Review Management of women with chronic renal disease in pregnancy

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Key content:

- A multidisciplinary team should manage pregnancy in women with chronic renal disease.
- The outcome is dependent upon prepregnancy renal function and the presence of hypertension and proteinuria.
- Women on dialysis and renal transplant recipients form a special group that needs expert care during pregnancy.

Learning objectives:

- To understand the basic principles in prepregnancy counselling of women with chronic renal disease.
- To be aware of the risks to the pregnancy as well as to long-term renal function.

Ethical issues:

- The risks of serious complications and adverse effects on long-term health raise complex ethical issues for the health professionals who counsel women with chronic renal disease and look after them during pregnancy.

Keywords haemodialysis / immunosuppressants / peritoneal dialysis / pregnancy outcome / proteinuria / renal transplant

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Introduction

Chronic renal disease, although uncommon, can have a major impact on the outcome of pregnancy. This article reviews the available evidence for the management of pregnancy in women with underlying renal dysfunction. The care of women who are on dialysis or who have had renal transplants is also outlined.

Incidence

The exact incidence of chronic renal disease in pregnancy cannot be ascertained from the available literature. The quoted rates vary from 2 per 10 000 women[1] to 12 per 10 000 women.[2] This low incidence may be related to the fact that many women with significant renal insufficiency are beyond childbearing age or infertile.[3]

Pathophysiology during pregnancy

Anatomical changes during pregnancy include an increase in renal size and marked dilatation of the pelvicalyceal system. Renal plasma flow increases early in pregnancy and reaches a maximum by the second trimester. It then falls to about 50% above nonpregnancy levels in the third trimester. The glomerular filtration rate (GFR) increases significantly and, therefore, serum levels of creatinine and urea fall. Proteinuria is common but should normally not exceed 300 mg/24 hours.

Outcome of pregnancy

The outcome of pregnancy in women with chronic renal disease depends on the following factors:

- the degree of renal impairment
- the presence of chronic hypertension
- the presence of proteinuria
- underlying renal pathology.

Although GFR increases in pregnancy, the magnitude of the rise can be attenuated and, indeed, the GFR could fall during or after pregnancy, especially in women with pre-existing renal disease. Imbasciati *et al.*[4] conducted a prospective, longitudinal multicentre cohort study of maternal and fetal outcomes in women with chronic kidney disease stages 3–5. They found that the association of low GFR and proteinuria >1 g/dl had a greater effect on pregnancy-related GFR decrease. Furthermore, the effect of this association was greater than other commonly considered factors such as arterial hypertension or underlying kidney disease.

Table 1 lists the likely pregnancy related complications, as well as long-term renal prognosis, depending on degree of renal dysfunction. **Box 1** shows the pregnancy related complications associated with various common renal pathologies. **Table 2** describes the National Kidney Foundation Classification for chronic kidney disease. This is based on estimated glomerular filtration rate (eGFR). It is calculated using serum creatinine values (Modification of Diet in Renal Disease [MDRD] formula) and is affected by the age, sex and race of the woman. Although this value is useful in nonpregnant women, the use of eGFR is not validated in pregnancy.[11]

The significance of proteinuria alone

Proteinuria can be an indicator of renal impairment in pregnancy. Stettler and Cunningham[12] reviewed 65 pregnancies in 53 asymptomatic women with significant proteinuria (>500 mg/24 hours) and no pre-existing renal disease or diabetes. They reported that renal insufficiency coexisted in 62% of the women and 40% of them had chronic hypertension. There was a preterm delivery rate of 50% and a fetal growth restriction rate of 25%. Importantly, 20% of these women progressed to end-stage renal disease within 5 years.

It is recommended, therefore, that women with positive proteinuria ≥1+ dipstick (in the absence of infection) should have this quantified. Baseline quantification should be undertaken by 24-hour collection of urine for protein estimation, or by protein:creatinine ratio on a random sample of urine (ideally, an early morning specimen) and followed up with protein:creatinine ratio measurements. Persistent proteinuria (>500 mg/24 hours) before 20 weeks of gestation should prompt consultation with a nephrologist.

