The Kidney in Pregnancy

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Introduction

A close relationship exists between kidney function and a successful pregnancy outcome. Renal disease can affect the outcome of pregnancy, pregnancy can affect the progression of pre-existing renal disease, and pregnancy itself can cause renal impairment. Women with renal disease who conceive and continue the pregnancy are at risk of adverse maternal and foetal outcomes. Although advances in antenatal and neonatal care continue to improve outcome, the risks remain proportionate to the degree of renal insufficiency.

The reproductive hormonal milieu in women with end-stage renal disease remains an enigma. Although chronic kidney disease is associated with infertility, the pregnancy rate in women with renal disease, including end-stage renal failure, is increasing. The reported frequency of conception in women of child-bearing age on dialysis ranges from 0.3-1.5%.[1] Although there is still a high rate of foetal loss, improved management of these high risk pregnancies seems to have improved outcomes. The apparent improvement in outcomes may be attributed to the more aggressive management of pregnant women on dialysis.

Kidney disease in pregnancy

Kidney disease in pregnancy may be due to:
- Known patients with pre-existing kidney disease
- Chronic kidney disease (CKD) diagnosed for the first time in pregnancy
- Kidney disease that develops for the first time during pregnancy

1) Known patients with pre-existing kidney disease in pregnancy

The successful outcome of pregnancy depends on the degree of renal failure rather than the specific underlying disorder. Patients are thus divided into three categories[1]:
- Mild disease if creatinine is <132µmol/l
- Moderate renal insufficiency if creatinine is 132-255µol/l
- Severe renal impairment when creatinine is >255µmol/l

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An elevated plasma creatinine concentration (>132µmol/l) and hypertension are the major risk factors for permanent exacerbation of underlying renal disease.[6] Pregnancy is associated with a permanent deterioration of renal function in up to 10% of women with normal or mild renal dysfunction. Others may experience a transient, but reversible, decline in their renal function.

On the other hand, women with moderate to severe disease may experience a modest decline in the first half of pregnancy. However, in the latter half of pregnancy the renal function may increase to above the initial baseline in up to 40% of patients. Studies suggest that one-third of patients experience irreversible decline.[8,9] The risk of acceleration of renal disease was greatest in patients with baseline creatinine >177µmol/l.[10] Thus, women with moderate to severe disease should be counselled against pregnancy as this worsens renal outcomes and may be irreversible.

The likelihood of conception and carrying a foetus to term is rare in women with creatinine >265µmol/l. These women usually have amenorrhoea or anovulatory menstrual cycles.

In summary, in women with renal disease who do conceive, the blood pressure should be well controlled as it is an important determinant of outcome. The presence of proteinuria has been associated with a worse foetal prognosis.

Kidney disease associated with systemic illness (CKD)

The following are most commonly encountered chronic renal diseases. However this list is not exhaustive. Other chronic renal diseases include reflux nephropathy, analgesic nephropathy, injury or trauma, scleroderma, congenital and vascular anomalies and the effects of toxins.

1.1) Diabetes Mellitus

Patients with either type I or type II diabetes mellitus may have diabetic nephropathy. Pregnancy is not contraindicated in a patient with diabetic nephropathy. Women with microalbuminuria, normal renal function and well controlled blood pressure have good outcomes, but are at increased risk of preeclampsia and urinary tract infections. When baseline blood pressure and creatinine are normal, pregnancy does not accelerate renal dysfunction.

Perinatal morbidity and mortality related to diabetic nephropathy has improved with strict glycaemic control. Despite good control, overt diabetic nephropathy is still associated with complications such as pre-eclampsia, foetal growth restriction and preterm birth. Overall, worldwide perinatal survival in pregnancies complicated by diabetic nephropathy was 95%. Preterm labour occurred in 22% of pregnancies and was associated with significant neonatal morbidity such as jaundice and respiratory distress syndrome. Intrauterine growth restriction occurred in 15% and congenital abnormalities in 8% of pregnancies. The degree of renal impairment correlated with the risk of pregnancy complications.[11,12]

