Renal disease in pregnancy

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Abstract

Pregnancy in women with chronic kidney disease (CKD) is associated with risks of accelerated decline in renal function in the mother and adverse outcomes for the infant, including prematurity and growth restriction. Managing these risks requires collaboration between patient, nephrologist, neonatologist and obstetrician. In this review we will discuss approaches to managing pregnancy in women with CKD.

Keywords chronic kidney disease; dialysis; pregnancy; transplant

Introduction

Chronic kidney disease (CKD) is defined as abnormalities in serum biochemistry, urinary constituents (blood and/or protein) or renal structure that are present for 3 months or more. The National Kidney Foundation K/DOQI classification of CKD divides CKD into five stages dependent on the estimated glomerular filtration rate (eGFR, Table 1).

CKD is rare in pregnant patients, affecting 0.15% of pregnancies and most affected patients have early stages of CKD (stages 1–3a, estimated eGFR >45 ml/minute). Pregnancy may be the first time that blood pressure and urine analysis are performed for some women; hypertension, proteinuria or haematuria detected at booking may uncover previously undiagnosed CKD. The development of hypertension and urinary dipstick abnormalities later in pregnancy may be a manifestation of CKD, but more commonly represents pre-eclampsia. Chronic pyelonephritis is the commonest known aetiology of CKD in pregnant women (Figure 1).

Renal physiology in normal pregnancy

During normal pregnancy, the maternal cardiovascular system undergoes important changes. Blood volume and red cell mass increase by up to 50%, systemic vascular resistance falls and cardiac output increases by up to 30%. These cardiovascular adaptations have profound effects on renal function:

- renal blood flow increases by 50%
- glomerular filtration rate (GFR) increases by 30%
- serum creatinine decreases by 20%

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Blood pressure falls in the first two trimesters and gradually returns to baseline as the pregnancy approaches term. Increased GFR, changes in glomerular haemodynamics and possibly alterations in renal tubular function lead to an increase in urine protein excretion in pregnancy from an upper limit of 150 mg/d to 260 mg/d.

Renal size increases by approximately 1 cm in bipolar length during normal pregnancy. Smooth muscle relaxation and compression of the ureters by the gravid uterus commonly lead to pelvicalyceal dilatation, more prominently on the right than the left.

The magnitude of these changes makes it unsurprising that limitation to adaptation by CKD can lead to adverse pregnancy outcomes.

Pregnancy in women with chronic kidney disease

Advice for women with CKD embarking upon pregnancy should focus on two issues:

- will kidney disease affect the pregnancy?
- will pregnancy affect the kidney disease?

Reports of pregnancy outcomes in women with CKD from the 1950s and 1960s painted a very bleak outlook for mothers and infants, however, the following decades have identified a large population of women who have little, if any, problems. Identification of women at higher risks can facilitate individualization of care and optimize outcomes.

Measuring renal function in pregnancy

Glomerular filtration rate: creatinine is a metabolic by-product of muscle metabolism that is filtered and excreted through the renal tract, and, as such, serum creatinine levels are inversely proportionate to GFR. Serum creatinine is also affected by age, ethnicity, medication, diet, gender and body composition, however, so absolute serum creatinine concentrations correlate poorly with GFR between individuals.

In the general population, serum creatinine has been superseded by eGFR as a marker of renal function. eGFR is calculated from serum creatinine, patient age, gender and ethnicity. Importantly, this calculation is not validated for use during pregnancy and should not be used. Alternatively, renal function during pregnancy can be estimated by creatinine clearance. The utility of calculated creatinine clearance is limited by the requirement for a 24 hour urine collection. This is inconvenient and frequently incomplete.

Since the eGFR equation is invalid during pregnancy and creatinine clearance is inconvenient, most centres continue to rely on changes in serum creatinine concentration to identify potential renal dysfunction during pregnancy, mindful that relative changes in creatinine have greater clinical utility than absolute values. Preconception baseline values of eGFR are useful in predicting maternal and fetal outcomes however (see below).

