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Chronic renal disease and antenatal care

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A B S T R A C T

In 2018, it is unusual for women with chronic kidney disease (CKD) to be told that pregnancy is not an option. Maternal and foetal outcomes have steadily improved over the last 50 years and a successful pregnancy, resulting in a healthy infant without detrimental to maternal health, is commonplace. Nevertheless, the incidence of adverse outcomes including pre-eclampsia, preterm birth and small-for-gestational age infants is higher for women with CKD than the general population, requiring enhanced monitoring. Furthermore, as women with more advanced renal disease including dialysis recipients are supported in contemplating pregnancy, the importance of an experienced multidisciplinary team (MDT) has become crucial. Pre-pregnancy planning underpins optimisation of pregnancy outcomes.

Introduction

The decision to start a family can be accompanied by a sense of apprehension and this is particularly true for patients with chronic medical conditions. For women with chronic kidney disease (CKD), concerns over the impact of pregnancy on their own health, and CKD on a pregnancy, can accentuate their anxiety.

There have been marked improvements in pregnancy outcomes for women with CKD over the last 50 years, meaning that it is unusual to recommend that women with CKD avoid becoming pregnant (Fig. 1) [1]. Nevertheless, risks of adverse maternal and infant outcomes are higher than in the general population, across the spectrum of severity of renal disease. Pre-pregnancy counselling and additional antenatal care are indicated to optimise outcomes.

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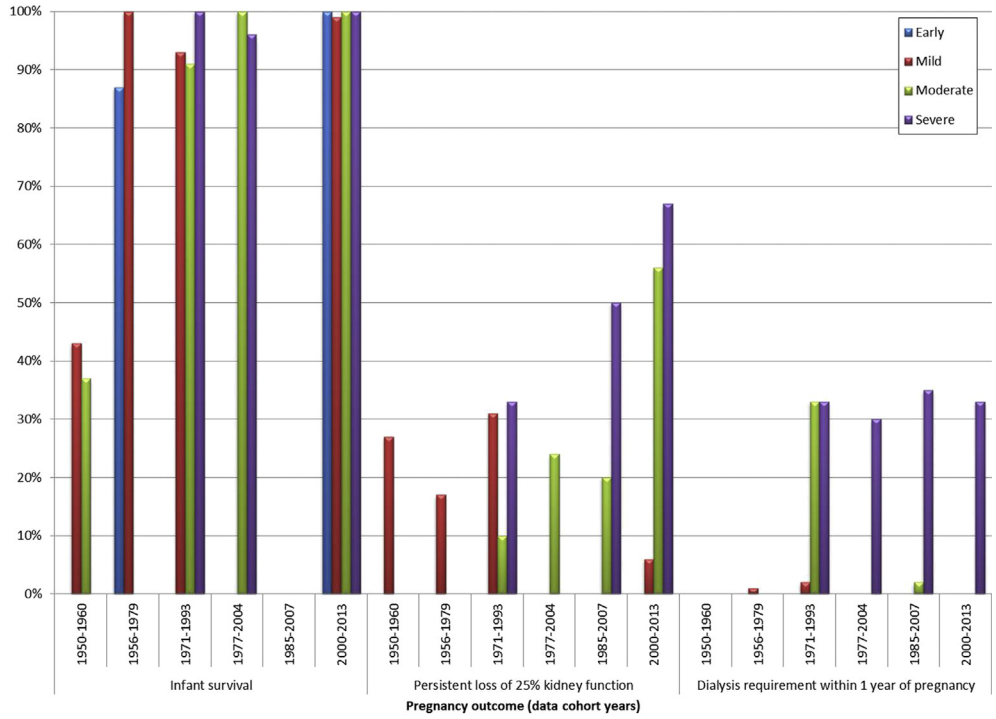

Fig. 1. Pregnancy outcomes by year of data collection and severity of renal disease. Early (baseline urea <7 mmol/l, creatinine <90 μmol/l, estimated glomerular filtration rate (eGFR) > 90 ml/min/1.73 m^2); mild (baseline urea 7–14 mmol/l, creatinine 90–125 μmol/l, eGFR 60–90 ml/min/1.73 m^2); moderate (baseline urea 14–21 mmol/l, creatinine 125–180 μmol/l eGFR 30–60 ml/min/1.73 m^2); severe (baseline urea >21 mmol/l, creatinine >180 μmol/l, eGFR <30 ml/min/1.73 m^2) [19,45,72–74].

Defining chronic kidney disease

CKD is defined as decreased excretory renal function, haematuria or proteinuria persisting for more than 3 months, anatomical abnormalities (such as reflux nephropathy or renal dysgenesis), or genetic variants associated with renal disease (such as Alport syndrome or polycystic kidney disease). Outside of pregnancy, severity of CKD can be staged based on estimated glomerular filtration rate (GFR) and urine albumin excretion rate, usually quantified by a urine albumin:creatinine ratio (uACR). The Kidney Disease Improving Global Outcomes (KDIGO) CKD classification stratifies stages according to patients' risk of developing progressive renal dysfunction, cardiovascular disease and premature mortality (Table 1).

Diagnosing CKD during pregnancy is challenging. Estimated GFR is a calculated value based on serum creatinine, age, gender and ethnicity. Neither the modification of diet and renal disease (MDRD) nor CKD-EPI formulae can be relied upon during pregnancy for accurate representation of kidney function, however. Both underestimate function (as measured by 'gold standard' inulin clearance) by about 20%, but not in a predictable manner. Weight-based formulae, such as the Cockcroft and Gault equation, are similarly unreliable, tending to overestimate kidney function by up to 40%. Measured creatinine clearance using paired 24 h urine collections and serum creatinine estimation does correlate closely to inulin clearance and can be used during pregnancy. Results are prone to inaccuracies caused by incomplete urine collections and timing of blood sampling however [2,3].

If pre-pregnancy estimated GFR is not available, CKD may be suspected in women with serum creatinine greater than approximately 80 μmol/l during pregnancy in the absence of causes of acute kidney injury. Clarification with serial readings and 24-hour urine creatinine clearance should be considered.

Table 1
Kidney Disease: Improving Global Outcomes classification of chronic kidney disease (CKD), with risk of progressive renal dysfunction, cardiovascular disease or premature mortality.

