

## ARTICLE

## Pregnancy and the kidneys

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Renal disease in pregnancy may cause a feeling of trepidation, even in the most experienced physician. However, before disease can be established, it is important to understand the substantial physiological changes that may occur during a normal pregnancy. Renal disease may take several forms and pregnancy may be the first medical review for women with a previously undiagnosed renal problem. Patients may have pre-existing renal disease, e.g. diabetic nephropathy. Additionally, women with renal transplants and renal diseases, e.g. lupus nephritis, require immunosuppression. Hypertensive disorders of pregnancy, including pre-eclampsia, are the commonest medical complications in pregnancy, and remain the most prevailing direct cause of maternal mortality in South Africa (SA). Both pre-existing hypertension and renal disease increase the risk of pre-eclampsia, which predisposes to preterm delivery, and maternal morbidity and mortality.

Pregnancy outcomes in renal disease are determined by baseline creatinine levels, hypertension and degree of proteinuria. The risk of progression of chronic kidney disease increases as renal function worsens. In SA, this is complicated by restricted access to dialysis in the state sector. To ensure the best outcome for mother and child, pre-pregnancy counselling and review of medication are essential. Renal patients and those with hypertension are at high risk of complications, and regular antenatal assessments by a multidisciplinary team are required to monitor blood pressure, proteinuria, diabetes control and fetal wellbeing.

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Renal disease in pregnancy may cause a feeling of trepidation, even in the most experienced physician, and may take several forms. Pregnancy may be the first medical review for women with a previously undiagnosed renal problem. Patients may have pre-existing renal disease, e.g. diabetic nephropathy. Additionally, women with renal transplants and renal diseases, e.g. lupus nephritis, require immunosuppression. Pregnancy outcomes in renal disease are determined by baseline creatinine levels, hypertension and degree of proteinuria. The risk of progression of chronic kidney disease (CKD) and maternal and fetal complications increases as the renal function worsens, and patients need to be counselled, preferably prior to conception. Pre-existing renal disease predisposes to pre-eclampsia, a condition occurring in up to 5% of pregnancies, making it one of the most common complications of pregnancy. A multidisciplinary team approach involving a physician/nephrologist and an obstetrician is essential to assess and care for pregnant women with kidney disease.

### Normal physiological adaptations of pregnancy

The kidneys increase in length (1 - 2 cm) and volume (70%) with dilation of the calyces, renal pelvis and ureters, features which are more prominent on the right. By the third trimester, 80% of women show evidence of hydronephrosis, which predisposes to urinary stasis, increasing the risk of urinary tract infections.<sup>[1]</sup> There is hormonal dilatation of the systemic blood vessels, leading to a decrease in systemic vascular resistance and a physiological lowering of blood pressure, especially during the first and second trimesters. Thereafter, there is a steady return of blood pressure to pre-pregnancy levels until term.

Plasma volume increases significantly, leading to a 30 - 50% increase in cardiac output and resulting in a steady increase in renal blood flow (50% by the mid-second trimester). This increases the glomerular filtration rate (GFR) and gives rise to frequency and nocturia, resulting in decreased creatinine blood levels. The increased vascularity of the kidneys makes a renal biopsy beyond 32 weeks risky. Despite the increase in renal blood flow, the pressure within the glomerulus remains unaltered owing to compensatory effects on the afferent and efferent arteriole, but this only occurs in a normal kidney. Any pre-existing disease in the kidney will be accelerated, often with deterioration in renal function.

Pregnancy also affects the renal tubules. There is decreased reabsorption of glucose and bicarbonate, leading to glycosuria and bicarbonaturia. Despite the loss of bicarbonate, there is a persistent alkalosis owing to an increased respiratory rate. There is hypercalciuria, although the risk of renal stones is not increased as inhibitors of stone formation also increase. It is also common to find mild proteinuria, <300 mg/d, which may remain up to 6 months postpartum. Isolated pyuria is common and disappears by 3 months postpartum. Serum sodium may decrease by 4 - 5 mEq/L and serum osmolality falls to a new osmotic setpoint of about 270 mOsm/kg.