Proteinuria: this is an independent predictor of progressive renal failure in patients with CKD and a diagnostic marker of pre-eclampsia in pregnancy. Traditionally, protein excretion is quantified by measurement of a 24 hour collection of urine. This is inconvenient for the patient and collections are often

National Kidney Federation K/DOQI classification of chronic kidney disease.

CKD stage	Estimated GFR	Comment
1	>90 ml/minute	Only classified as CKD if associated with renal structural or urinary dipstick abnormalities
2	60–89 ml/minute	
3	30–59 ml/minute	May be subclassified into: 3a: 45–59 ml/minute 3b: 30–44 ml/minute
4	15–29 ml/minute	
5	<15 ml/minute or on dialysis	

GFR; glomerular filtration rate. Estimated GFR calculations are not valid during pregnancy.

Table 1

incomplete. Nevertheless, if performed correctly, this remains the most accurate method available.

In general nephrological practice and obstetric medicine, the protein:creatinine ratio (PCR) or albumin:creatinine ratio (ACR) are accepted as surrogates for 24 hour collections. Assuming steady production and excretion of creatinine, this method corrects for variations in urine concentration and correlates closely with complete 24 hour urine collection data, including in pregnant patients with CKD. PCR or ACR can be used for quantitative monitoring of proteinuria during pregnancy.

Fetal outcomes

Adverse fetal outcomes (preterm delivery, SGA, neonatal intensive care admission, persistent congenital disability or death) occur in 18% of pregnancies in mothers with CKD compared to 9% in those without CKD. Risks can be stratified according to baseline maternal renal function, blood pressure control, proteinuria and, to a lesser extent, aetiology of renal disease.

Aetiology of CKD in patients presenting to renal-obstetric clinics in the UK

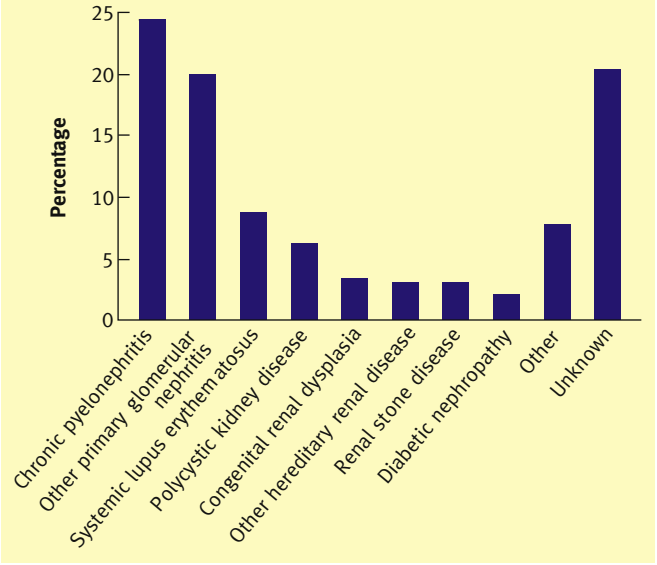

Figure 1

Renal function: the risks of adverse fetal outcomes increase with the severity of baseline renal dysfunction. Even early CKD (preconception estimated GFR >60 ml/minute) is associated with increased risk of prematurity and intrauterine growth restriction as compared to the general population, predominantly due to an increased risk of developing pre-eclampsia. Mothers with more severe renal dysfunction (baseline serum creatinine greater than 180 μmol/litre) are faced with risks of intrauterine growth restriction 65%, preterm delivery 90% and perinatal mortality 10%.

Aetiology of CKD: the aetiology of CKD has minimal impact on fetal outcome with a few exceptions. Asymptomatic bacteriuria and recurrent urinary tract infection, secondary to vesicoureteric reflux or structural abnormalities, are associated with an increased risk of preterm delivery. Diabetes mellitus and SLE may cause CKD, but adverse fetal outcomes are also associated with non-renal components of these conditions, such as hyperglycaemia, thrombophilia and antinuclear antibodies.

