fetal outcome. Longer and more frequent hemodialysis sessions increase the live birth rate from 48% in those dialyzed <20 hours/week compared to 85% in those dialyzed >36 hours/week [43, 44]. The spontaneous abortion rate is as high as 50% in women on dialysis, but in pregnancies that continue, overall fetal survival has been reported as high as 80%. Despite significant improvement in outcomes with intensified dialysis, patients are at high risk for complications (e.g., preeclampsia, preterm birth, fetal growth restriction, low birth weight for gestational age) and require a multidisciplinary team care approach. Infant survival is higher when pregnancies are conceived before dialysis is initiated [45].

Nutritional support and proper weight gain assessment are essential for successful pregnancy with recommended weight gain of 0.3–0.5 kg/week in second and third trimesters. Recommended daily intake of protein during pregnancy in the setting of ESRD requiring dialysis is approximately 1.5–1.8 g/kg/day [46]. Blood pressure is to be monitored closely due to increased risk of worsening hypertension or superimposed preeclampsia. Simultaneously, intra-dialytic hypotension is to be avoided to lessen the risk of placental hypoperfusion and fetal distress. Peritoneal dialysis with small volume and frequent exchanges can be used successfully to prevent intermittent hypotension episodes.

Pregnancy and Renal Transplantation

Kidney transplantation restores fertility in women with ESRD. Pregnancies are typically successful, especially in living-related donor transplant recipients and in patients with stable allograft function as evidenced by serum creatinine <1.5 mg/dL without an episode of rejection within the past year, with no or minimal proteinuria,

and with use of a minimal antihypertensive regimen. In general, in patients with stable non-impaired allograft function, pregnancy does not significantly affect long-term graft function. The recommended immunosuppression regimen during pregnancy is prednisone, azathioprine, and calcineurin inhibitors (CNIs). Calcineurin inhibitor levels should be monitored closely due to an increase in volume of distribution. Mycophenolate mofetil and sirolimus are contraindicated and should be stopped 6 weeks before conception is attempted. Despite better outcomes compared to women undergoing dialysis, patients with renal transplantation are still at higher risk for complications compared to the general population [47–49].

In Summary

Management of pregnant women with CKD is difficult and challenging. To improve both maternal and fetal outcomes, a multidisciplinary approach should be taken, including appropriate pre-pregnancy counseling on risk stratification, optimization of maternal health prior to conception, and management of potential pregnancy-associated complications.

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