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Postpartum care of women with renal disease

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A B S T R A C T

Twenty-three percent of women with known chronic kidney disease (CKD) have been reported to demonstrate the first decline in kidney function between giving birth and six-weeks postpartum. As such, these women warrant close monitoring during the postpartum period irrespective of their pregnancy journey. Substantial haemodynamic variability during pregnancy and postpartum renders estimated glomerular filtration rate inaccurate, and poorly defined normal ranges of markers of kidney function at this time pose challenges for accurate assessment of renal complications. Multi-disciplinary specialist care is therefore essential, with consideration of specific implications of any known renal diagnosis and with observation for the development of postpartum complications of pregnancy. Furthermore, the postpartum period affords time to further investigate and diagnose kidney disease revealed by pregnancy. Good care planning and communication in the postpartum period has the potential to improve long-term health outcomes for women with known or new CKD and will be discussed in this review.

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Postpartum renal outcomes and survival in chronic kidney disease

In clinical practice, chronic kidney disease (CKD) represents a clinical syndrome defined by reduction in estimated glomerular filtration rate (eGFR) to less than 60 ml/min/1.73 m^2 of greater than three months' duration in the presence of haematuria, proteinuria, tubulointerstitial disease, abnormalities in renal morphology (including renal dysgenesis, single kidney, or scarring secondary to reflux nephropathy) or genetic variants of renal disease (including autosomal dominant polycystic kidney disease and Alport's syndrome).

Current recommendations have categorised renal impairment into five stages alongside the quantification of albuminuria (Table 1) [1]. The earlier stages [1,2] of CKD are far more common, with a reported prevalence of up to 3% among women of child-bearing age (aged 20–39 years); fewer than 1% of women of reproductive age have CKD stages three to five [2–4]. These stages categorise women according to long-term prognosis on the basis of their eGFR (ml/min/1.73 m^2) and degree of albuminuria (urine albumin:creatinine ratio, uACR, mg/mmol). Risks for progression of renal disease and development of cardiovascular disease are stratified from low to very high.

Considerations when interpreting renal function in pregnancy and the postpartum

Important physiological adaptations to systemic and renal vasculature are perceptible within the first four weeks of gestation. These include a reduction in systemic vascular resistance and dilatation of pre- and post-glomerular arterioles that gives rise to an increase in renal blood flow (by 80%) and GFR (by more than 50%) [2] Together with plasma volume expansion, this leads to a reduction in serum urea and serum creatinine (SCr) [5–7] with variable reports of increment back to pre-pregnancy concentrations towards term [8]. Many estimates of pregnancy SCr used in clinical practice are from several small studies (N = 5–30) [5]. However, recently published population-based data from 243,534 pregnancies in Canada [9] demonstrates a mean SCr of 60 μmol/l before pregnancy with a nadir between 16 and 32 weeks gestation of 47 μmol/l with a steady rise, peaking at 64 μmol/l within two weeks postpartum before settling to pre-pregnancy level by 18 weeks postpartum. The 95th percentile was approximately 15 μmol/l above the mean throughout pregnancy but 20 μmol/l at postpartum. This increased variability postpartum may reflect the range of intrapartum events that influence postpartum renal recovery and incidence of acute kidney injury (AKI), including blood loss, duration of labour, dehydration, drug exposure, and infection. These data do not enable interpretation of ethnic variation in SCr nor address the lack of validity of equations that estimate GFR from SCr concentrations as they rely on stable SCr [10,11]. Indeed the Modification of Diet in Renal Disease (MDRD) and CKD-epidimiology (CKD-EPI) algorithms underestimate GFR in pregnancy, and therefore, they should not be used to assess kidney function during pregnancy or postpartum [12]. There is no clear guidance on when eGFR becomes valid post-delivery, although 18 weeks postpartum (when SCr returns to pre-pregnancy levels) is a reasonable time point [9].

Confirmation of a clinically significant deterioration in renal structure and/or function is further challenged by pregnancy-associated changes and our incomplete understanding of the timing of their

Table 1
Categorisation of renal function for CKD Stage and degree of albuminuria. Adapted from Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012 [1]].