			Persistent albuminuria (albumin:creatinine ratio)		
			<3 mg/mmol	3–30 mg/mmol	>30 mg/mmol
			A1	A2	A3
Estimated GFR (ml/min/1.73m^2)	>90	G1	Low[a]	Moderate	High
	60–89	G2	Low[a]	Moderate	High
	45–59	G3a	Moderate	High	Very high
	30–44	G3b	High	Very high	Very high
	15–29	G4	Very high	Very high	Very high
	<15	G5	Very high	Very high	Very high

[a] In the absence of haematuria, anatomical abnormalities or pathogenic genetic variants, individuals with estimated glomerular filtration rate (GFR) > 60 ml/min/1.73 m^2 should not be defined as having CKD.

Pre-pregnancy counselling

Consensus statements published in 2018 recommend that women with CKD should be offered pre-pregnancy counselling by a MDT including an obstetrician, renal/obstetric physician and a specialist midwife [4]. Counselling is not always possible because pregnancy may not be a planned event; however, the aims of pre-pregnancy counselling are to:

- discuss optimal timing for a planned pregnancy
- assess and optimise disease stability
- change agents that are not safe or ideal for use in pregnancy
- outline the risks of adverse maternal and infant outcomes, and discuss pregnancy expectations
- discuss assisted conception options, surrogacy and adoption when appropriate

Observational data suggest that patients find pre-pregnancy counselling useful. A survey in a UK specialist clinic reported that 90% found such consultations informative and 92% felt that the process had helped them to make a decision about pursuing pregnancy [5]. Although intuitive that better-planned pregnancies should lead to better outcomes for women with CKD, there is inadequate data to confirm that this is the case.

Fertility and conception

Fertility decreases with progressive severity of CKD. The reasons for this are multifactorial.

First, CKD affects the hypothalamic-pituitary-ovarian access. Prolactin levels are increased in the majority of patients with advanced CKD; a result of decreased renal clearance and suppressed dopaminergic activity (Fig. 2) [6,7]. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels are elevated and, particularly in women receiving dialysis, fail to display the cyclical changes in concentration that are required for ovulation [8]. Menstrual disturbances are common, reported in 76% of women receiving conventional haemodialysis [9].

Second, ovarian reserve is lower in women with CKD than controls. Follicle count correlates with serum anti-Müllerian hormone (AMH) and both follicle count and AMH are lower in women with pre-dialysis CKD. The utility of AMH measurement in women with CKD is unclear at present, however, because treatment modality and degree of renal function appear to affect values to a greater degree than follicle count and age [10–12].

Thirdly, previous or current medication may affect fertility. Cumulative exposure to cyclophosphamide - commonly used in the treatment of lupus nephritis or vasculitis – diminishes ovarian reserve. Mycophenolate derivatives, commonly prescribed for lupus nephritis or renal transplantation, are very effective immunosuppressant agents with a generally favourable side effect profile, however first trimester exposure is associated with a 25% risk of significant congenital abnormalities and 50% miscarriage rate [13,14]. Effective contraception is mandatory for women taken these agents.

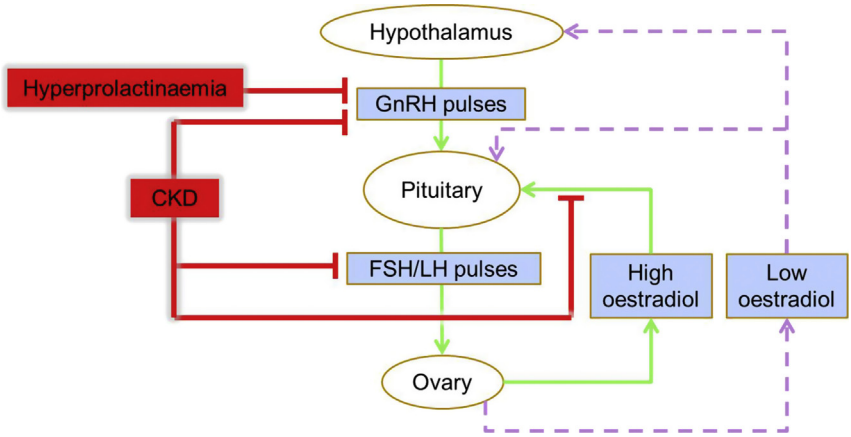

Fig. 2. CKD inhibits the hypothalamus-pituitary-ovarian access by inhibiting FSH and LH pulses and preventing ovulation. Hyperprolactinemia suppresses gonadotropin secretion. CKD, chronic kidney disease; FSH, follicle stimulation hormone; LH, luteinizing hormone; GnRH, gonadotropin releasing hormone [7].

Finally, libido is reduced in patients with CKD, fatigue is greater (as a result of anaemia, vascular disease or uraemia) and psychosocial concerns regarding personal health, finance and relationships are common [15].

Other factors to consider when discussing fertility include the aetiology of renal disease, other comorbidities and maternal age. For example, diabetes mellitus, antiphospholipid syndrome, obesity and hypertension may all affect a woman's ability to conceive. Women with genetic renal diseases (such as polycystic kidney disease) should be offered referral to clinical genetics and assisted reproduction specialists to discuss the option of pre-implantation genetic diagnosis.

Despite all the above, most women of childbearing age with mild to moderate CKD have regular menstrual cycles and the capacity to conceive. For those at the highest risk of subfertility, pre-pregnancy counselling should include discussion of assisted conception, surrogacy and adoption options.

Timing of pregnancy

The optimum time to plan a pregnancy will be determined by social and relationship factors rather than their disease status for most women with CKD; however there are some scenarios when specific advice is required.

Following renal transplantation, published advice has been to wait for one or two years after transplantation before considering conception [4,16]; the rationale being that immunosuppressive medication can be weaned down to minimum doses and the risk of acute rejection is lower at this stage, acknowledging that treatment options for acute rejection are limited during pregnancy. Women receiving mycophenolate agents need time to consider the risks of changing to alternative immunosuppression, such as azathioprine (see Medication management below) [13,14,17]. There are numerous case reports of successful pregnancies occurring within 12 months of transplantation without significant complications, however, so termination of pregnancy is not recommended for women who conceive in the first year post-transplant, but risks need to be explained.

Women with unstable immunological disease – transplant rejection, lupus flare or active vasculitis – and those treated for a current relapse of nephrotic syndrome should wait until their disease is back under control on minimised 'pregnancy-safe' immunosuppression. For example, compared with patients with systemic lupus erythematosus (SLE) but no history of nephritis, active lupus nephritis at the time of booking was associated with a 17.7-fold increased risk in preterm delivery compared with a 5.3-fold increased risk for patients with previous renal flares but controlled quiescent disease [18].