Hypertension: uncontrolled hypertension in patients with CKD prior to conception or in early pregnancy is a key independent predictor of adverse fetal outcome. Blood pressure increases in the second half of pregnancy may be exaggerated in women with CKD due to limitations in vascular relaxation and increasing circulating volume as a result of relative over-activity of the renin-angiotensin system. Elevated blood pressure at baseline predicts the occurrence prematurity, intrauterine growth restriction and neonatal mortality.

In optimizing fetal outcomes, blood pressure treatment targets for women with CKD are controversial. Fetal outcomes are similar in those with mild to moderate high blood pressure (<160/100 mmHg) and in patients treated for hypertension. Aggressive treatment of maternal hypertension during pregnancy (less than 120/80 mmHg) may lead to intrauterine growth restriction. In the absence of high quality evidence, consensus guidelines from the Royal College of Obstetricians and Gynaecologists state that in patients with CKD it is recommended to target a blood pressure of <140/90 mmHg, predominantly to reduce maternal complications (see below).

Proteinuria: elevated urine protein excretion is associated with intrauterine growth restriction and preterm delivery. In women without CKD this effect can be almost wholly accounted for by concurrent comorbidity (predominantly hypertension, diabetes mellitus or pre-eclampsia). In women with CKD, however, increased proteinuria (greater than 1 g/d) at baseline is associated with early delivery and small infants in the absence of pre-eclampsia, although it remains unclear whether this reflects early induction of labour or spontaneous premature labour.

Nephrotic syndrome (proteinuria greater than 3 g/d, serum albumin less than 30 g/litres and oedema) occurs rarely in pregnancy and is almost always a result of pre-eclampsia. Nephrotic syndrome in the first trimester represents intrinsic

renal disease and previous case series reported perinatal mortality of greater than 40%. More recent series suggest that outcomes are much more favourable, however, with mortality less than 5% in the UK.

Maternal outcomes

Adverse maternal outcomes for women with CKD include pre-eclampsia, transient decline in renal function, persistent loss of renal function, requirement dialysis and death. As with fetal outcomes, risks can be stratified according to baseline maternal renal function, blood pressure control, proteinuria and aetiology of renal disease.

Pre-eclampsia: the risk of developing pre-eclampsia for mothers with CKD is greatly increased compared to the general population, and increases with worsening renal function; 20% for patients with mild renal dysfunction (serum creatinine <125 μmol/litre) and 60–80% with severe impairment (serum creatinine >180 μmol/litre), compared to approximately 5% in the general population. These estimations vary between studies as a result of heterogeneity between study cohorts and variations in diagnostic criteria used. CKD is commonly associated with proteinuria and hypertension prior to conception and the diagnosis of 'superimposed pre-eclampsia' relies on arbitrary increases in these parameters with or without additional clinical features of pre-eclampsia (Box 1).

Renal function: decline in renal function during pregnancy occurs rarely in patients with mild renal impairment at baseline (serum creatinine <125 μmol/litre) and often reflects an episode of obstruction, pyelonephritis or pre-eclampsia. In such cases, return to baseline renal function almost always occurs within 3 months post-partum.

In contrast, women with moderate CKD (serum creatinine >125 μmol/litre) have a 25% risk of permanently losing 25% of their kidney function as a result of pregnancy, increasing to a 50% risk in those with baseline creatinine >180 μmol/litre. Furthermore, women with a preconception serum creatinine greater than 180 μmol/litre have a one in three chance of requiring dialysis during pregnancy or within 6 months of delivery.

Aetiology of CKD: the underlying aetiology of CKD has little impact on maternal outcome independent of renal function and blood pressure control.