Management issues

Prepregnancy counselling

This is the most vital (yet underused) tool available for optimum management. Women should be

Table 1
Pregnancy complications in women with renal disease[1,5–7]

	Degree of renal impairment		
	Mild: serum creatinine <125 micromol/l (%)	Moderate: serum creatinine 125–220 micromol/l (%)	Severe: serum creatinine >220 micromol/l (%)
Chronic hypertension	20	62	82
Pre-eclampsia	20	58	64
Anaemia	10	73	≤100
Fetal growth restriction	4	35	43
Preterm delivery	5	30	86
Live birth rate	98	88	64
Loss of renal function	5	50	75
Postpartum deterioration	0	50	60
End-stage renal disease	0	23	40

Note: renal disease associated with hypertension increases fetal loss by a factor of 10 at comparable serum creatinine levels.[13]

Renal disease	Effects
Chronic glomerulonephritis and focal glomerular sclerosis	Usually no adverse effects in the absence of hypertension One view is that glomerulonephritis is adversely affected by the coagulation changes of pregnancy Urinary tract infection is more common
IgA nephropathy	Risk of uncontrolled/sudden escalating hypertension and worsening renal function
Pyelonephritis	Bacteriuria in pregnancy can lead to exacerbation Multi-organ failure, including acute respiratory distress syndrome, may ensue
Reflux nephropathy	Thought to be at risk of sudden, escalating hypertension; however, the consensus now is that results are satisfactory when preconception function is only mildly affected and hypertension is absent Vigilant screening for urinary tract infection is necessary
Urolithiasis	Infection may be more frequent Stents can be successfully placed and ureterostomy performed during pregnancy There is limited data on lithotripsy in pregnancy
Polycystic kidney disease	Functional impairment and hypertension are minimal during childbearing years
Diabetic nephropathy	Usually there is no adverse effect on the renal lesion but there is increased risk of infection and pre-eclampsia
Systemic lupus erythematosus	The prognosis is most favourable if disease is in remission for >6 months preconception Higher doses of steroids may be needed postpartum
Periarteritis nodosa	Fetal prognosis is poor and maternal death often occurs Therapeutic termination should be considered
Scleroderma	If the onset occurs during pregnancy there can be rapid overall deterioration Reactivation of quiescent disease can occur postpartum
Previous urinary tract surgery	May be associated with other malformations of the urogenital tract Urinary tract infection is common Renal function may undergo reversible decrease Caesarean section may be necessary to maintain continence mechanism if an artificial sphincter is *in situ* There are no other significant obstructive problems
After nephrectomy, solitary/pelvic kidney	May be associated with other malformations Pregnancy well tolerated Dystocia rarely occurs with pelvic kidney
Wegener's granulomatosis	Proteinuria and hypertension are common from early pregnancy Immunosuppressive drugs are safe Cytotoxic drugs should be avoided
Renal artery stenosis	May present as chronic hypertension or as recurrent isolated pre-eclampsia If diagnosed, transluminal angioplasty can performed in pregnancy

Box 1
Effects of chronic renal disease on pregnancy[8–10]

counselled by a multidisciplinary team as fertility, as well as pregnancy outcome, depends on the degree of renal insufficiency. A discussion about the risks of pre-eclampsia, fetal growth restriction and preterm delivery is essential. They should also be counselled about the long-term risks to their own health and the risk of deterioration in renal function following pregnancy. Single embryo transfer should be recommended to women undergoing *in vitro* fertilisation. This is the ideal opportunity to establish baseline renal function and achieve optimal control of hypertension. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are contraindicated in pregnancy.[13] They do, however, provide significant renal protection and hence the current recommendation is to change over to safer drugs after the woman becomes pregnant.

Medical management

Management guidelines for pregnant women with renal disease are based solely on retrospective and observational series and clinical opinion. The following recommendations are based on our experiences of caring for women at the South West Thames Renal Unit. We have also incorporated the recommendations of the 54th RCOG study group on renal disease in pregnancy.[14]

These women should be cared for by a multidisciplinary team that includes midwives, specialists in maternal medicine and nephrologists, ideally in a tertiary centre. They should be seen as early as possible in pregnancy. A baseline renal profile, including serum urea, creatinine, electrolytes, albumin and full blood count; urinalysis; and urine culture, should be performed. In addition, an assessment of proteinuria is necessary. This can be performed either by using a 24-hour collection of urine or by a spot test for total urine protein:creatinine ratio. We recommend the spot protein:creatine ratio, as it is less cumbersome to perform than the 24-hour urine protein. It can also be done straightaway in the outpatient setting, rather than requiring the woman to return on another day with the 24-hour urine collection. These tests should be repeated every 4 weeks or more frequently, depending on the clinical situation.