Women with diabetic nephropathy are at increased risk of renal failure during and after pregnancy and eventual morbidity and death from macrovascular disease. Whether pregnancy hastens the progression of diabetic nephropathy to end-stage renal disease is controversial. Historically, these women were discouraged from pregnancy. More recent studies have shown promising results with improved maternal and neonatal outcomes. Although women may experience a temporary decline in renal function during gestation, this does not seem to accelerate progression to end-stage renal disease. However, this depends on the initial degree of renal impairment. The impact of pregnancy on the long-term outcome of renal disease remains unclear. There is concern that worsening hypertension, proteinuria, and glomerular filtration rate during pregnancy may accelerate progression to end-stage renal disease. Women with mild to moderate disease generally do not experience any worsening of renal function post-partum. This is also true for women with microalbuminuria, who did not show any acceleration in the deterioration of renal function following pregnancy.[13,14]

However, permanent renal damage, including renal failure may be more common among women with poorly controlled hypertension or moderate to severe renal impairment at the onset of pregnancy. Some of these women appear to require dialysis and renal transplantation sooner than if they had not become pregnant.[15]

Ideally, women with diabetes mellitus should be staged, receive counselling and have good glycaemic control prior to pregnancy. Preconception evaluation of diabetic nephropathy should include an evaluation of renal function and staging of nephropathy, if present. A 24-hour urine specimen should be collected to quantify proteinuria and creatinine clearance. Women on ACE-inhibitors should be changed to calcium channel blockers for hypertensive control prior to conception as ACE-inhibitors are teratogenic. They should be evaluated for cardiac disease and retinopathy. The four major factors associated with acceleration of diabetic nephropathy are microalbuminuria, degree of glycaemic control, blood pressure and pregnancy. Improving glycaemic and hypertensive control and reducing microalbuminuria have a protective effect and decrease the rate of decline of renal function over the long term.

Women with diabetic nephropathy require an intensive program of maternal and foetal evaluation. Thus adequate counselling is imperative as a motivated patient is more likely to adhere to an intensive treatment regimen.

1.2) SLE
Management of a patient with lupus is similar to one with diabetes with regards to creatinine and blood pressure. However, lupus is more unpredictable as it can suddenly flare. Whether pregnancy induces flares is still debated. Recent prospective data suggests that it does. Women with lupus should conceive once the disease has been in remission for six months. Additional concerns in a patient with SLE include antiphospholipid syndrome and neonatal lupus (secondary to transfer of antibodies).

It is difficult to distinguish a lupus flare from preeclampsia. Both diseases present with increased blood pressure, elevated creatinine, significant proteinuria and low platelets. However, in SLE the complement is decreased and the liver function will only be deranged in preeclampsia. Preeclampsia occurs after twenty weeks gestation.

Drug therapy in the patient with lupus should be optimised prenatally. Azathioprine and corticosteroids are safe in pregnancy. Cyclophosphamide and mycophenolate mofetil (MMF) are teratogenic and are contraindicated in pregnancy.[16,17]

1.3) Chronic glomerulonephritis (GN)
There is insufficient data to suggest a difference in prognosis with a specific glomerulonephritides (e.g. minimal change GN, focal segmental glomerulosclerosis, membranous GN, IgA nephropathy, etc.). The general principles of management of a patient with renal disease are applicable.[1,6]

1.4) Autosomal Dominant Polycystic Kidney Disease
Young women may be asymptomatic and this is often an incidental diagnosis. Patients with progressive disease and poorly controlled hypertension are at greatest risk for preeclampsia and preterm labour. Patients are also at increased risk of urinary tract infections. Increased oestrogen levels cause the liver cysts to enlarge. Patients should be screened for cerebral aneurysms. Considering that this is an autosomal dominant condition, the patient should be referred to a genetic counsellor.[1,6]

1.5) Chronic pyelonephritis
These patients have an increased incidence of urinary tract infections due to dilatation of the urinary tract. A high fluid intake and more frequent voiding should be encouraged. These patients should be screened frequently for bacteriuria, which should be treated promptly.[1,6]

Effect of chronic kidney disease on pregnancy
The rate of live births is above 90% in women with normal renal function and lower in those with mild disease, as long as the blood pressure is well controlled. However, pregnancy in the setting of chronic kidney disease is associated with some severe maternal and foetal risks.

