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Renal disease and hypertension in pregnancy

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ABSTRACT – Because women are becoming pregnant at a later age, hypertension is more commonly encountered in pregnancy. In addition, with increasing numbers of young women living with renal transplants and kidney disease, it is important for physicians to be aware of the effects of pregnancy on these diseases. A multidisciplinary approach is essential to assess and care for pregnant women with kidney disease. Pre-pregnancy counselling should be offered to all women with chronic kidney disease. A review of medication to avoid teratogenicity and optimise the disease prior to conception is the ideal. Pregnancy may be the first medical review for a young woman, who may present with a previously undiagnosed renal problem.

KEY WORDS: hypertension, pregnancy, renal disease

Introduction

Because women are delaying pregnancy until a later age, hypertension is more commonly encountered in pregnancy. In addition, increasing numbers of young women are living with renal transplants and kidney disease. It therefore is important for physicians to be aware of the effects of pregnancy on these diseases and vice versa.

Kidney disease during pregnancy may take several forms. These include pre-existing renal disease diagnosed before conception (for example, diabetic nephropathy, lupus nephritis and reflux nephropathy), chronic kidney disease (CKD) diagnosed for the first time during pregnancy and renal disease that develops for the first time during pregnancy.

A multidisciplinary team (MDT) approach involving the physician/nephrologist and obstetrician is essential to assess and care for pregnant women with kidney disease. Timing of pregnancy and pregnancy outcomes are determined by baseline creatinine levels and pre-pregnancy disease status. Pre-pregnancy counselling is vital for women with conditions such as lupus nephritis and renal transplantation, which require long-term immunosuppression that may need to be reviewed to avoid teratogenicity while maintaining disease control and graft function. The aims of this article are to review the normal renal adaptation to pregnancy and to discuss the effects of renal disease on pregnancy outcome and management in women with kidney disease and hypertension.

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Renal adaptations in pregnancy

During pregnancy, cardiac output increases by 50% and blood volume by 2 litres. Structural and functional changes occur in the kidney and renal tract due to hormonal changes in pregnancy; these are summarised in Box 1. Estimated glomerular filtration rate (eGFR) is not validated for use in pregnancy, when it is customary to use serum creatinine levels.

Total peripheral resistance falls and so blood pressure (BP) tends to decrease during the first and second trimester of pregnancy. A nadir is reached by 22–24 weeks' gestation, after which there is a steady return of BP to pre-pregnancy levels until term.

Hypertensive disorders in pregnancy

Hypertension is the most common medical problem seen during pregnancy (10–15%) and can predate pregnancy or be diagnosed during pregnancy, when it is described as pregnancy-induced hypertension (PIH). Pre-eclampsia and eclampsia occur in 3–5% and 0.03% of pregnancies, respectively, and are leading causes of maternal mortality and morbidity in the UK.[1]

Hypertension in pregnancy is defined as diastolic BP >90 mmHg on two occasions or one reading >110 mmHg. An increase in systolic BP >30 mmHg or diastolic BP >15 mmHg above the earliest reading in pregnancy can also be considered to represent hypertension. The different hypertensive categories found in pregnancy are described below.

Box 1. Summary of renal adaptations in pregnancy.

- Decrease in serum creatinine levels
- Dilatation of the urinary collecting system; pronounced on the right, with pelvicaliceal diameter ⩽2 cm within normal limits for pregnancy
- Increased renal blood flow
- Increase in glomerular filtration rate by 50–80%
- Increased size of kidneys by 1 cm

Modifications in tubular function

- Increased glycosuria
- Increased bicarbonaturia
- Increased calciuria
- Reduced plasma osmolality

Pre-existing hypertension

In this case, the diagnosis is made prior to or early in the pregnancy. Risk factors include increasing age, obesity and insulin resistance. Secondary causes such as hyperaldosteronism and phaeochromocytoma should be considered and excluded, if appropriate. One prospective study has shown that 22% of affected women may have superimposed pre-eclampsia.[2]

Pregnancy-induced hypertension

Pregnancy-induced hypertension develops in the second half of pregnancy and resolves within 6 weeks of delivery. The relative risk of progression to pre-eclampsia depends on the timing of the initial presentation: from 40% before 30 weeks' gestation to 7% after 38 weeks. Affected women have an increased risk of PIH in future pregnancies.