#### Important renal adaptations in pregnancy

- Increase in kidney size 1 - 2 cm
- Dilatation of the urinary collecting system
- Increase in renal blood flow
- Increase in glomerular filtration rate
- Decrease in creatinine
- Glycosuria and bicarbonaturia
- Decrease in plasma sodium and osmolality

## Estimating glomerular filtration rate in pregnancy

The modification of diet in renal disease (MDRD) is a creatinine-based formula that measures GFR. It has become a standard clinical method used to estimate renal function in patients with CKD. The use of this formula has not been well studied in the pregnant population and guidelines for its use exclude pregnant women,<sup>[2]</sup> because creatinine falls in pregnancy owing to a pregnancy-induced increase in GFR and haemodilution from plasma expansion. The MDRD formula is also known to be inaccurate once the GFR is >60 ml/min/m<sup>2</sup>, even in non-pregnant women. This inaccuracy is more pronounced in pregnancy.<sup>[3]</sup> Weight-based formulas, such as those used in the Cockcroft-Gault method, are likely to overestimate GFR because the increased body weight in pregnancy does not typically reflect increased muscle mass or creatinine production.<sup>[4]</sup> Given this, 24-hour urine collection for creatinine clearance remains the gold standard for GFR estimation in pregnancy.

## Estimating proteinuria in pregnancy

Proteinuria needs to be measured first to monitor pre-existing proteinuria, which may increase substantially during pregnancy. The protein-creatinine ratio (PCR) is the preferred method for quantitating proteinuria in the non-pregnant state<sup>[5]</sup> and its use is recommended to monitor pre-existing proteinuria during pregnancy. The second indication is for the diagnosis of pre-eclampsia, which is defined as the new onset of hypertension (blood pressure (BP) >140/90 mmHg) and proteinuria (>300 mg protein in a 24-hour urine collection) after 20 weeks' gestation.<sup>[6]</sup> Although there are limitations to 24-hour urine collections, the use of PCR for the diagnosis of pre-eclampsia has been controversial, with discordant conclusions compared with 24-hour urine collections.<sup>[7]</sup>

## Specific diseases of the kidney

### Hypertensive disorders, including pre-eclampsia

Hypertensive disorders of pregnancy are the commonest medical complications in pregnancy, and remain the most prevailing direct cause of maternal mortality in SA.<sup>[8]</sup> In the UK, 3 - 5% of pregnant women have hypertension that predates conception.<sup>[9]</sup> It is more common in advanced maternal age, obesity and blacks.<sup>[10]</sup> A secondary cause should be excluded if appropriate. About 22 - 25% of women with pre-existing hypertension are likely to develop pre-eclampsia.<sup>[11]</sup> Pregnancy-induced hypertension is defined as a BP >140/90 mmHg arising after 20 weeks of gestation and returning to normal within 6 weeks postpartum.<sup>[6]</sup> Pre-eclampsia is a multisystem disorder that is commonly associated with oedema and hyperuricaemia. It is a leading cause of maternal mortality and morbidity in developed<sup>[12]</sup> and developing countries, where it continues to claim the lives of >60 000 mothers every year.<sup>[13]</sup>

Pre-eclampsia appears to be initiated by abnormal implantation of the placenta, leading to hypoperfusion and ischaemia. There is accumulating evidence supporting the release of several placental anti-angiogenic factors including soluble fms-like tyrosine kinase-19 (sFlt1) and its synergist, soluble endoglin (sEng). These anti-angiogenic factors are induced or exacerbated by placental ischaemia, with sFlt1 being a circulating antagonist to both vascular endothelial growth factor (VEGF) and placental growth factor. Circulating VEGF is mopped up by sFlt1 to prevent the former's protective effects on the endothelium. When administered to pregnant rats, sFlt1 and sEng produce a syndrome resembling that of HELLP (haemolysis, elevated liver enzymes, and low platelets).<sup>[14,15]</sup> Subsequent studies have demonstrated the role of these anti-angiogenic factors in the pathogenesis of pre-eclampsia in humans.<sup>[16-18]</sup>

Clinically, vascular endothelial dysfunction and microangiopathy are present in the mother, but not in the fetus. The predominant target organ may be the brain (seizures or eclampsia), the liver (HELLP syndrome), or the kidney (glomerular endotheliosis and proteinuria). Predisposing factors include pre-existing hypertension, CKD, obesity, diabetes mellitus, thrombophilias, and multiple gestations.<sup>[19]</sup> These women may be more susceptible to endothelial dysfunction and hence more responsive to anti-angiogenic factors.