Chronic kidney disease is associated with higher rates of adverse maternal outcomes. These patients are more likely to develop gestational hypertension, pre-eclampsia, and eclampsia. Maternal mortality was higher in women in chronic kidney disease although this difference was not statistically significant.[10]

Pre-eclampsia may be more difficult to diagnose in patients with chronic kidney disease who have pre-existing hypertension and proteinuria. Features of pre-eclampsia in these patients may include worsening hypertension and proteinuria, in association with decreasing platelets and increasing liver enzymes, i.e. development of HELLP syndrome. In women with chronic kidney disease pre-eclampsia was more likely to develop in the second trimester rather than in the third trimester.

Foetal outcomes are worse in women with chronic kidney disease. The rate of premature births, intrauterine growth restriction, small for gestational age and stillbirths are higher. Foetal survival is lower if hypertension is poorly controlled.

In addition to the effect of kidney disease on pregnancy, the possible effects of drugs used in kidney disease on the foetus need to be considered. Angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and some immunosuppressive drugs should be discontinued as soon as pregnancy is diagnosed. Women of child-bearing age who are not pregnant should also be warned of the potential adverse effects of these drugs on the developing fetus.

2) Chronic renal disease diagnosed for the first time in pregnancy

Pregnant women are examined more frequently in pregnancy than during a non-pregnant state. Blood and urine tests are routinely performed and therefore there is a greater likelihood of picking up an abnormality. The workup for renal disease is essentially the same as in the non-pregnant patient, but renal biopsy is usually deferred until post-partum. If only proteinuria is present, delay the biopsy by one to two months post-partum, since the proteinuria may improve once the haemodynamic changes of pregnancy have resolved. If renal function is impaired then a renal biopsy should be performed within a few weeks. Renal biopsy can be performed safely in women with well-controlled blood pressure and normal coagulation profiles at or before 32 weeks gestation. Beyond 32 weeks renal biopsy is not recommended, and should be deferred till post-partum.[20]

3) Kidney disease that develops for the first time in pregnancy

Acute renal failure requiring dialysis is rare in pregnancy. The incidence is 1:20 000 pregnancies. Although acute renal failure in pregnancy can result from any of the causes associated with the non-pregnant woman, there are a number of causes specific to pregnancy that must be considered.

Conditions that need to be considered in evaluating the pregnant woman with acute renal failure include:
- Pyelonephritis
- Pre-renal failure
- Acute tubular necrosis
- Bilateral cortical necrosis
- Acute fatty liver of pregnancy
- Thrombotic microangiopathies
- Obstructive uropathy
- Nephrolithiasis

Table 1: Approach to prenatal and antenatal care in a patient with chronic kidney disease

Approach for a Successful Pregnancy in a Patient with Chronic Kidney Disease (CKD)[1,6,9,10,18,19]
Patients with renal disease should be managed jointly by a nephrologist and an obstetrician familiar with the effects of renal disease on pregnancy.

Prenatal Counselling of Women with CKD:
- Renal function may decline as a result of pregnancy among patients with renal disease, especially if creatinine >132µmol/l and hypertensive
- Maternal risks in pregnancy with renal disease - increased gestational hypertension, preeclampsia, eclampsia and death
- Foetal risks in pregnancy with renal disease – increased premature birth, intrauterine growth restriction, small for gestational age and stillbirth
- Fertility improves after renal transplantation, but still lower than the general population
- Pregnancy has little or no effect on renal function of the transplant recipient. Recommended to wait 1 year after living related donor transplant, and 2 years after cadaveric transplantation to avoid complications of immunosuppressive therapy and transplant rejection
- Immunosuppressive regimens need to be adjusted prior to conception. MMF and sirolimus are teratogenic. Change the former to azathioprine, and the latter to cyclosporine or tacrolimus.

Renal Management of Pregnant Women with CKD
- 0.3-1.5% frequency of conception in women of child-bearing age on dialysis.
- Supportive measures include:
    - Intensive dialysis aiming at urea <16mmol/l
    - Haemoglobin 10-11g/dL
    - Correct metabolic acidosis and hypocalcaemia
    - Careful uterine and foetal monitoring during dialysis
    - Prevent dialysis-induced hypotension
- Attention to nutrition and weight gain – weekly evaluation to detect volume overload unrelated to pregnancy