Pre-eclampsia

Pre-eclampsia is a pregnancy-specific multisystem disorder. It is characterised by new-onset hypertension and proteinuria after 20 weeks' gestation:

- Proteinuria >300 mg/24 hours or spot urinary protein to creatinine ratio >30 mg/mmol
- Blood pressure >140/90 mmHg

To prevent maternal complications and maintain adequate uteroplacental perfusion, maternal BP is usually maintained at about 140/90 mmHg. Treatment is mandatory if BP >160/110 mmHg because of the risk of maternal cerebral haemorrhage and placental abruption. In the presence of CKD; aim for BP <140/90 mmHg.[3] Common pharmacological agents are summarised in Table 1.[4]

Table 1. Common pharmacological agents used to treat hypertension in pregnancy and postpartum period.[4,5]

Agent	Dose	Side effects	Comments
Antenatal period*			
Methyldopa	• 250 mg bd–1 g tds	• Lethargy • Depression	• Documented safety profile • Seven-year follow up of offspring
Labetalol	• 200 mg bd–500 mg tds		• Avoid in women with asthma
Nifedipine	• 10 mg SR bd–30 mg SR bd	• Headache • Flushing • Swollen lower limbs	• Possible interference with labour (tocolytic) • May interact synergistically with magnesium sulphate
Hydralazine	• 25–75 mg tds	• Headache • Flushing • Tachycardia	
Amlodipine	• 5–10 mg od		
Doxazocin	• 1 mg od–8 mg bd		

ACE inhibitor/ARB	• Contraindicated in antenatal period	• First trimester:
		  • 2.6-fold increase in congenital cardiac and central nervous system anomalies
		• Second and third trimester: associated with:
		  • Fetopathy
		  • Oligohydramnios
		  • Growth restriction
		  • Neonatal anuric renal failure (may be fatal)	

Postpartum period†			
ACE inhibitor			
Enalapril	• 5–20 mg twice daily		• Safe in breastfeeding
Calcium channel antagonist			
Nifedipine SR	• 10–40 mg twice daily		• Safe in breastfeeding
Amlodipine	• (5–10 mg)		
Beta blocker			
Atenolol	• 25–50 mg once daily		• Safe in breastfeeding
Labetalol	• 200 mg bd–500 mg tds		

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; bd = twice daily; od = once daily; SR = sustained release; tds = three times daily.
*Diuretics are to be avoided in the treatment of hypertension. However, diuretics are safe in pregnancy and postpartum period, but are to be used with caution.
†Insufficient evidence is available on the safety of ARBs and doxazocin in the postpartum period.

Acute kidney injury

Incidence of acute kidney injury (AKI) in pregnancy remains unknown, and a consensus on classification of AKI in pregnancy has not been established. However, serum creatinine >90 µmol/l is considered indicative of renal impairment in pregnancy.[6] The most common cause for AKI in pregnancy is pre-eclampsia. Other causes and clinical manifestations of AKI specific to pregnancy are listed in Table 2.[7,8]

The management of AKI is similar to that in a non-pregnant patient. Fluid management is important, especially in the context of pre-eclampsia. Renal function can deteriorate further due to reduction of renal blood flow if there is postpartum haemorrhage or non-steroidal anti-inflammatory drugs (NSAIDs) are used. Women with pre-eclampsia are at risk of pulmonary oedema with overzealous fluid resuscitation. Nephrotoxins such as NSAIDs and aminoglycosides should be used with caution. Particular attention is required to adjust the dose of drugs such as magnesium sulphate, which remains the standard obstetric drug of choice for the treatment and prevention of eclampsia in the presence of AKI.