Women receiving medication associated with a teratogenic or fetotoxic risk – most notably mycophenolate agents and renin-angiotensin-aldosterone system antagonists, respectively – will require counselling and advice on when to stop these and consider alternatives (see Medication management below).

Pregnancy outcomes are far better for women following successful renal transplantation than for those with advanced CKD [19,20]. Therefore, most women with progressive CKD 4 to 5 and those receiving dialysis should be advised to consider waiting for transplantation prior to planning a pregnancy to improve the likelihood of success. Exceptions to this would be women for whom transplantation is not possible (due to vascular or urological issues, lack of organ availability, immunological sensitisation or patient choice) and women with slowly progressive or non-progressive CKD who are approaching the limits of their reproductive age. In these cases, options should include in-depth counselling of the potential risks of a pregnancy to the mother and baby, but with an acknowledgement that a renal-obstetric MDT – including renal medicine, maternal/obstetric medicine and specialist midwife expertise – would be there to support them through a pregnancy if they felt that was their right choice.

If timing were not felt to be right for a pregnancy, women with CKD should receive advice regarding appropriate contraception. Comprehensive reviews on this topic have recently been published [21,22].

Medication management

It is essential that pre-pregnancy counselling considers a woman's current medication and suitability to continue these during a subsequent pregnancy. Balanced decisions need to be made between protecting a developing foetus from potential adverse effects of treatments versus destabilising maternal health by changing or withdrawing treatment options.

Hypertension medication

Effective treatment of hypertension is a critical strategy in preserving renal function in patients with CKD. Current guidance from Kidney Disease: Improving Global Outcomes recommends targeting blood pressure <140/90 mmHg for patients with CKD, or <130/80 mmHg for patients with CKD and albuminuria [23]. These, and other, guidelines are subject to review following publication of the SPRINT trial, however, that reported fewer cardiovascular endpoints and deaths in non-diabetic patients with an increased cardiovascular risk treated to systolic blood pressure <120 mmHg than those treated to <140 mmHg [24].

There are no published data to confirm the optimal blood pressure target for women with CKD during attempted conception and during pregnancy. Results from the Control of Hypertension in Pregnancy (CHIPS) trial support the safety of blood pressure treatment during pregnancy to reduce the incidence of severe hypertension (>160/110) by targeting diastolic blood pressure 85 mmHg in women taking antihypertensive medication (albeit without CKD) without causing increased pregnancy loss or maternal morbidity [25]. Consensus guidelines for women with CKD recommend a target blood pressure of 120–139/70–85 mmHg during pregnancy [4].

There is extensive experience of the safety of labetalol, methyldopa and nifedipine during pregnancy. Women with CKD receiving treatment for hypertension should be converted to one of these agents prior to pregnancy when feasible. In the UK, the National Institute for Health and Care Excellence (NICE) recommend that labetalol is used as the first line treatment [26] and labetalol was also the first line treatment of choice in the CHIPS trial [25]. All three agents require multiple daily dosing regimens (unless sustained release preparations are available) and methyldopa should probably be avoided in patients prone to depressive disorders.

Amlodipine is a very commonly used agent for the treatment of hypertension in CKD. Anecdotal reports have not raised concerns about use in pregnancy but data are limited. Amlodipine crosses the placenta but there have not been any confirmed reports of teratogenicity [27,28]. At present, there is inadequate data to confirm amlodipine's safety in pregnancy. Diltiazem also lacks safety data to support its use during pregnancy, with some evidence of toxicity in animal studies, and is therefore not recommended during pregnancy.

Thiazide diuretics (for example, bendroflumethiazide and hydrochlorthiazide) should be discontinued prior to pregnancy, if feasible, due to reported foetal effects of neonatal thrombocytopenia and jaundice and increased maternal nausea and vomiting. The theoretical risk of intravascular fluid depletion caused by thiazide diuretics leading to decreased placental perfusion and lower birth weight infants was not identified in clinical trials [29–31]. Loop diuretics (for example, furosemide or bumetanide) are not generally used for the treatment of hypertension but may be required (and can be used) to control oedema in advanced CKD or proteinuric patients, and have less reported adverse foetal effects than thiazides.

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB)

Drugs that block the renin-angiotensin system – ACEi and ARB – are renoprotective and antihypertensive for patients with proteinuric renal disease and, hence, commonly prescribed to women with CKD.

Angiotensin-2 has a prominent role in the normal development of the definitive renal system (metanephros) and there is clear evidence of a fetotoxic effect of ACEi or ARB exposure in the second and third trimesters of pregnancy. Renal failure, oligohydramnios, growth restriction, pulmonary vascular disease, limb and skull defects and foetal death are described with 50% of children exposed to these agents in the second or third trimester of pregnancy experiencing a poor outcome. Adverse events appear to be more common with ARB exposure than ACEi exposure [32].

Since the development of the definitive renal tract is relatively late *in utero* compared with other organ synthesis, it had been initially assumed that first trimester exposure to ACEi or ARB should not lead to adverse foetal renal effects. This assumption was challenged by Cooper *et al* in 2006 in an observational study of 29507 infants in Tennessee. They reported major congenital abnormalities in 7.1% of infants exposed to ACEi in the first trimester only, compared with 1.7% in infants exposed to other antihypertensive agents and 2.6% in those on no antihypertensive treatment [33]. Two larger studies followed, from California and District of Columbia, that facilitated statistical adjustment for additional factors associated with congenital abnormalities. As shown in Table 2, an increased incidence of congenital abnormalities was identified in all patients receiving treatment for hypertension but, after adjustment for confounding variables, the risk associated with first trimester exposure to ACEi was no greater than that with other blood pressure treatments, raising the possibility that hypertension itself (or its underlying aetiology) is teratogenic [34,35].