Stage	Description	eGFR (ml/minute/1.73 m^2)
1	Kidney damage and normal/raised GFR	>90
2	Kidney damage and mildly reduced GFR	60–90
3	Moderately reduced GFR	30–59
4	Severely reduced GFR	15–29
5	Kidney failure	<15 (or dialysis)

Table 2
National Kidney Foundation classification of chronic kidney disease

Maternal anaemia in women with renal impairment occurs due to decreased erythropoietin production and shortened red cell survival. This anaemia can usually be managed by oral/intravenous iron therapy. Ramin *et al.*[15] recommend using recombinant erythropoietin when the haematocrit falls below 19%. Erythropoietin can cause hypertension, or aggravate pre-existing hypertension. As such, blood transfusions may be required in rare cases to maintain the haematocrit where erythropoiesis stimulating agents are not felt to be safe to use.

There are no scientific data on which to base specific clinical recommendations for renal biopsy during pregnancy. The procedure, although usually straightforward, can be associated with complications such as severe bleeding, which can require blood transfusion and further invasive procedures for their management. Hence, most specialists prefer to deliver early and investigate postnatally. It is our practice to perform renal biopsy in pregnancy only in cases of florid nephrotic syndrome early in pregnancy or suspected rapidly progressive glomerulonephritis.

All renal units, in conjunction with obstetric units, should have a protocol for commencing dialysis in pregnant women. The indications for acute dialysis during pregnancy are similar to those in non pregnant women. They include:

- severe refractory metabolic acidosis
- electrolyte imbalance, especially severe refractory hyperkalemia
- volume overload leading to congestive heart failure
- pulmonary oedema that is unresponsive to diuretics.

Dialysis may be initiated earlier in pregnancy if there is an acute deterioration in renal function because of the increased risk of fetal demise.[16]

Obstetric management

Pregnant women with chronic renal disease should have an early dating scan to estimate gestational age accurately. They may need more frequent hospital visits, depending on the clinical situation. Nuchal and anomaly scans are performed as in all other pregnant women. Serum screening is not a reliable screening tool in these women. The anomaly scan must include a detailed scan of the urinary tract to look for evidence of inherited conditions such as obstructive uropathy. Regular scans are recommended every 4 weeks from 28 weeks of gestation onwards to check growth as well as liquor volume. Consideration should be given to prophylactic low dose aspirin for the prevention of pre-eclampsia. Blood pressure monitoring and adequate control are important determinants of outcome. There is controversy over 'tight' versus 'non-tight' blood pressure control, based on the fact that every 10 mm fall in mean arterial pressure is associated with a 145 g reduction in mean birthweight. The current consensus is that blood pressure should be maintained at no higher than 140/90 mmHg. Drugs such as methyldopa, calcium channel blockers, hydralazine and labetalol are safe to use in these women.

Preterm labour is common. The prompt treatment of bacterial vaginal and urinary tract infections, including asymptomatic bacteriuria, can be helpful in prevention of preterm labour. Women with recurrent urinary tract infections should be given antibiotic prophylaxis throughout pregnancy. There is no evidence to suggest safety of the oxytocin receptor antagonist atosiban in women with renal insufficiency.

In the absence of maternal or fetal deterioration, delivery should be planned at or near term. Early delivery is usually necessary for obstetric indications such as pre-eclampsia and fetal growth restriction or for rapidly deteriorating maternal renal function. Obstetric considerations should be the main determinant for caesarean section. Women with nephrotic syndrome should receive prophylactic heparin in pregnancy as well as for 6 weeks postpartum.

Following delivery, women should be seen at a postnatal combined clinic. They should continue their established care with their nephrology team. Appropriate contraceptive advice must be given at this time.