Obstetric Management of Women with CKD
- Increased frequency of antenatal visits – fortnightly till 28-weeks; weekly thereafter
- Early detection and treatment of asymptomatic bacteriuria. Recommend monthly urine MCS
- Serial monitoring (1-2 weekly) of maternal renal function
- Close monitoring for the development of preeclampsia. Low dose aspirin from the first trimester
- Foetal surveillance with ultrasound to assess foetal growth, including umbilical artery Dopplers and liquor volume
- Aggressive treatment of maternal hypertension
- Preterm intervention in presence of deteriorating renal function, severe preeclampsia, foetal growth restriction or foetal distress
- High risk of preterm labour – use MgSO4 cautiously (prevent respiratory depression, toxicity)
- Debate over elective early delivery at 34-34 weeks
- Caesarean section reserved for obstetric indication
- Prophylactic antibiotics to cover any surgical procedure
- Parenteral steroids to cover labour if woman is on maintenance steroids

Figure 1: Approach to a patient with newly diagnosed renal failure
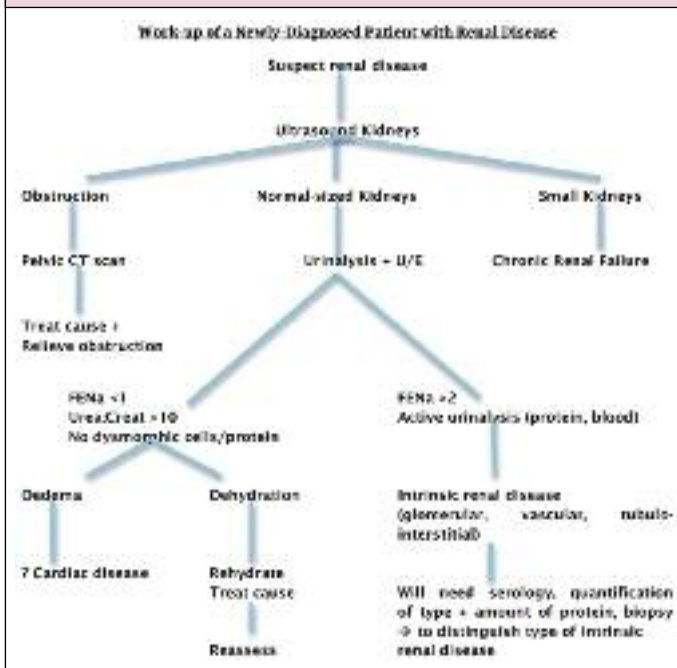
The management of acute renal failure in pregnancy is the same as that for the non-pregnant patient. Haemodialysis and peritoneal dialysis can be used. In fact, peritoneal dialysis may be gentler, and less likely to precipitate labour.

3.1) Urinary tract infections[21]
3.1.1) Asymptomatic bacteriuria
Asymptomatic bacteriuria affects 4-7% of pregnancies. Most infections are caused by E. coli. Women with a previous history of a urinary tract infection are 10-times more likely to develop acute cystitis or acute pyelonephritis in pregnancy. Most women will develop asymptomatic bacteriuria early in pregnancy. Bacteriuria is only significant if there are >100 000 colonies/ml on a midstream urine specimen. Dipsticks for nitrites and leucocytes may help exclude a urinary tract infection.

Dilatation of the upper urinary tract in pregnancy increases the risk of pyelonephritis. Thus asymptomatic bacteriuria should be treated. Treating asymptomatic bacteriuria decreases the incidence of preterm labour and low birth weight babies.

Penicillins and cephalosporins are safe and appropriate antibiotics to use in pregnancy. Alternatives include nitrofurantoin and trimethoprim. The patient should be treated for three days. Urine cultures should be repeated following treatment to ensure eradication of the organism.

3.1.2) Acute cystitis
Cystitis complicates 1% of pregnancies. Symptoms include urinary frequency, urgency, dysuria, haematuria, and suprapubic pain. Urinary tract infections are more common in immunocompromised pregnant women, such as diabetics and those on immunosuppressive therapy. Diagnosis is confirmed by microscopy and culture of a midstream urine specimen.

Treatment is the same as for asymptomatic bacteriuria. Antibiotics are continued for 5-7 days. Non-pharmacological measures include increased fluid intake, emptying the bladder following sexual intercourse, double voiding and improved perineal hygiene to minimise the risk of bowel organisms colonising the urethra.

3.1.3) Acute pyelonephritis
Pyelonephritis is more common in pregnancy as the upper urinary tract is dilated. Pyelonephritis is usually more severe in pregnancy and warrants aggressive therapy. Symptoms include fever, abdominal and flank pain, vomiting, rigors as well as concomitant features of cystitis.