To avoid unintended second trimester exposure to ACEi or ARBs, women with CKD on these agents should be transitioned to alternative agents prior to pregnancy when this is feasible. Exceptions to this would include women for whom the risk of ACEi or ARB withdrawal would lead to a significant detriment to their renal health prior to successful conception, notably those with proteinuria including diabetic nephropathy, idiopathic glomerulopathies and hereditary nephritis. Similarly, women at risk of subfertility due to age, previous treatment with cyclophosphamide or advanced CKD, may have a

Table 2
Risk ratio for major congenital abnormality following first trimester exposure to angiotensin converting enzyme inhibitors (ACEi) and other antihypertensive agents.

	n			Risk ratio for congenital abnormalities		
	ACEi exposure	Other antihypertensive exposure	Controls	ACEi *vs* controls	Other antihypertensive *vs* controls	ACEi *vs* other antihypertensives
Cooper et al. (2006)	209	202	29 096	2.71 (1.72–4.27)	0.66 (0.25–1.75)	–
Li et al. (2011)	755	17 507	416 218	1.63 (1.15–2.32) 1.20 (0.84–1.72)[a]	1.31 (1.04–1.64) 1.22 (0.97–1.54)[a]	–
Bateman et al. (2017)	2631	15 884	1 351 831	1.82 (1.61–2.06)		1.35 (1.13–1.61) 0.89 (0.75–1.06)[b]

[a] Ratio adjusted for pre-existing diabetes, maternal age, ethnicity, parity and maternal weight.
[b] Ratio adjusted for pre-existing diabetes, chronic hypertension, dyslipidaemia, congestive heart failure, ischaemic heart disease, renal disease, maternal weight, illicit drug or alcohol use, tobacco use, multiple gestation, additional maternal medications, recent pre-pregnancy healthcare system utilisation frequency and distinct comorbidities [33–35].

period of years prior to conceiving during which renal parenchymal exposure to uncontrolled proteinuria as a result of ACEi or ARB withdrawal could exacerbate progression of CKD. For these women, consensus guidelines recommend that pregnancy tests are performed at least monthly if adequate contraception is withdrawn, and that ACEi and ARBs are discontinued immediately if pregnancy is confirmed [4].

Immunosuppression

Amongst agents commonly used to suppress the immune system in autoimmune renal disease or renal transplantation, extensive experience has supported the safety of prednisolone, azathioprine, hydroxychloroquine and the calcineurin inhibitors ciclosporin and tacrolimus during pregnancy. Significant pharmacokinetic changes occur during pregnancy, however, so it is prudent to inform women with CKD on such agents (and their other care providers) that enhanced monitoring will be required during a pregnancy. This is discussed in more detail below.

Mycophenolate derivatives (mycophenolate mofetil or mycophenolic acid) are not suitable, however. First trimester exposure was reported to lead to a 49% risk of miscarriage, with 23% of surviving infants born with significant structural abnormalities – cleft lip and palate, microtia, skeletal defects and congenital heart disease [13]. Pre-pregnancy counselling allows an opportunity to discuss the risks of altering immunosuppression regimes. Given the high early miscarriage rates and early teratogenic effects of mycophenolate, it is not advisable for patients to continue on therapy until pregnancy is confirmed (as compared to ACEi above). Manufacturer and licensing authority guidance recommends at least 3 months off mycophenolate prior to attempted conception to minimise foetal exposure or genotoxicity. In addition to this, confirmation of disease or transplant function stability on a new treatment regimen (using azathioprine instead of mycophenolate, for example) must be established so, in practice, it is prudent to recommend a six-month period of continued contraception after discontinuing mycophenolate.

There are case reports describing the use of cyclophosphamide [36], sirolimus [17,37,38] and rituximab [39] during pregnancy with successful outcomes; however, there is inadequate evidence to support their safe use and, in the case of cyclophosphamide, confirmed evidence of teratogenicity with first trimester exposure is lacking [40,41].

Infant outcomes

The likelihood of women with CKD having a successful pregnancy – that is, delivery of a live infant without life-affecting congenital abnormalities – has improved considerably over the last 5 decades. It is unusual to advise women with CKD that pregnancy is not an option; however, there is an increased risk of adverse foetal outcomes across the range of CKD severity stages that should be discussed (Fig. 3).

As expected, the risk of adverse foetal outcomes increases with the severity of maternal renal disease. Notably, however, women with normal excretory renal function but other evidence of CKD (for example, structural renal disease or haematuria/proteinuria) has a greater incidence of adverse outcomes than women without CKD. In an observational cohort study including 370 women with CKD stage 1 (baseline eGFR>90 ml/min/1.73 m^2), the rate of Caesarean section (28% vs 48%), preterm delivery (<34 weeks) (1% vs 7%) and need for neonatal ICU (NICU) admission (2% vs 10%) were all higher than low risk controls [42].

Although preterm delivery is commonly reported across stages of CKD, this is rarely a result of spontaneous preterm labour. More often, concern from clinicians prompts induction of labour or Caesarean section following confirmed or suspected imminent problems. Indications for delivery were concerns regarding maternal health in 65% of cases, concerns regarding foetal health in 20% and concerns regarding both mother and baby in 7.5% [43].

The aetiology of maternal renal disease has less of an effect on foetal outcomes than the degree of renal functional impairment, with some exceptions.

Women with known genetic renal disease should receive counselling regarding the risk of transmission to their children. The commonest monogenic disorders in women with CKD are autosomal dominant polycystic kidney disease (ADPKD) and hereditary nephritis resulting from collagen IV subunit mutations (Alport syndrome and thin basement membrane nephropathy). There is a less

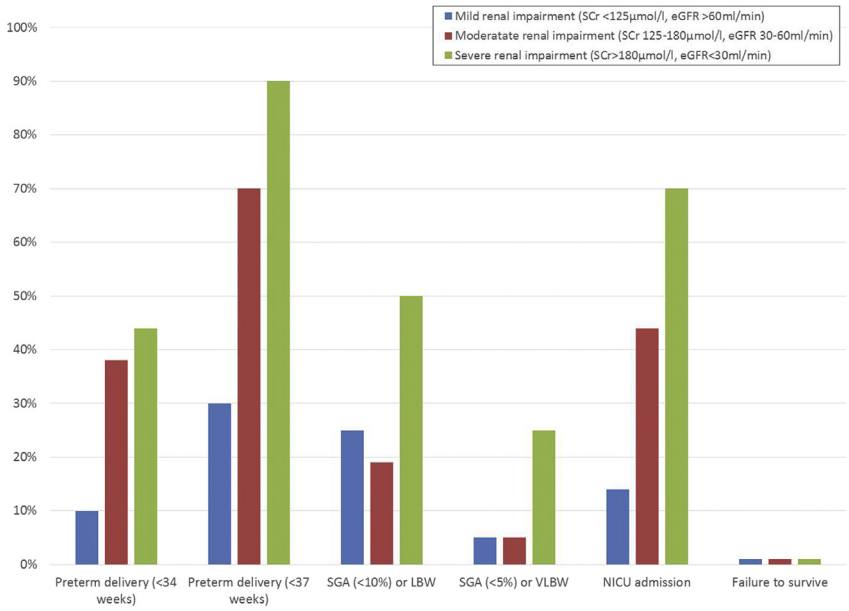

Fig. 3. Risk of adverse foetal outcomes. Data summarised from Refs. [19,42]. SCr, serum creatinine; eGFR, estimated glomerular filtration rate; SGA, small for gestational age; LBW, low birth weight (<2500 g); VLBW, very low birth weight (<1500 g); NICU, neonatal intensive care unit.

defined inheritance pattern for women with congenital abnormalities of the kidney and urinary tract (CAKUT) although familial clustering occurs in some kindreds.