National High Blood Pressure Education Program Report on High Blood Pressure in Pregnancy criteria for the diagnosis of superimposed pre-eclampsia

- Blood pressure >160/110 mmHg
- Blood control suddenly worsening after a period of good control
- Development of proteinuria >2000 mg/d or abrupt worsening of proteinuria
- Serum creatinine increasing to >110 μmol/litre

Box 1

There is an increased risk of asymptomatic bacteriuria progressing to overt infection and pyelonephritis during pregnancy. Patients with recurrent urinary tract infection or vesicoureteric reflux are at particular risk and should be screened for bacteriuria by dipstick analysis and urine culture. Asymptomatic bacteriuria should be actively treated to reduce the risk of potentially serious sepsis and reduce the incidence of preterm delivery.

Lupus nephritis often enters a phase of quiescence during pregnancy as a result of increased endogenous corticosteroid production. Consequently, flares can often occur in the puerperium when increased vigilance is recommended. If lupus flares do occur during pregnancy they can be difficult to distinguish from pre-eclampsia – hypertension, proteinuria and decline in renal function, often with thrombocytopenia. The presence of invisible haematuria, depressed serum complement levels, a rise in anti-double-stranded DNA titre and cutaneous manifestations of SLE support a diagnosis of a lupus flare and should be treated promptly. Renal biopsy may be required if renal function declines quickly, or if nephrotic syndrome develops, in order to determine the most appropriate treatment for the renal disease. Patients with SLE and antiphospholipid antibodies are at greatly increased risk of thromboembolic disease and pre-eclampsia.

Hypertension: chronic hypertension is common in patients with CKD. Control may become more difficult during pregnancy due to cardiovascular adaptations in the second and third trimesters and the unsuitability of some antihypertensives during pregnancy, even in the absence of pre-eclampsia. Most notably, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are commonly prescribed for patients with proteinuric CKD due to their effectiveness and renoprotective properties, however, they are associated with severe congenital abnormalities and should be avoided during pregnancy (see below).

There are contradictory reports of the impact of blood pressure during pregnancy on progression of maternal renal disease; however, contemporary prospective data suggest that baseline diastolic blood pressure greater than 75 mmHg or use of antihypertensive agents is predictive of accelerated decline in renal function post-partum. Severe hypertension (>160/100 mmHg) in the third trimester requires treatment to reduce the risk of intracerebral haemorrhage in labour.

Proteinuria: increased urine protein excretion is predictive of progressive renal dysfunction in general nephrology where proteinuria *per se* is believed to be nephrotoxic. During normal pregnancy, where urinary protein excretion can double, the impact of proteinuria on kidney function is less clear, certainly in the short to medium term.

In patients with eGFR less than 40 ml/minute before conception, proteinuria greater than 1 g/d is associated with an increased rate of renal decline post-partum compared with than those with less proteinuria. No similar effect was seen in patients with preserved renal function.

Mothers who develop nephrotic syndrome during pregnancy are at increased risk of venous thromboembolism. Loss of antithrombotic serum components in the urine leads to increased thrombotic tendency and strong consideration should be given to the use of prophylactic anticoagulation with low molecular weight heparin (see below).

In the absence of nephrotic syndrome or renal dysfunction, proteinuria does not appear to have a prominent independent effect on maternal outcomes during pregnancy, however, there is emerging evidence that baseline proteinuria may predict the risk of loss of renal function or dialysis post-partum.

Management

Preconception counselling: ideally, all patients with CKD should be offered counselling prior to conception in order to evaluate the risks of proceeding with pregnancy and the likely outcomes. Medications known to be harmful to the developing fetus can be discontinued or substituted for safer alternatives (see Tables 3 and 4 below).

Patients with active lupus nephritis or vasculitis, and those with poorly controlled blood pressure should be advised to wait until these are optimized before trying to conceive. Similarly, patients with significant renal dysfunction (serum creatinine > 180 μmol/litre) may not accept the risks associated with proceeding with pregnancy and may be better advised to wait until they have received a renal transplant (see below).