Pre-eclampsia

The common clinical features of and risk factors for pre-eclampsia are summarised in Table 3. Routine antenatal care involves screening for pre-eclampsia through regular BP measurements and urinalysis to detect proteinuria. Pre-eclampsia is also associated with increased risks of fetal growth restriction and placental abruption.

Once diagnosed, the only cure is delivery; however, this may need to be delayed to improve fetal outcome. Severe hypertension will require intravenous labetalol or hydralazine according to local protocols. Once this situation is reached, it is a medical emergency and a decision on the timing of delivery is necessary, with senior obstetric input.

Early-onset pre-eclampsia (<34 weeks) has a worse outcome. Those who have proteinuria at the postnatal review (6–8 weeks after delivery) should be offered a further review at 3 months after delivery to assess renal function and should be referred to a nephrologist as they may have underlying renal disease.

Prevention of pre-eclampsia

A meta-analysis of 115 trials found that antiplatelet therapy was beneficial in reducing the relative risk (RR) of pre-eclampsia to 0.90 (95% confidence interval (CI) 0.84 to 0.97) and of preterm delivery (<34 weeks' gestation) to 0.90 (95% CI 0.83 to 0.98).[9] All patients with the risk factors outlined in Table 3 should be offered low-dose aspirin (75 mg daily) throughout pregnancy to reduce the risk of pre-eclampsia developing. In patients allergic to aspirin, dipyridamole (100 mg three times daily) can be considered.

Risk of recurrent pre-eclampsia

The risk of pre-eclampsia in a subsequent pregnancy is 16% and up to 25% if the first pregnancy was complicated by severe pre-eclampsia and delivery <34 weeks' gestation. When delivery is before 28–weeks' gestation, the risk of recurrent pre-eclampsia is 55%.

Long-term effects of pre-eclampsia on the mother

Women with pre-eclampsia have a 3–4-fold increased risk of developing chronic hypertension and a two-fold increased risk of developing ischaemic heart disease, stroke and venous thromboembolism later in life. These women should undergo annual assessment of cardiovascular risk factors (that is, hypertension, diabetes, obesity, dyslipidaemia and smoking).[10]

Chronic kidney disease

The physiological adaptation of pregnancy is often impaired or absent in women with CKD. The common chronic renal conditions, which include diabetic nephropathy, lupus nephritis and solid organ transplantation, are described below.

Pre-pregnancy counselling

Women of childbearing age with CKD should be made aware of the implications of pregnancy for their long-term renal function and potential risks for the fetus before conception.[11] Pre-pregnancy assessment should include targeting modification of remediable risk factors and optimisation of medications. Consideration should be given to recommending single-embryo transfer if in-vitro fertilisation is required.

Generic management of chronic kidney disease in pregnancy

Maternal and fetal outcomes for women with any nephropathy can be optimised using an MDT approach. The MDT may comprise a consultant obstetrician and nephrologist, as well as other specialists (for example, obstetric physician or urologist), as needed. Management should focus on renal function, as well as features such as hypertension and proteinuria, rather than the specific condition.[12] Women with >3 g protein/24 hours should be prescribed low molecular weight heparin for venous thromboprophylaxis throughout pregnancy and for 6 weeks postpartum. They should be monitored every 4–6 weeks, with further investigations performed as required (for example, renal ultrasound if a urological obstruction is suspected). Inpatient admission should be considered if the woman develops worsening hypertension, deteriorating renal function or proteinuria. Superimposed pre-eclampsia is more frequent and poses a challenge.[13] Vaginal delivery is not contraindicated in pregnant women with renal disease; caesarean section should be performed only for obstetric indications.

Women with CKD stages 1–2 who become pregnant can expect an uneventful pregnancy and good outcome. In contrast, complications such as superimposed pre-eclampsia, preterm labour and fetal growth restriction are more common in women with CKD stages 3–5. Table 4 correlates these complications with worsening renal function. Uncontrolled hypertension, heavy proteinuria (>1 g/24 hours) and recurrent urinary tract infection all impact negatively on pregnancy outcomes independent of CKD stage.