Multisystem diseases that include renal impairment within their syndrome may affect pregnancies independently of any renal dysfunction. Diabetes mellitus and SLE are prime examples, and a multidisciplinary approach to counselling is required to explore the additional complexity of managing pregnancy with these conditions.

Maternal outcomes

In years gone by, women with CKD may have been routinely advised to avoid pregnancy due to the risk to their health [44]. From the 1950s and 1960s, case series of women with advanced renal dysfunction usually resulted in maternal mortality [45] and it was not until the 1970s and 1980s that it was appreciated that pregnancy could be a high-risk but realistic option for women with CKD [1]. By the start of the 21st century, women on dialysis were not only being 'permitted' to consider a pregnancy, but also actively supported to do so [46].

The risks to women with CKD due to pregnancy are accelerated progression of renal disease, destabilisation of the renal disease due to medication changes, pre-eclampsia and associated complications including uncontrolled hypertension, sepsis due to urinary tract infection and venous thromboembolism (VTE).

Pregnancy-associated loss of renal function

Pregnancy induces profound changes in systemic and renal vascular physiology from as early as 6 weeks gestation. Renal arteriolar vasodilation, mesangial relaxation and increased cardiac output result in an increase in GFR of up to 50% in healthy pregnancies. These adaptations contribute to a high volume, low pressure maternal circulation capable of preserving placental perfusion in times of relative dehydration and maternal perfusion in the event of significant peripartum haemorrhage [47]. In women with CKD, these adaptations in renal physiology may be impaired by inadequate 'renal

reserve' – glomerular sclerosis, maximised arteriolar vasodilation, arteriolosclerosis, renin-angiotensin system over-activation. Rather than creating a low pressure, high volume circulation, placenta-initiated endocrine effects can induce an 'overloaded' high pressure maternal circulation with glomerular hyperfiltration and possible renal damage.

The risk of pregnancy-induced loss of renal function is low with preserved baseline renal function. Conversely, for 1 in 3 women with CKD stage 4 or 5 (baseline eGFR <30 ml/min/1.73 m^2), pregnancy will result in a requirement for dialysis within 12 months of delivery (Fig. 4). Renal transplants appear to be more sensitive to the physiological changes of pregnancy than native kidneys, possible due to the altered anatomy and denervation, although a persistent loss of renal transplant function is rare in patients with baseline creatinine <150 μmol/l [48].

Urinary tract infection (UTI)

UTIs are common during pregnancy, with or without CKD. For women with renal tract anatomical abnormalities, a history of recurrent infections or immunosuppression, the incidence is particularly high. The risk of lower urinary tract infections ascending to cause pyelonephritis is also increased during pregnancy. Reports from the 1960s identified a correlation between episodes of UTI, spontaneous preterm labour and infant mortality prompting advice to screen for, and treat, asymptomatic bacteriuria during pregnancy [49]. More recent results suggest that the impact of treating asymptomatic bacteriuria has less of an impact on foetal outcomes than previously suggested, however the absolute risk of adverse outcomes was much lower [50].

Irrespective of the impact of bacteriuria, UTI or pyelonephritis on pregnancy progression, advice that women at increased risk of infection should be screened and treated for asymptomatic bacteriuria during pregnancy seems sensible for women with CKD to minimise the risk of overt or covert ascending infection and renal parenchymal damage.

Pre-eclampsia

Pre-eclampsia is a pregnancy-specific syndrome of new onset hypertension in the second half of pregnancy, accompanied by either end-organ damage (such as impaired renal function, liver

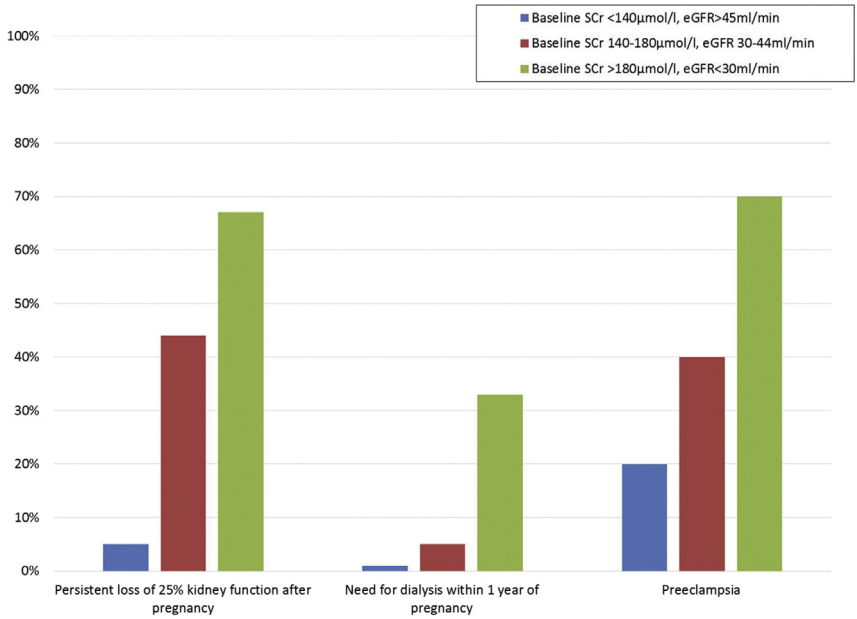

Fig. 4. Risk of adverse maternal outcomes in women with CKD [19,73–75]. SCr, serum creatinine; eGFR, estimated glomerular filtration rate.

abnormalities, neurological manifestation or haematological abnormalities), foetal growth restriction or new onset proteinuria [51]. Defining pre-eclampsia in women with CKD is therefore challenging since women will often have impaired renal function, proteinuria and/or hypertension prior to pregnancy. Definitions of 'superimposed pre-eclampsia' are less precise. Differentiating pre-eclampsia from progressive CKD or a flare of (for example) lupus nephritis can be impossible sometimes. Extra-renal manifestations of pre-eclampsia (such as liver involvement) or lupus (such as skin and joint involvement) may be helpful. Changes in serum angiogenic markers (soluble fms-like tyrosine kinase-1 (s-Flt-1) and placental growth factor) may also help, but their role in routine clinical practice is yet to be determined [52].