Screening for pre-eclampsia has the greatest impact on clinical outcomes, but to date there is no effective preventive treatment. Although two large meta-analyses have suggested a small, but significant, overall benefit in patients treated with aspirin,<sup>[20,21]</sup> the delivery of the fetus is currently the only definitive treatment.

Considerable evidence suggests that pre-eclampsia predisposes women to late cardiac and vascular diseases<sup>[22]</sup> and also increases the risk of subsequent CKD. The risk is greater if a pre-eclamptic pregnancy results in the birth of a low-birth-weight or preterm infant or if pre-eclampsia occurs in more than one pregnancy.<sup>[23]</sup>

### Chronic kidney disease in pregnancy

Women with CKD who become pregnant are at increased risk for adverse maternal and fetal outcomes, including a rapid decline in renal function, intrauterine growth retardation, perinatal mortality and pre-eclampsia.<sup>[24,25]</sup> The major determinants of outcome are pre-existing proteinuria, hypertension, urinary tract infection and degree of renal dysfunction. Obstetric outcomes are also partly related to the level of available neonatal care. Very importantly, maternal renal function may decline irreversibly proportional to the level of pre-existing dysfunction. In a SA setting, this is an important consideration as access to dialysis is limited in the state sector.

#### Maternal renal function declines proportional to the level of pre-existing renal dysfunction<sup>[24,26]</sup>

- Creatinine <123 µmol/L: considered safe
- Creatinine 130 - 170 µmol/L: 40% have deterioration in renal function, of whom half recover
- Creatinine >176 µmol/L: two-thirds have an accelerated decline in renal function and one-third require dialysis

The stress of increased renal blood flow and inability of the glomerulus to regulate intraglomerular pressure, which normally remains unaltered during pregnancy, may exacerbate renal damage in pre-existing disease.

## Managing dialysis and renal transplant patients

CKD is generally characterised by menstrual disturbances and infertility, and is reversed by transplantation but not by dialysis.<sup>[27]</sup> Although conception in patients on dialysis is unusual, it is not impossible, and adequate contraception remains important. When pregnancy does occur, it needs to be co-managed by a nephrologist and an obstetrician as significant changes in management are required to improve maternal and neonatal outcomes. Transplant patients should also be co-managed as immunosuppressive drugs may need to be altered and their plasma levels will need to be carefully monitored. Pregnant women who have a transplanted kidney with renal dysfunction should be considered in the same way as other patients with CKD.

## Pregnancy-induced acute kidney injury

Acute kidney injury (AKI) in pregnancy may be caused by any of the disorders leading to renal failure in the general population, e.g.

acute tubular necrosis (ATN) due to infection, glomerulonephritis or drug toxicity. There are, however, pregnancy-related complications characteristic of each trimester that can result in renal failure.<sup>[28,29]</sup> Early in pregnancy the most common problems are pre-renal disease due to hyperemesis gravidarum or ATN following a septic abortion. In the second and third trimesters, pregnancy-specific conditions, e.g. pre-eclampsia, HELLP syndrome, acute fatty liver of pregnancy, haemolytic-uraemic syndrome and thrombotic thrombocytopenic purpura, can be complicated by acute renal failure. At delivery, placental abruption can be associated with severe ATN and bilateral cortical necrosis. The management of AKI is similar to that in a non-pregnant patient, with fluid management being especially important, particularly in the context of pre-eclampsia, as the vascular endothelium is very leaky. Potential nephrotoxins such as the non-steroidal anti-inflammatory drugs (NSAIDs) and aminoglycosides should be used with caution throughout the pregnancy.