Pregnancy in women on chronic dialysis

Incidence

In 1971, Confortini *et al.*[17] reported the first successful pregnancy in a woman who conceived while on chronic dialysis. There is evidence that the frequency of pregnancy in women on chronic dialysis appears to be increasing, ranging from 1–7% in recent reports.[18–20] Conception is more likely in women with residual renal function and those just beginning dialysis.[21] The incidence of pregnancy is lower in women on peritoneal dialysis than on haemodialysis.[22]

Pregnancy outcome

Spontaneous miscarriage is common and occurs in 21% of pregnancies reaching the second trimester.[23] Preterm delivery is common. The mean gestational age at delivery is 32 weeks.[19] Premature deaths contribute to the low infant survival rate of 30–50%.[19] Perinatal outcome is better for women who conceive prior to starting dialysis than those who conceive after starting dialysis (73.6% versus

40.2%).[18] There is no significant difference in overall infant survival between women who receive peritoneal dialysis and those who receive haemodialysis.[20] Polyhydramnios is found in 42–79% of pregnancies.[22]

Maternal complications include hypertension (40–80%), hypertensive crisis, pre-eclampsia, anaemia and placental abruption. Approximately half of these women will be delivered by caesarean section.[24]

Recommendations for management

Nutrition

Protein intake can be increased to 1.5 g/kg/day in women on haemodialysis and 1.8 g/kg/day in women on peritoneal dialysis. Weight gain of 0.5 kg/week can be expected. Fluid intake should be determined individually, taking into account native urine output and the type/frequency of renal replacement therapy the woman is receiving.

The calcium requirement in these women is around 1.5 g/day. This can be achieved by using a high calcium dialysate. They also need measurement of 25-hydroxy vitamin D levels in each trimester and supplementation if these are found to be low. Most people on dialysis tend to have high phosphate levels but if the levels are low, oral phosphate supplements can be used. All women will need folate supplementation in the dosage of 5 mg/day. In addition, vitamin C, thiamine, riboflavin, niacin and vitamin B6 need to be supplemented.

Management of haemodialysis

The frequency of dialysis should ideally be increased to at least 20 hours per week. Retrospective studies suggest that 24 hours of haemodialysis per week is associated with better fetal survival.[25,26] Successful pregnancies using a haemodialfiltration protocol[27] and nocturnal haemodialysis[28] have been reported. The aim is to maintain a predialysis blood urea of $<$15–20 mmol/l. Maternal volume depletion and hypotension should be avoided during dialysis and as such, a biocompatible, smaller surface area dialyser to reduce the ultrafiltration rate per treatment is recommended.

The maternal diastolic blood pressure should be maintained at between 80–90 mmHg. The amount of bicarbonate and potassium in the dialysate should be adjusted based on serum chemistries to avoid the electrolyte imbalance that can occur as a result of more frequent dialysis.

Management of peritoneal dialysis

Peritoneal dialysis can be continued safely during pregnancy.[29] It is necessary to increase the number of exchanges during pregnancy and the fill volumes of peritoneal dialysis fluid may need to be reduced to 1–1.5 l. It is more practical to do this by switching to automated peritoneal dialysis. As pregnancy progresses, due to the size of the enlarging uterus it may become impossible to continue with peritoneal dialysis and there should be a switch to haemodialysis.

Although the possibility of peritonitis exists, increased incidence has not been reported during pregnancy. If caesarean section is necessary, it must be performed extraperitoneally. Alternatively, temporary haemodialysis can be instituted postpartum following traditional caesarean section.[22,30]

Management of anaemia

The erythropoietin dose may need to be increased by 50–100% to maintain the haemoglobin between 10–11 g/dl. In addition, intravenous iron supplementation may be required to maintain iron saturation of at least 30%.

Pregnancy in renal transplant recipients

Incidence

Pregnancy is estimated to occur in 12% of transplanted women of childbearing age and the number of kidney transplant recipients who conceive seems to be increasing.[31]

Pregnancy outcome

The miscarriage rate is similar to the general population.[32] Ninety-five percent of gestations end successfully.[33] The incidence of congenital anomalies is similar to the general population.[34] The ectopic pregnancy rate is higher and this is related to adhesions from previous surgery and peritoneal dialysis.

Hypertension pre-dates pregnancy in about 70% of kidney transplant recipients. Superimposed pre-eclampsia and urinary tract infection occur in up to 40% of these women.[35] Acute bacterial pyelonephritis is relatively common.[34] There is also a higher risk of developing gestational diabetes.