Pre-eclampsia (or superimposed pre-eclampsia) is, nevertheless, recognised to occur more frequently in patients with CKD than healthy controls. The pathophysiology of pre-eclampsia is likely to initiate from multiple different aetiologies, coalescing in a common pathway resultant from placental hypoperfusion and ischaemia. The diminished physiological adaptation to pregnancy seen in women with CKD is a plausible route by which placental blood flow may be reduced and the syndrome of pre-eclampsia initiated. Reported incidence of pre-eclampsia increases with CKD severity (Fig. 4) and may occur early - up to a third of cases being prior to 34 weeks gestation in one study [53].

Clinically overt long term renal damage is unusual following pre-eclampsia in women with normal renal function. For most women with CKD, acute kidney injury (AKI) as a result of pre-eclampsia tends to resolve to baseline following delivery, although this recovery may take months.

Clinician suspicion that pre-eclampsia is imminent – based on progressive increases in blood pressure, proteinuria or serum creatinine – is a common indication for induction of labour or Caesarean section in women with CKD [43]. However it is unclear whether some or all of these situations reflect the physiological effects of normal pregnancy on impaired kidneys – renal plasma flow reduces to pre-pregnancy levels around term - or the placenta-derived syndrome of pre-eclampsia.

Antenatal care

Confirmation of successful pregnancy is usually straightforward in women with CKD and preserved renal function. For women with advanced CKD, including those requiring dialysis, serum beta-human chorionic gonadotrophin (β-HCG) levels are elevated as compared to healthy controls at equivalent gestational age due to diminished urinary clearance [54,55]. This is of clinical significance when a serum β-HCG suggesting 8 weeks gestation is not confirmed by an identified foetal heart rate on ultrasound screening. Missed miscarriage, intrauterine demise or ectopic pregnancy may be considered in this circumstance but not assumed, and serial β-HCG measurement and scans over 1–2 weeks should be performed.

Women receiving dialysis may be oligo-anuric hence urine β-HCG point-of-care tests are neither reliable nor feasible options for pregnancy confirmation.

First trimester

Upon confirmation of pregnancy in women with CKD, published consensus guidelines recommend the early involvement of a renal-obstetric MDT. Geographical considerations, resource availability and the complexity of maternal disease will determine the practicalities of these arrangements [4].

First trimester care involves re-iteration of advice given in pre-pregnancy counselling, confirmation of medication management plans, initiation of prophylactic treatments when appropriate and establishment of follow-up arrangements and responsibilities for the forthcoming months (Table 3). It is important to establish communication between women with CKD, community midwifery and medical teams, local maternity units (where applicable), pharmacists and the renal-obstetric MDT.

Women inadvertently exposed to potentially teratogenic medications – particularly mycophenolate derivatives – should receive additional counselling and assessment of the risks and options. Early involvement of foetal medicine experts should be considered.

International guidelines recommend aspirin (60–152 mg daily) for all women with CKD, particularly when taken at night, from 12 weeks gestation until delivery to reduce the risk of pre-eclampsia by approximately 25% [56,57]. A recent meta-analysis suggests that aspirin doses >100 mg per day

Table 3
First trimester renal-obstetric care checklist.

Confirmation of pregnancy	• Consider serial transvaginal viability scans for women with severe renal impairment, elevated serum β-HCG and absent foetal heart beat
Medication management	• Discontinue ACEi and ARB upon confirmation of pregnancy (if not before) • Discontinue non-essential medication that has uncertain safety profile during pregnancy (for example, statins for primary cardiovascular disease prevention) • Discontinue anti-hypertensive treatments and replace, if necessary with labetalol, methyldopa or nifedipine to maintain blood pressure control (<140/90 mmHg) • Optimise immunosuppression. Refer for specialist foetal medicine input if inadvertent first trimester exposure to mycophenolate derivatives
Assess baseline disease activity and severity	• Blood pressure control • Proteinuria quantification (spot urine albumin:creatinine or protein:creatinine ratio adequate) • Serum urea and electrolytes, albumin. • Consider 24-hour urine collection for creatinine clearance • Full blood count and haematinics • Markers of immunological activity in women with autoimmune disease (anti-nuclear antibody, double stranded DNA, anti-neutrophil cytoplasmic antibody, C-reactive protein) • Urine microscopy and culture
Prophylactic therapies	• Initiate aspirin 60–152 mg daily from 12 weeks gestation to reduce the risk of pre-eclampsia by 25% • Initiate calcium supplements for women with low calcium intake diets • Consider prophylactic antibiotic therapy in women (a) on these treatments prior to pregnancy, (b) women at very high risk of UTI due to immunosuppression or anatomical issues or (c) women with proven bacteriuria episode(s) in early pregnancy • Consider low molecular weight heparin prophylaxis against VTE for women with nephrotic syndrome, and also for women with lesser degrees of proteinuria and additional risk factors for VTE
Schedule of care	• Outline frequency and location of monitoring appointments dependent on geography, service set-up and severity of maternal disease

β-HCG, beta subunit human chorionic gonadotrophin; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ANA, anti-nuclear antibody; VTE, venous thromboembolism.

commenced prior to 16 weeks gestation are required to reduce the risk of preterm pre-eclampsia [58], and a 62% relative risk reduction in preterm (<37 weeks) pre-eclampsia (1.6% versus 4.3%) was reported with 150 mg aspirin commenced between 11 and 14 weeks gestation [59].

Women with CKD and hyperemesis require enhanced monitoring of fluid status and biochemistry. Consequent fluid depletion and AKI can lead to significant electrolyte disturbance in the context of reduced renal reserve.

Later pregnancy

Monitoring women with CKD during the second and third trimesters of pregnancy should be individualised based on the previous pregnancy progression, severity of maternal disease and trajectories in biophysical parameters. In practice, most women benefit from clinical review at least monthly from 20 weeks onwards, with more frequent visits for patients with adverse trajectories of blood pressure, proteinuria or renal function. As with all pregnancies, emphasis is on maintaining maternal health and reviewing foetal development to identify complications early and optimise timing of delivery. As discussed during pre-pregnancy counselling, the likelihood of adverse maternal and infant outcomes is predominantly dependent on maternal renal function, outlined in Table 4 and Figs. 3 and 4.