### Managing the complicated patient Diabetic nephropathy

Diabetic nephropathy is frequently encountered during pregnancy. Pre-pregnancy counselling is important, as obstetric and renal outcomes are determined by the degree of peripartum CKD. There is no increased risk of overt nephropathy or end-stage renal disease in women with normal renal function at conception.<sup>[30]</sup> However, diabetic nephropathy is associated with a 2 - 4-fold increased risk of pre-eclampsia, preterm delivery and perinatal death.<sup>[31]</sup> Management includes low-dose aspirin from the first trimester to reduce the risk of pre-eclampsia, regular renal function monitoring, good BP control and tight glycaemic control.

### Lupus nephritis

Women with lupus nephritis should be advised to conceive after a 6-month period of quiescent disease. Predictors of poor obstetric outcomes include active disease at conception and early pregnancy, >0.5 g protein/24 h, CKD stage >3, hypertension and antiphospholipid antibodies. There is also an increased risk of pre-eclampsia.

Extra-renal disease flare-ups are more common in the second and third trimesters, and postpartum flare-ups have been described.<sup>[32]</sup>

Flare-ups can be managed with corticosteroids. Maintenance therapy with azathioprine and hydroxychloroquine is considered safe. Tacrolimus and cyclosporin can be used in pregnancy with therapeutic drug level monitoring. Differentiating between a flare-up of lupus nephritis and pre-eclampsia may be challenging. A low C3/C4, a rising double-stranded DNA (dsDNA) and an active urine sediment with red cell casts are suggestive of recurrence of lupus.

### Drugs and the kidney

Methyldopa is the first-line agent of choice to treat hypertension in pregnancy and has a well-documented safety profile,<sup>[33,34]</sup> while the calcium channel blocker, nifedipine,<sup>[35]</sup> and the selective  $\alpha_1$ - and non-selective  $\beta$ -adrenergic receptor-blocker, labetalol, also appear to be safe.<sup>[36]</sup> Diuretics are generally not recommended as they can theoretically compromise the pregnancy-associated increase in plasma volume, although outcome data have not supported these concerns.<sup>[37]</sup> Angiotensin-converting enzyme (ACE) inhibitors are teratogenic and can cause renal dysgenesis, oligohydramnios, calvarial and pulmonary hypoplasia, intrauterine growth restriction, and neonatal renal failure, leading to death of the fetus as early as the first trimester.<sup>[38,39]</sup> Similar anomalies have been reported with angiotensin II receptor blockers (ARBs).<sup>[40]</sup> ACE inhibitors and ARBs should be discontinued prior to conception, with appropriate birth control measures while on these agents.

Calcineurin inhibitors, glucocorticosteroids and azathioprine are the mainstay of safe immunosuppressive therapy in pregnant transplant recipients and lupus patients. Mycophenolate mofetil has been reported to cause developmental toxicity, malformations, and intrauterine death in animals, with growing evidence confirming its teratogenic effects in humans. The drug should be discontinued 6 weeks before conception.

### Conclusion

Because there are substantial physiological changes that occur in a normal pregnancy, it is necessary to understand these in order to determine whether the kidney developed disease during pregnancy. Both pre-existing hypertension and renal disease increase the risk of adverse pregnancy outcomes and increase the risk of pre-eclampsia, which predisposes to preterm delivery. Pregnancy in a patient with CKD may cause progression of renal failure, and in the SA setting this is complicated by restricted access to dialysis in the state sector. To ensure the best outcome for mother and child, pre-pregnancy counselling is essential. Attention must be paid to the numerous teratogenic drugs that are commonly used to treat hypertension and the immunosuppression necessary to treat renal transplant recipients and those with glomerulonephritis (e.g. lupus nephritis). Patients with renal disease and hypertension are at high risk of complications and regular antenatal assessments are required that should involve a multidisciplinary team to monitor BP, proteinuria, diabetic control and fetal wellbeing.

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