Diabetic nephropathy

Diabetic nephropathy is the most frequently encountered nephropathy in pregnancy. Pre-pregnancy counselling is important, as obstetric outcomes are determined by worsening renal function (see Table 4) and CKD may also progress during pregnancy. Diabetic nephropathy is associated with a 2–4-fold increased risk of pre-eclampsia, preterm delivery and perinatal death.[14] Management includes 5 mg folic acid, ideally three months before conception in view of the increased risk of neural tube defects in women with diabetes; commencement of low-dose 75 mg aspirin from the first trimester to reduce the risk of pre-eclampsia; regular surveillance throughout the antenatal period; optimisation of BP control; and tight glycaemic control.

Polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is a common familial disease. Women with ADPKD who have normal renal function and are normotensive have a high rate of successful uncomplicated pregnancies.[15] Pregnant women with ADPKD with compromised renal function or pre-existing hypertension during pregnancy require careful monitoring for the development of superimposed pre-eclampsia and bleeding into cysts. Pregnancy itself has no adverse long-term effect on renal function in women with ADPKD.

Lupus nephritis

Women should be advised to conceive after a 6-month period of quiescent disease. Extra-renal disease flares are more common in the second and third trimester. Lupus nephritis seems to be more common in the postpartum period.[16,17]

Predictors of poor obstetric outcomes in lupus nephritis include active disease at conception and in early pregnancy, >0.5 g protein/24 hours, CKD stage >3, hypertension and the presence of antiphospholipid antibodies.

Disease flares can be managed with corticosteroids. Maintenance therapy with azathioprine and hydroxychloroquine is safe during pregnancy. Other immunosuppressants, such as tacrolimus and ciclosporin, can be used in pregnancy with appropriate monitoring of drug levels.

Obstetric complications are more common in women with lupus nephritis, and the risks of pre-eclampsia, preterm delivery and low birth weight are higher for this patient population. Differentiating between a flare of lupus nephritis and superimposed pre-eclampsia may be challenging.

Table 2. Common causes and clinical manifestations of acute kidney injury in pregnancy.

Causes	Clinical features
Prerenal	
Hyperemesis gravidum	• Presents in first trimester with persistent nausea, vomiting and ptyalism
Postpartum haemorrhage	• Immediately postpartum
Placental abruption	• Presents in second and third trimester with acute abdominal pain and bleeding
Septic abortion	• Uncommon in UK • Presents with signs of septic shock
Renal	
Pre-eclampsia	• Presents in second and third trimester with new-onset hypertension and proteinuria
Thrombotic thrombocytopenic purpura	• Presents in the antenatal and postpartum period • Presents with headache, irritability, drowsiness • Reduced ADAMTS-13 level
Acute fatty liver of pregnancy	• Occurs in the third trimester • Presents with nausea and vomiting, anorexia, malaise, coagulopathy, hypoglycaemia, lactic acidosis and hepatic derangement
Acute interstitial nephritis	• Related to medication
Post-renal	
Acute urinary retention	• Usually presents in third trimester • Relating to increasing size of the uterus • Relating to the transplanted kidney

ADAMTS = disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13

Reflux nephropathy

Women with known reflux nephropathy should be screened regularly for urinary tract infections and treated promptly. Reflux nephropathy is associated with increased risks of pre-eclampsia (25%) and hypertension (33%).

Urolithiasis and renal colic

Most renal stones present as pain or symptoms of obstruction in the second and third trimester. The frequency of renal stone formation is not affected by pregnancy. Magnetic resonance imaging can be used for diagnosis but should be avoided in the first trimester of pregnancy. Isolated microscopic haematuria in women with normal kidneys does not require investigation in the antenatal period. If haematuria persists in the postpartum period, further investigations are warranted.