Diagnosis is made on microscopy and culture of a midstream urine specimen. Renal function should be assessed since renal failure can complicate acute pyelonephritis. An ultrasound of the kidneys should be obtained to exclude hydronephrosis, renal calculi and congenital abnormalities.

Pyelonephritis increases the risk of preterm labour, in part due to the associated pyrexia. There is also a risk of low birth weight babies.

Treatment requires hospitalisation and the administration of intravenous fluids and antibiotics. Ceftriaxone is an appropriate choice for initial therapy. Antibiotics should be given intravenously for at least 24-48 hours. Thereafter the patient can be changed to oral antibiotics. Antibiotics should be continued for two weeks.[22]

3.2) Pre-renal failure / dehydration
Pre-renal azotaemia can be caused by hyperemesis gravidarum, which is associated with metabolic acidosis. Haemorrhage can also result in pre-renal azotaemia. Management of this condition requires the replacement of intravenous fluids and correction of electrolytes.[23] The underlying cause of the pre-renal failure needs to be timeously addressed.

3.3) Acute tubular necrosis (ischaemic and toxic)
There are two major causes of acute tubular necrosis, i.e. ischaemic and toxic. Ischaemic acute tubular necrosis may be caused by severe volume depletion associated with hyperemesis gravidarum, haemorrhage from spontaneous abortion or shock following septic abortion. In later pregnancy it is most often caused by pre-eclampsia, HELLP syndrome, or by uterine haemorrhage following abruption placentae. Toxic acute tubular necrosis is caused by intrinsic (free haemoglobin, myoglobin) or extrinsic (antibiotics, antivirals, ethylene glycol, herbal medications) toxins. The diagnosis can be established via history, urinalysis, and evaluation of renal function. Granular casts are seen on urinalysis and the patient will have an elevated fractional excretion of sodium. Treatment includes fluids, antibiotics, and if necessary, dialysis.[23] Complete recovery of renal function following acute tubular necrosis may take up to six weeks. The patient will require supportive care, including dialysis as necessary, in the interim.

3.4) Bilateral cortical necrosis

Bilateral cortical necrosis is most likely initiated by disseminated intravascular coagulation and severe renal ischaemia. It is a rare cause of acute renal failure, although it occurs more commonly with relation to obstetric haemorrhage (e.g. abruption placentae). The patient presents with oliguria or anuria, haematuria and flank pain. Ultrasonography or CT scan may show hypoechoic or radiolucent renal cortices. Most patients will require dialysis. Recovery is usually incomplete.[22,23]

3.5) Acute fatty liver of pregnancy

Acute fatty liver of pregnancy is a rare disorder characterised by the onset of abdominal pain and jaundice. It typically occurs after 34 weeks gestation. Pathogenesis is thought to be related to mitochondrial dysfunction. Patients have increased bilirubin, mildly elevated transaminases, hypoglycaemia and deranged clotting profiles. They can also have fulminant liver failure. This disorder often presents with acute renal failure. Treatment consists of delivery and supportive care.[22,24]

3.6) Thrombotic microangiopathies

The thrombotic microangiopathies include thrombotic thrombocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS). This rare spectrum of disorders includes haemolytic anaemia, thrombocytopaenia and renal failure. They have similar features to pre-eclampsia and acute fatty liver of pregnancy, making it important to distinguish, as treatment differs. Management of TTP is plasmapharesis and treatment for HUS is supportive.[25]

3.7) Obstructive uropathy

Obstructive uropathy should be considered in a woman with oliguria or anuria, with moderate to severe dilatation of the renal collecting system. The causes of this condition include the gravid uterus, polyhydramnios, a multifibroid uterus and kidney stones.