In the majority of cases, patients need not be discouraged from trying to conceive as long as the potential risks are understood and the pregnancy is closely monitored.

Investigations – pre-existing CKD: if preconception results are unavailable, serum creatinine, and either urine PCR/ACR or 24 hour urine collection should be performed early in pregnancy to determine baseline renal function and urine protein excretion.

Patients should have the following recorded at every subsequent visit:

- blood pressure
- urine dipstick
- urine PCR or ACR, and/or urine culture, if dipstick positive

Depending on the level of renal function at baseline the following should be measured every 6–8 weeks during pregnancy:

- serum creatinine and urea
- haemoglobin

More frequent measurement is required if renal function is abnormal or deteriorating. Serum ferritin, folate and vitamin B12 should be measured if anaemia is identified; serum albumin,

Immunological investigation of suspected intrinsic renal disease

Test	Comments
Anti-nuclear antibodies (ANA)	Associated with connective tissue diseases and SLE. Antibodies against double-stranded DNA (anti-dsDNA) and extractable nuclear antigens (ENA) should be performed if positive
Anti-neutrophil cytoplasmic antibodies (ANCA)	Associated with small vessel vasculitis (Churg Strauss disease, granulomatosis with polyangiitis and microscopic polyangiitis)
Complement components C3 and C4	Decreased levels are found in active SLE, post-infectious glomerulonephritis, mesangiocapilliary glomerulonephritis, subacute bacterial endocarditis, cryoglobulinaemia and heavy chain-deposition disease
Other tests	Rheumatoid factor, cryoglobulins and C3 nephritic factor measurement may be indicated

Table 2

Medications use in CKD and pregnancy.

Antihypertensives

Commonly used	Rarely used	Contraindicated
Nifedipine	Beta-blockers	ACE inhibitors
Labetalol	Alpha-blockers	Angiotensin receptor blockers
Methyldopa	Amlodipine	Aliskiren
Hydralazine	Verapamil	Spironolactone
		Moxonidine
		Minoxidil (3rd trimester)
		Thiazide diuretics
		Diltiazem

Immunosuppressants

Likely to be safe	Likely to be harmful	Contraindicated
Prednisolone	Anti-thymocyte globulin	Mycophenolate
Azathioprine	Rituximab	Sirolimus
Ciclosporin		Methotrexate
Tacrolimus		

ACE, angiotensin converting enzyme.

Table 3

Medications used in CKD and breastfeeding.

Antihypertensives

Likely to be safe	Likely to be harmful	Contraindicated
Hydralazine	Most dihydropyridine calcium channel blockers	Aliskiren
Nifedipine	Celiprolol, nebivolol	Most ACE inhibitors
Methyldopa	Alpha-blockers	Angiotensin receptor blockers
Most beta-blockers	Moxonidine	
Enalapril	Spironolactone	
Furosemide		
Thiazide diuretics		
Minoxidil		

Immunosuppressants

Prednisolone	Mycophenolate	Sirolimus
Azathioprine	Ciclosporin	Rituximab
	Tacrolimus	Methotrexate
	Anti-thymocyte globulin	

ACE, angiotensin converting enzyme.

Table 4

calcium and vitamin D are indicated in women with heavy proteinuria (PCR >100 mg/mmol) or advanced renal dysfunction (creatinine >180 μmol/litre).

Women with a history of recurrent UTI or structural abnormalities should submit a urine sample for culture every month irrespective of symptoms to identify asymptomatic bacteriuria.

A renal ultrasound is required during pregnancy if:

- there is a sudden decline in renal function
- there are signs or symptoms suggestive of obstruction or renal stone disease

As above, mild pelvicalyceal dilatation is commonly identified during normal pregnancy. Functional ureteric obstruction should only be suspected if there is progressive dilatation on serial renal ultrasound scans, suggestive signs and symptoms or obstruction, or worsening renal function.