Maternal health

Women with relatively preserved baseline renal function (estimated GFR>45 ml/min/1.73 m^2, serum creatinine <125 μmol/l) are unlikely to sustain a loss of kidney function as a result of pregnancy [19]. Monitoring serum biochemistry every 4–8 weeks during pregnancy is reasonable, however, to assess renal reserve and to facilitate early identification of AKI that might represent impending pre-eclampsia or relapse of an underlying renal disease (Fig. 4).

Table 4
Estimated frequency of infant and maternal outcomes.

	Early preterm birth (<34 weeks)	Preterm birth (<37 weeks)	SGA (<10th centile) or LBW (<2500 g)	NICU admission	Caesarean Section	Persistent loss of >25% renal function post-partum	Renal replacement therapy within 12 months of pregnancy
CKD stage 1–2	16%	35%	15%	14%	50%	<1%	<1%
CKD stage 3a	30%	65%	18%	30%	70%	6%	<1%
CKD stage 3b	35%	80%	25%	45%	75%	56%	<5%
CKD stage 4–5	45%	90%	50%	70%	75%	67%	33%

CKD, chronic kidney disease; SGA, small-for-gestational age; LBW, low birth weight; NICU, neonatal intensive care unit.
Data summarised from Refs. [19,42,73–75].

Alterations in renal blood flow, glomerular permeability and tubular reabsorption and secretion create a doubling of protein excretion in normal pregnancy although physiological effects rarely lead to >300 mg/day losses [60,61]. The effect of pregnancy on women with proteinuric CKD is more likely to be clinically significant. Physiological changes plus the withdrawal of anti-proteinuric ACEi or ARB can result in asymptomatic low level proteinuria progressing to nephrotic range (urine protein:creatinine ratio >300 mg/mmol, 24 h protein excretion > 3 g/day). Nephrotic syndrome (heavy proteinuria plus hypoalbuminemia plus oedema) is uncomfortable and associated with high infection risk and VTE. Urinary protein excretion can be measured from spot urine samples during pregnancy [62,63] and should be performed every 4–8 weeks in women with CKD – more frequently in those with baseline proteinuria. Increasing proteinuria may be an indication for enhanced monitoring of foetal growth (see below), closer assessment of maternal fluid status and consideration of VTE prophylaxis with low molecular weight heparin (LMWH). Loop diuretics can be initiated if progressive symptomatic peripheral oedema or orthopnoea develop.

The benefit of LMWH VTE prophylaxis for women with sub-nephrotic proteinuria is debatable. There is a lack of consensus on a general approach with some practitioners advocating treatment for all women with urine protein:creatinine ratio >100 mg/mmol and others only recommending treatment for women with overt nephrotic syndrome and additional VTE risk factors. In the absence of data to confirm the best strategy, it has been suggested that proteinuria is included in VTE risk assessment tools utilised at local centres and a shared decision on treatment made with patients based on approach to risk and tolerance of treatment.

Target blood pressure during pregnancy in women with CKD has long been a topic of debate, balancing the known risks of under-treated hypertension on CKD progression against the risks of drug toxicity and effect on foetal growth. Since publication of the CHIPS trial, increased confidence in the safety of reducing blood pressure to target levels during pregnancy resulted in consensus statements recommending a target of 120–139/70–85 mmHg during pregnancy [4,25].

Given the increased risk of pre-eclampsia and the challenges in defining 'superimposed pre-eclampsia' in women with CKD, a lower threshold of investigation, admission and monitoring is required during the second half of pregnancy. Imminent or suspected pre-eclampsia is the commonest maternal indication for preterm delivery [43].

Anaemia management may require parenteral iron supplementation and erythropoietin. Urine culture for asymptomatic bacteriuria should be performed at each visit, and at least monthly in women at high risk of UTI.

Foetal health

A detailed anomaly scans at about 20 weeks gestation may identify inheritance of parental genetic traits including CAKUT or, rarely, ADPKD. There is an increased incidence of low birth weight and growth restriction (see Fig. 3); hence, foetal growth scans from approximately 28 weeks' gestation are recommended, especially in women with hypertension, proteinuria and/or impaired excretory renal function (baseline eGFR <60 ml/min/1.73 m^2).

Uterine artery dopplers at 23–24 weeks can assist in assessment of placental perfusion. Increased utero-placental vascular resistance can affect the amplitude and character of doppler traces with increased resistive index (the ratio of peak to nadir blood flow) and appearance of a diastolic 'notch'

thought to be a result of inflexible distal artery recoil from the systolic pressure wave. These findings help identify patients at higher risk of subsequent pre-eclampsia, intrauterine growth restriction and preterm delivery. Their utility and interpretation are best assessed by maternal medicine MDT members.

Delivery and the puerperium

CKD is not an indication for elective preterm induction or Caesarean section. Timing and method of delivery will normally be determined by obstetric indications, markers of foetal progression or evidence of deteriorating maternal health.

Women with hypertension (but not CKD) may benefit from elective delivery at 38^{+0} to 39^{+6} weeks to reduce the incidence of stillbirth and severe neonatal mortality [64]. Extrapolating this approach to women with proteinuric non-hypertensive CKD or non-proteinuric non-hypertensive CKD lacks supportive evidence; however, given the increased incidence of pre-eclampsia and adverse foetal outcomes identified (even in women with CKD stages 1–2 [42]), it is reasonable to consider early term delivery or heightened surveillance pending randomised controlled trial evidence.

During delivery, non-steroidal anti-inflammatory drugs (NSAIDS) and ergot derivatives should be avoided. Paracetamol, cautious use of opiates and spinal/epidural anaesthesia are appropriate. Accurate fluid balance and regular clinical assessment of fluid status are essential to minimise the risk of acute kidney injury. For women with CKD and (superimposed) pre-eclampsia, and those with more severe renal disease (baseline eGFR <30 ml/min/1.73 m^2) a low threshold for high dependency care unit admission is recommended.

Blood transfusion can be life-saving in the event of severe peripartum haemorrhage, but careful thought should be given before offering a blood transfusion to women with CKD in the absence of cardiovascular compromise or severe symptomatic anaemia. CKD increases the risk of transfusion-associated circulatory overload (TACO) and exposes women to exogenous human leukocyte antigens (HLA) to which they may develop antibodies, limiting the availability of transplant organs in the future.