Dialysis and pregnancy

Fertility is reduced in women on dialysis, but the overall success of pregnancy for women on dialysis has improved.[18] The risks for the pregnancy include miscarriage, intrauterine death, hypertension, superimposed pre-eclampsia and preterm delivery.[19] A recent retrospective case series of 52 pregnancies found an 87% overall successful rate of delivery; a poorer prognosis was associated with the presence of superimposed pre-eclampsia (in the presence of pre-eclampsia 60% had a successful pregnancy vs 92.9% when there was absence of pre-eclampsia).[20] The rate of pre-eclampsia can approach 50%. Predictors of poor prognosis include age >35 years, dialysis >5 years and delayed diagnosis of pregnancy. Management involves increased frequency (5–7 days a week) and duration of dialysis (>20 hours). Optimisation of BP control and anaemia, which are exacerbated by pregnancy, is important. Erythropoietin, intravenous iron and transfusion requirements may increase.

Renal transplantation and pregnancy

Pre-pregnancy counselling and contraception should be offered to all young women receiving kidney transplants, as fertility can return to normal soon after transplantation. The Kidney Disease: Improving Global Outcomes (KDIGO) guideline on transplantation advises women to delay pregnancy until at least one year after transplantation to allow for stabilisation of graft function on the minimum number of immunosuppressive drugs.[21] Prednisolone, azathioprine, ciclosporin or tacrolimus are safe in pregnancy, but the latter two require frequent monitoring of drug levels. Mycophenolate mofetil is teratogenic and should be changed to azathioprine before pregnancy if possible. The safety of sirolimus, everolimus and rituximab is undetermined.

Pregnancy outcome and effects on renal allograft are dependant on the baseline creatinine level and the presence and severity of pre-existing hypertension, proteinuria and diabetes. Women with simultaneous pancreas–kidney transplants experience more complications (particularly when the pancreas drains into the bladder). Successful outcomes are reported, but such women have increased risks of infection and urinary retention.

Table 3. Pre-eclampsia: common risk factors, symptoms and signs.

Risk factors	Symptoms	Signs
• Age >40 years • Obesity • Previous personal history or family history of pre-eclampsia • Primiparity • Long inter birth interval • Multiple pregnancy • Pre-existing hypertension • Chronic kidney disease • Diabetes/gestational diabetes • Connective tissue disorders and presence of antiphospholipid antibodies	• Headache • Visual disturbances including flashing lights • Epigastric/right upper quadrant pain • Nausea and vomiting • Rapidly increasing/severe swelling of face, hands and lower limbs	• Hypertension • Proteinuria (new onset) • Epigastric/right upper quadrant tenderness • Papilloedema • Clonus (>3 beats is significant) • Convulsions/mental disorientation Biochemical parameters • Elevated serum transaminases • Thrombocytopenia • Haemolysis • Raised creatinine • Raised uric acid

Table 4. Stages of chronic kidney disease and pregnancy outcome. Modified from Davison *et al* (2008); Nelson-Piercy (2010); and Williams and Davison (2008).[3,8,12]

Creatinine prior to conception (µmol/l)	Pre-eclampsia (%)	Preterm delivery (%)	Fetal growth restriction (%)	Long-term renal problems (%)
<125	22	30	25	<3
125–180	40	60	40	<30
>180	60	>90	65	53
Dialysis	75	>90	>90	–

Pregnancies can be complicated by superimposed pre-eclampsia, low birth weight and premature delivery.[22] A recent review of pregnancy outcomes from international transplant registries and single centres report that most pregnancies have a successful outcome.[23]

Summary

Both pre-existing hypertension and renal disease increase the risk of adverse pregnancy outcomes, most notably via an increased risk of superimposed pre-eclampsia, which may be associated with preterm delivery, fetal growth restriction and deterioration in renal function. Optimal outcomes are achieved with informed prepregnancy counselling, transfer to medications that are safe in pregnancy, regular antenatal assessment by a multidisciplinary team to include adequate control of hypertension, and close fetal surveillance.

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