Investigations — suspected new diagnosis of CKD: renal disease might be discovered during pregnancy and should be suspected in women with hypertension, proteinuria or haematuria identified at booking or in early pregnancy.

A renal ultrasound is helpful to characterize the aetiology and chronicity of CKD. Large kidneys on ultrasound may reflect polycystic kidney disease, diabetic nephropathy or chronic obstruction. Focal scarring of kidneys may reflect a congenital abnormality of the kidney and urinary tract (CAKUT) in the mother, most commonly vesicoureteric reflux. Small kidneys may be the result of any chronic process and further diagnosis may be difficult.

Immunological investigations should be requested if there is suspicion of intrinsic renal disease — haematuria, proteinuria, decreased renal function and/or hypertension (Table 2). Aetiology of intrinsic renal disease may be confirmed by renal biopsy and can be performed during pregnancy, but should be reserved for:

- unexplained decline in kidney function in CKD or acute kidney injury
- newly diagnosed nephrotic syndrome
- features suggestive of systemic disease or vasculitis

A renal biopsy is not indicated to investigate stable CKD, non-nephrotic range proteinuria or pre-eclampsia, and not after 32 weeks' gestation when the pregnancy should be brought to an end prior to renal investigation.

Blood pressure control (Tables 3 and 4): methyldopa, labetalol, nifedipine and hydralazine are the most frequently used agents to treat hypertension in pregnancy. All appear to be safe and well-tolerated in pregnancy. Methyldopa should be avoided in patients with depression.

ACE inhibitors and ARBs should be avoided throughout pregnancy as they are associated with congenital malformations and fetal urinary tract agenesis. Women for whom there is a strong indication for these agents (heavy proteinuria, diabetic nephropathy or heart disease) may be advised to continue therapy until conception is confirmed but a discussion regarding the potential risks should be had as part of preconception counselling. Labetalol appears safe but other beta-blockers have been associated with intrauterine growth restriction (IUGR). Diuretics can exacerbate intravascular volume depletion in hypertensive disorders of pregnancy and lead to IUGR.

For patients with CKD it is well-recognized that control of hypertension is essential to abrogate decline in renal function. Consensus guidelines derived from the RCOG Study Group on renal disease and pregnancy recommend that a target blood pressure of 140/90 mmHg is maintained during pregnancy. Data to support blood pressure treatment targets for patients with CKD during pregnancy are lacking however.

Pre-eclampsia prophylaxis: CKD is identified as a 'high risk' group for developing pre-eclampsia by the National Institute for Health and Clinical Excellence (NICE). Published data supports the increased incidence of the condition from severe to mild CKD. In high-risk patients, aspirin (75 mg/d) reduces the incidence of pre-eclampsia by approximately 25%. Although not licenced for this indication, it is recommended that aspirin prophylaxis is offered to all women with CKD during pregnancy.

Venous thromboembolism prophylaxis: pregnancy is a prothrombotic state and this is exacerbated by heavy proteinuria. Consensus opinion recommends that patients with nephrotic syndrome should receive prophylactic LMWH during pregnancy and until 6 weeks post-partum. There is less evidence to support prophylaxis for women with heavy proteinuria but no nephrotic syndrome, or more modest proteinuria. Nevertheless, many practitioners encourage the use of LMWH throughout pregnancy for women with a PCR >100 mg/mmol, particularly if women are obese or have other risk factors for venous thromboembolism. Advice on thromboprophylaxis in pregnancy is published by the Royal College of Obstetricians and Gynaecologists. LMWH should be continued for at least 6 weeks following delivery.

Urinary tract infection prophylaxis (Tables 3 and 4): confirmed asymptomatic bacteriuria and symptomatic UTI during pregnancy should be treated with antibiotics to reduce the risk of ascending infection and preterm delivery. If more than one episode of bacteriuria is confirmed during pregnancy, prophylactic antibiotics should be prescribed.