Following delivery, systemic and renal physiology quickly reverts to pre-pregnancy status and subsequently, it is usual to see creatinine increase to baseline values. Conversely, women with CKD and limited renal reserve or pre-eclampsia can develop a markedly elevated serum creatinine towards delivery that can fall postpartum. Either way, monitoring renal function immediately following delivery and at 1- to 2-weekly intervals until at baseline is prudent.

A review at 6 weeks post-partum (or earlier if blood pressure or laboratory tests are not plateauing) is an opportunity to:

- discuss the pregnancy and delivery and answer any patient queries
- plan contraception
- repeat laboratory assessments of renal function to identify new baseline results
- assess the need and interval for ongoing renal medicine follow-up
- offer counselling on future pregnancies
- review medications and recommence reno-protective and cardiovascular treatments dependent on breastfeeding status

For women with an indication to (re)commence renal-angiotensin-aldosterone antagonism after pregnancy, enalapril, captopril or quinapril are acceptable agents to take during breastfeeding. Only low level amounts of these agents are found in breast milk, although caution is still advised if feeding premature infants. LactMed (https://toxnet.nlm.nih.gov/pda/lactmed.htm) is a helpful online resource offering advice acceptable treatment options for women who wish to breastfeed.

Dialysis and pregnancy

It is rare for patients receiving dialysis to become pregnant because of patient choice, impaired fertility (see Fig. 2) and reduced libido [65]. There are less than 200 pregnancies reported worldwide in women receiving peritoneal dialysis [66], however, the possibility of pregnancy with haemodialysis is no longer inconceivable.

For most women receiving dialysis, the best chance of a successful pregnancy would follow successful renal transplantation. If this is not feasible (due to urological issues, immune sensitisation or lack of organ availability, for example), then fertility can be improved with increased dialysis frequency, with reported conception rates of 32/1000 women/year (compared with 5/1000 women/year with 'conventional' dialysis) [46,67]. Indeed, compared with only modest increases in dialysis (<20 h per week), daily nocturnal haemodialysis (37–56 h per week) improves live birth rate from 48% to 85%, with over half of deliveries after 37 weeks and over half of infants born >2500 g [68]. Daily nocturnal haemodialysis is not a feasible option for most dialysis recipients or units however. Positive results using a short daily dialysis regimen (2.5 h, 5 to 7 times per week) have been reported recently and might be a valid alternative option, particularly for women with residual renal function [69].

Women receiving dialysis who are contemplating pregnancy or who have successfully conceived require the input of specialist and experienced teams to optimise outcomes. Each patient should have an individualised weekly schedule of care addressing fluid status, dialysis adequacy, nutritional assessment, pre-eclampsia risk, foetal wellbeing, anaemia management and delivery planning.

Renal transplantation and pregnancy

The general principles of managing pregnancy in a renal transplant recipient are the same as for any women with CKD – close attention to fluid status, blood pressure, proteinuria and foetal growth with optimisation of timing of delivery.

Standard care should be supplemented by consideration of the following:

Immunosuppression monitoring

Low dose corticosteroids and azathioprine are well-tolerated in pregnancy without significant risk of adverse foetal effects. Calcineurin inhibitors, of which tacrolimus is most commonly used, have also been used extensively during pregnancies with an acceptable safety profile.

The pharmacokinetics of tacrolimus metabolism is altered during pregnancy due to the increased volume of distribution and hormonal changes in hepatic metabolism. These effects are unpredictable, however, and calcineurin inhibitors have a narrow therapeutic index. Trough tacrolimus levels should be routinely measured every 2–4 weeks during pregnancy. Maintaining blood levels within target (that will vary between patient and transplant centre) can require an increase in dose of up to 2- to 3-fold [70]. Caution is required in interpreting these results in women who are anaemic and/or hypoalbuminemic, as reduced protein binding may lead to an increase in free active tacrolimus. Measuring free tacrolimus is cumbersome and not routinely available so a lower target blood level and increased index of suspicion for tacrolimus toxicity is required [71].

Urinary tract infection

Immunosuppression and altered renal tract anatomy lead to a high incidence of UTI in renal transplant recipients during pregnancy. Monthly screening for asymptomatic bacteriuria with prompt treatment is required. Given patients' immunosuppressed state, a low threshold for initiating prophylactic antibiotics for the duration of pregnancy should be considered if an episode of bacteriuria is confirmed.

Gestational diabetes

Corticosteroids and tacrolimus increase glycaemia and are associated with gestational diabetes. Reported incidence rates range from 8% to 25% [20]. The ideal diagnostic strategy is unclear, but early screening may be prudent, such as by oral glucose tolerance tests at 16–18 and 24–28 weeks gestation.

Caesarean section

Renal transplantation is not an indication for Caesarean section, however operative delivery is more common than in the general population due to the higher incidence of maternal or foetal adverse

progress. Care must be taken to avoid inadvertent damage to the renal transplant and ureter which might traverse the uterine surface. Consensus guidelines recommend that obstetric teams liaise with transplantation teams to confirm anatomy prior to elective procedures and that any Caesarean section in a renal transplant recipient should be performed by the most experienced obstetrician available [4].

Practice points

- Pre-pregnancy counselling should be offered to all women with CKD of childbearing age, to discuss options, optimise medications and disease control, and set expectations.
- All women with CKD have a greater risk of adverse pregnancy outcomes than the general population necessitating enhanced monitoring during pregnancy to promptly identify impaired foetal growth, impending pre-eclampsia, pregnancy-associated renal impairment, complications of heavy proteinuria or flares of underlying disease activity.
- Prophylactic treatment against urinary tract infection and VTE should be considered for selected women with CKD during pregnancy, and low dose aspirin considered for all women with CKD to reduce the risk of pre-eclampsia.
- Women receiving dialysis, renal transplant recipients, advanced CKD and those with lupus or other immunological-mediated disease require the input of expertise from a broad – often regional – MDT to optimise outcomes.

Research agenda

- Reporting from active prospective observational cohorts.
- More accurate risk assessment tools for VTE in women with sub-nephrotic proteinuria.
- Assessment of long term outcomes of children born to women with CKD.
- Develop strategies to prevent pregnancy-associated decline in renal function.
- Optimising time of initiation of dialysis during pregnancy in women with advanced or progressive CKD.
- Development of decision aids to aid women with CKD in contemplating pregnancy choices.

Conflicts of interest

Nil.

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