The incidence of preterm delivery, preterm premature rupture of membranes and fetal growth restriction is as high as 60%. Opportunistic infections are more common in immunosuppressed, pregnant kidney transplant patients. Of these, rubella, cytomegalovirus, toxoplasmosis, herpes simplex and hepatitis B and C can affect the fetus.

Recommendations for management

Timing of pregnancy

The following guidelines have been recommended for women who have had renal transplants who are contemplating pregnancy:[36,37]

- there should have been no rejection in the previous year

- graft function should be adequate and stable
- there should be no or minimal proteinuria (<500 mg/24 hours)
- the woman should be on maintenance immunosuppression and stable dosage (for example, prednisolone ≤15 mg/day, azathioprine ≤2 mg/kg/day, ciclosporin ≤5 mg/kg/day)
- there should be no acute infections that can affect the fetus (for example, cytomegalovirus)
- co-morbid conditions (for example, hypertension, diabetes) should be optimally assessed and managed.

Prepregnancy counselling

This must include a discussion on the impact of pregnancy on acute rejection and graft loss. The risk of acute rejection correlates with the prepregnancy serum creatinine levels as well as the interval between transplant and pregnancy. Long-term survival of the graft appears similar in those undertaking pregnancy to those who do not become pregnant. Acute rejection in pregnancy occurs in 9–14% of women but the incidence of serious episodes of rejection is 5%, which is similar to the rates observed in nonpregnant transplant patients. Little is known about the impact of pregnancy on chronic rejection.

Management of immunosuppressive regimens

Immunosuppressive agents should be continued at prepregnancy dosages. Prednisolone, azathioprine, ciclosporin and tacrolimus are all safe to use in pregnancy.[38,39] Mycophenolate mofetil ('MMF') has traditionally been considered unsafe in pregnancy. Its use has been associated with an increased risk of malformations and first-trimester pregnancy loss. The most frequent malformations include external ear and other facial malformations such as cleft palate and lip.[40] Current opinion is to avoid using MMF in pregnancy. There is little evidence regarding the safety of rituximab, sirolimus or everolimus and they should be avoided. Breastfeeding while on immunosuppressive drugs is controversial because of concerns for the effects on the baby. However, these recommendations are not absolute. New evidence is emerging regarding low levels of drug excretion into breast milk (for example, on azathioprine).[41]

Antenatal management

Women should be tested for cytomegalovirus, HIV, herpes simplex virus and hepatitis B and C. Those found to be cytomegalovirus negative should have their titres rechecked in each trimester. Oral glucose tolerance tests or, in cases where there is strong suspicion, blood sugar monitoring, should be arranged to diagnose gestational diabetes.

Management of hypertension

Alpha methyldopa, labetalol and nifedipine are safe to use in these women. Magnesium sulphate prophylaxis can also be used safely in severe pre-eclampsia. The loading dose of magnesium remains the same. The infusion of magnesium must be decreased according to the level of elevated creatinine over the normal pregnancy level. Uric acid is a less helpful marker since it can be raised in transplant patients without pre-eclampsia.

Labour management

In the absence of any obstetric complications, delivery is timed for 38–40 weeks of gestation. Vaginal birth is the preferred route. Prostaglandins and syntocinon are both safe to use for cervical ripening or induction. The allograft, located in the false pelvis, does not obstruct delivery of the fetus. Caesarean section may be necessary for obstetric indications or if there are concerns related to severe pelvic osteodystrophy. Early liaison with and involvement of the urology surgical team or renal transplant surgeons is advisable when elective caesarean section is planned. Stress dosage steroids should be administered to women who are on immunosuppressive dosages of steroids.

Neonatal problems

Neonates can have thymic atrophy, transient leucopenia or thrombocytopenia, adrenocortical insufficiency, septicaemia and cytomegalovirus/hepatitis infection.

Conclusion

Pregnancy in women with chronic renal disease presents a challenge to obstetricians as well as nephrologists. The key to achieving optimum outcome in these women is a multidisciplinary team approach. Women with mild renal impairment do well in pregnancy with few problems. However, those with moderate to severe kidney dysfunction face the prospect of significant pregnancy-related complications as well as long-term renal deterioration. These women require accurate prepregnancy counselling and expert care during pregnancy.

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