The choice of antibiotic is determined by stage of pregnancy, sensitivities of the cultured organisms and local practice. Cephalosporins and penicillins are safe and well-tolerated throughout pregnancy. Gentamicin may be used for severe pyelonephritis with appropriate monitoring. Trimethoprim is a folate antagonist and should be avoided in the first trimester. Nitrofurantoin is associated with neonatal haemolysis if used in the third trimester and should be avoided. Quinolones should not be used throughout pregnancy.

Other medication (Tables 3 and 4): anti-rejection medications used in renal transplantation are discussed below. Erythropoietin, vitamin D analogues and intravenous iron appear safe in pregnancy.

Dialysis and pregnancy

End stage renal failure reduces maternal fertility and conception is rare in patients receiving dialysis. It is estimated that an average sized renal unit in the United Kingdom will see one case of dialysis and pregnancy per 4 years.

Approximately 25% of pregnancies in patients on dialysis end with spontaneous abortion or termination in the first trimester. Of those that progress to later pregnancy, adverse events are common:

- intrauterine growth restriction in 90%
- preterm delivery in 90%
- pre-eclampsia in 75%
- perinatal death in 50%

Haemodialysis and pregnancy (Table 5)

The efficiency of haemodialysis (HD) in removing toxic metabolites is affected by the duration of dialysis session, the frequency of dialysis, the surface area of semipermeable membrane and the blood flow rate. As it is an intermittent process, fluid and circulating uraemic toxins accumulate between treatments.

'Standard' haemodialysis schedules are 4-hour sessions three times per week. Observational data suggests that dialysis duration and frequency should be increased during pregnancy to reduce the accumulation of uraemic toxins and interdialytic fluid accumulation between sessions. Dialysis times should be increased to at least 20 hours a week during pregnancy to achieve:

- pre-dialysis urea less than 20 μmol/litre (ideally less than 15 μmol/litre)
- intradialytic fluid loss of less than 1000 ml per session

Much improved maternal and fetal outcomes have been described in women undergoing nocturnal daily haemodialysis five to seven times a week. This is feasible for patients on haemodialysis at home but might not be practical for patients dialyzing in units.

Peritoneal dialysis and pregnancy

Successful pregnancies can proceed in patients using peritoneal dialysis (PD) although there is limited clinical experience worldwide. The continuous nature of the process limits uraemia and avoids rapid fluid shifts. As pregnancy progresses the gravid uterus can reduce peritoneal blood flow and prevent instillation of sufficient fluid to make PD effective. In the absence of residual renal function, patients on PD may be unable to control fluid status adequately during pregnancy, necessitating transfer to haemodialysis (HD). Nevertheless, an elective change from PD to HD is not mandatory for patients who are already established on PD at the time of conception.

Pre-eclampsia and dialysis

Pre-eclampsia is common, can occur early and may be severe. The diagnosis of pre-eclampsia is made in the context of worsening hypertension with additional clinical features such as coagulopathy, liver dysfunction, intrauterine growth restriction or neurological symptoms. Dialysis patients usually display urinary dipstick abnormalities or may be anuric, so testing for proteinuria is unhelpful.

Management on dialysis

Intensive dialysis and fluid removal can accentuate the haemodynamic changes in pregnancy causing blood pressure instability and hypotension. However, many dialysis patients have treated chronic hypertension prior to conception, and medication may need to be reduced to maintain a diastolic blood pressure greater than 80 mmHg. Lower blood pressure may contribute to IUGR. Later in pregnancy blood pressure may rise due to pre-eclampsia necessitating further changes in medication. Blood pressure in patients receiving dialysis is predominantly driven by fluid status. A patient's "dry weight" is an estimation of their weight when euvolaemic. During pregnancy, dry weight will increase by approximately 1.5 kg in the first trimester and then 0.5 kg per week until delivery. These changes should be supervised by careful clinical evaluation of the patient's fluid status.