Correct diagnosis of obstructive uropathy requires an adequate appreciation of the normal anatomical renal changes of pregnancy. In pregnancy both kidneys increase by 1.0-1.5cm. Kidney volume increases by 30%. The renal pelvises and calyceal systems may be dilated. Dilatation of the ureters and renal pelvises is more prominent on the right than on the left, and occurs in up to 80% of pregnancies. These changes can be visualised on ultrasound, and can take up to 6-12 weeks post-partum to resolve. Obstructive uropathy usually resolves with delivery, although ureteral stenting may be necessary preterm.[26]

3.8) Nephrolithiasis

Urinary calcium excretion increases in pregnancy due to increased intake and increased intestinal absorption. The presentation is the same as in the non-pregnant state, and urinary tract infections are more common. Ultrasonography is the primary diagnostic method employed. Ureteral stenting may be required if the stones cannot be passed.[27]

End-Stage Renal Disease in Pregnancy
1) The Pregnant patient on dialysis

End-stage renal disease requiring dialysis is associated with a marked decline in fertility. Pregnancy does occur in up to 1% of patients, usually in the first few years after starting dialysis.[1] In general, pregnancy is contraindicated whilst a patient is on dialysis. However, a review of new evidence suggests that we may have to rethink this approach.[18] The fetal outcome is poor, mostly due to the high rate of spontaneous abortions and prematurity. 23-55% of pregnancies result in surviving infants. The incidence of very low birth weight, small for gestational age and growth restricted infants is high. Worsening hypertension, which occurs in up to 80% of pregnant women on dialysis, is a major concern.[2,19,28] The diagnosis of pregnancy in these women is also difficult as many have irregular menstruation, and beta-human chorionic gonadotropin (β-hCG) levels are usually elevated in patients receiving dialysis. Thus, if pregnancy is suspected, an ultrasound is recommended to aid in the diagnosis.[1]

Pregnant patients on dialysis require close monitoring. An increased frequency of dialysis may improve mortality and morbidity. Aggressive daily dialysis may be indicated. The major components of the dialysis regimen are[29]:

- More intensive dialysis to achieve urea <16mmol/l. This may be achieved by more frequent dialysis or switching to longer nightly dialysis. This may help avoid polyhydramnios, control hypertension, increase birth weight and gestational age, and improve the mother's nutritional status.
- Pregnant women require higher doses of erythropoietin as physiological changes of pregnancy may lead to worsening anaemia. Erythropoietin should be used with caution as it may worsen hypertension.
- Metabolic acidosis and hypocalcaemia should be corrected.
- The uterus and foetus should be monitored during haemodialysis. Every attempt should be made to avoid dialysis-induced hypotension. The use of heparin should be minimised to decrease the risk of bleeding.
- If the patient is on peritoneal dialysis, the volume of the dialysate should be decreased and the frequency of dialysis increased.
- The patient's blood pressure should be controlled and anaemia treated timeously.[29]

2) Pregnancy post renal transplantation

Pregnancy occurs in up to 12% of female patients of child-bearing age post transplantation. More than 90% of pregnancies post renal transplantation is successful. In the correct setting, pregnancy can be planned. Factors such as uncontrolled hypertension, worsening proteinuria and poor pre-pregnancy renal function are prognostic indicators of deteriorating renal function. The renal graft is not adversely affected by pregnancy in patients on prednisone or azathioprine and creatinine level <123μmol/l.

However corticosteroid use impairs glucose control, increases blood pressure, increases the incidence of infections and may cause ectopic pregnancies and uterine rupture. Fetal complications include increased incidence of

preterm deliveries, intrauterine fetal growth restriction, congenital anomalies and decreased platelet counts.[30,31]

Patients should meet the following criteria before falling pregnant:
• Good health and stable renal function for 2 years
• Absent proteinuria
• Normal blood pressure
• No pyelocalyceal distension
• Normal creatinine
• Drugs:
  - Prednisone <15mg
  - Azathioprine 2mg/kg
  - Cyclosporine <5mg/kg/day

Conclusion

Kidney disease in pregnancy poses a complex problem. One needs to take into consideration the effects of the pregnancy on renal disease, the effects of renal disease on pregnancy, as well as the effects of the drugs that are used to manage kidney disease.

Thus, a multidisciplinary approach is required when managing the pregnant patient with renal disease. The team should consist of an obstetrician familiar with the effects of renal disease on pregnancy, a nephrologist familiar with the effects of pregnancy on renal disease, nutritionists, nurses and neonatologists. Pre-pregnancy counselling, close antenatal monitoring, and skilled obstetric management are critical to a successful pregnancy outcome in these patients. A planned pregnancy with an informed, motivated patient presents the best hope of a good maternal and neonatal outcome. Recent evidence, with more aggressive management of renal disease in pregnancy, now provides hope of a successful pregnancy without negatively influencing the renal outcome of the mother.

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