Anaemia is likely to be accentuated during pregnancy as a result of haemodilution and increased anabolic demand. Erythropoietin replacement during pregnancy appears safe. Required doses may increase by up to 3-fold and intravenous iron is usually required to maintain stores. A target haemoglobin of 10—11 g/dl has been suggested.

Kidney transplantation and pregnancy

The first successful pregnancy in a recipient of a kidney transplant occurred in March 1958. Over 15 000 children have been born to mothers with renal transplants since then.

Maternal and fetal outcomes for pregnancies following renal transplantation are far superior to those for mothers on dialysis. The risks are predominantly related to the level of renal function at conception and blood pressure control. Transplant rejection and function are not affected by pregnancy assuming the following are met:

- at least 12 months post-transplant
- stable renal function
- proteinuria <1 g/d
- minimal or well-controlled hypertension
- no recent or on-going transplant rejection
- minimal levels of appropriate immunosuppression (see below)

For mothers with baseline creatinine less than 125 μmol/litre, successful pregnancy occurs in 97% of cases reaching the second trimester. The incidence of preterm delivery, intrauterine growth restriction and pre-eclampsia is greater than the general population and 30% of pregnancies may be affected.

With more severe baseline renal dysfunction, the incidence of adverse fetal outcome increases. The likelihood of accelerated maternal renal decline is also higher. In one study, all transplant patients with creatinine greater than 200 μmol/litre at conception progressed to dialysis within 2 years.

There is no evidence of delayed development in children born to mothers with a renal transplant, independent of complications associated with preterm delivery.

Indications for initiation of renal replacement therapy during pregnancy

Absolute indications	Relative indications
Refractory hyperkalaemia	Moderate uraemia (urea >25 μmol/litre)
Refractory fluid overload	Resistant hypertension
Refractory metabolic acidosis	
Severe uraemia causing encephalopathy or pericarditis	

Table 5

Normal vaginal delivery is not contraindicated following renal transplantation. If Caesarean section is indicated then a lower segment approach may be difficult due to the course of the transplanted ureter.

In transplantation, a combination of prednisolone, azathioprine and tacrolimus or cyclosporine can be used during pregnancy (see Table 3). Although there is many decades' experience of use of these agents during pregnancy, women should be informed of the recognized patterns of reported side effects:

- at high doses (>20 mg/d) prednisolone can lead to fetal adrenal insufficiency and risk of maternal infection. Maintenance doses of less than 10 mg/d appear safe and well-tolerated in pregnancy
- cyclosporine and tacrolimus may exacerbate hypertension and limit renal adaptation to pregnancy. Fetal growth restriction may be associated with these agents
- azathioprine is teratogenic in high doses in animal studies. In humans it has been used without obvious teratogenicity. It may be associated with fetal growth restriction

Trough serum levels of the calcineurin inhibitors tacrolimus or cyclosporine should be measured at every visit. Altered pharmacodynamics during pregnancy necessitates careful titration of doses of these drugs to maintain adequate levels whilst avoiding toxicity. A dose increase of up to 4-fold may be required and close monitoring in the puerperium is as important as during pregnancy, if not more so.

Mycophenolate mofetil (and mycophenolic acid) is commonly prescribed following renal transplantation but should be avoided during pregnancy due to a high incidence of specific congenital abnormalities being reported. Patients should also be switched from sirolimus prior to conception. ◆

FURTHER READING

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Practice points

- Maternal and fetal risks are proportional to renal function and blood pressure control prior to conception
- Women with CKD should be offered aspirin prophylaxis during pregnancy to reduce the risk of pre-eclampsia
- Women with heavy proteinuria are at increased risk of thromboembolism and should be considered for prophylaxis during pregnancy
- Asymptomatic bacteriuria and urinary tract infection should be promptly treated during pregnancy
- Optimizing timing of delivery requires multidisciplinary input from nephrologists, neonatologists, obstetricians and patients