Stages of CKD and degree of renal impairment (eGFR, ml/min/1.73m^2)	Categorisation of albuminuria Urine ACR (mg/mmol)		
	A1 <3	A2 3–30	A3 >30
Stage 1: ≥ 90 (normal)	Low	Moderate	High
Stage 2: 60–89 (mild)	Low	Moderate	High
Stage 3a: 45–59 (mild to moderate)	Moderate	High	Very high
Stage 3b: 30–44 (moderate to severe)	High	Very high	Very high
Stage 4: 15–29 (severe)	Very high	Very high	Very high
Stage 5: < 15 (end-stage renal disease, ESRD)	Very high	Very high	Very high

resolution. In pregnancy, renal blood flow is increased, resulting in a rise in GFR and increase in proteinuria (up to 300 mg/day). Physiological hydronephrosis is evidenced by an increase in pelvicalyceal diameter due to progesterone-associated smooth muscle relaxation and uterine enlargement and compression. There is also a reduction in resting blood pressure (BP) observed within the first and second trimester with normotension restored by the end of pregnancy. Other changes include a reduction in solute and electrolyte reabsorption of and increased urinary excretion of uric acid, calcium and glucose. Bicarbonaturia is compensated for a progesterone-induced chronic respiratory alkalosis. A reduction in plasma osmolality (to 10 mosmol/kg) in response to increase in total body sodium is associated with a concomitant fall in plasma sodium to 5 mmol/l [5].

How does pregnancy affect renal survival and disease progression postpartum?

CKD has a mainly indolent course in pregnancy with normal or mild impairment to renal function and low-level proteinuria with or without structural kidney damage (CKD Stages 1–2). Conversely, women with moderate to severe chronic renal impairment (CKD Stages 3a-5) adapt poorly to the physiological demands of pregnancy and have an observed accelerated decline in renal function during and after pregnancy [13]. Our understanding of the risks of renal disease progression and lowered renal survival postpartum in women with CKD has remained reliant on observational data. Cohort, case-control studies and meta-analyses have demonstrated that the risks of pregnancy-associated complications (to include maternal pre-eclampsia, stillbirth, pre-term delivery at < 37 weeks) occurring at earlier stages of pregnancy increases with moderate to severe renal impairment ante-partum [14–16] (see Case Scenario (Fig. 2)).

In a prospective study of 49 women with CKD Stages 3–5 prior to pregnancy, mean GFR after delivery was less than that before conception (30 ± 13.8 vs. 35 ± 12.2 ml/min/1.73 m^2 P < 0.001), but the rate of GFR decrease did not change. However, a combination of both an eGFR of less than 40 ml/min/1.73 m^2 and urinary protein excretion of greater than 1g/24h ante-partum was associated with an accelerated reduction in eGFR postpartum [17]. Similar findings were also reported in a hallmark retrospective cohort study identifying a 20% reduction in eGFR sustained postpartum in 14/70 (20%) pregnant women at a median follow-up time of ≥12 months [18]. Although 51% of women demonstrated stable eGFR from early in pregnancy to six months postpartum, 33% of pregnancies were associated with a decline in eGFR between delivery and six months postpartum despite stable function throughout pregnancy (Fig. 1) and 31% of pregnancies were associated with a decline in eGFR at ≥ six months postpartum [18] with postpartum decline seen in women with all stages of CKD [15,19], thus emphasising the importance of postpartum surveillance irrespective of severity of renal disease or pregnancy outcome.

Following pregnancies complicated by preeclampsia, there is a large variation in the duration of postpartum persistence of proteinuria and hypertension [20] making assessment of renal deterioration more challenging in women with superimposed disease.

Postpartum care of women with CKD – the management of disease-specific and common complications of renal disease

Delivery of multi-disciplinary care postpartum will focus on control of the primary renal disease diagnosis and plans for the immediate postpartum period should be documented with plans for birth. All women should be given confident advice on the safety of medicines commonly used in the intrapartum and immediate postpartum in light of their CKD and on the safety of their disease specific medications should they chose to breastfeed. All women with renal disease should be advised on pregnancy spacing, with general consensus being to wait at least one year between delivery and conception; therefore, early contraceptive advice is essential. The use of oestrogen-containing contraceptives is commonly contraindicated in women with CKD due to the association with hypertension and thrombosis, exacerbating pre-existing risks in this population [12]. Progesterone-only contraceptives can be recommended including the mini-pill, intra-uterine device, or the subdermal implant [21,22]. Condoms are safe to use, and of course provide protection against sexually transmitted infections; however, the failure rate is high with one in five women conceiving within a year [23].

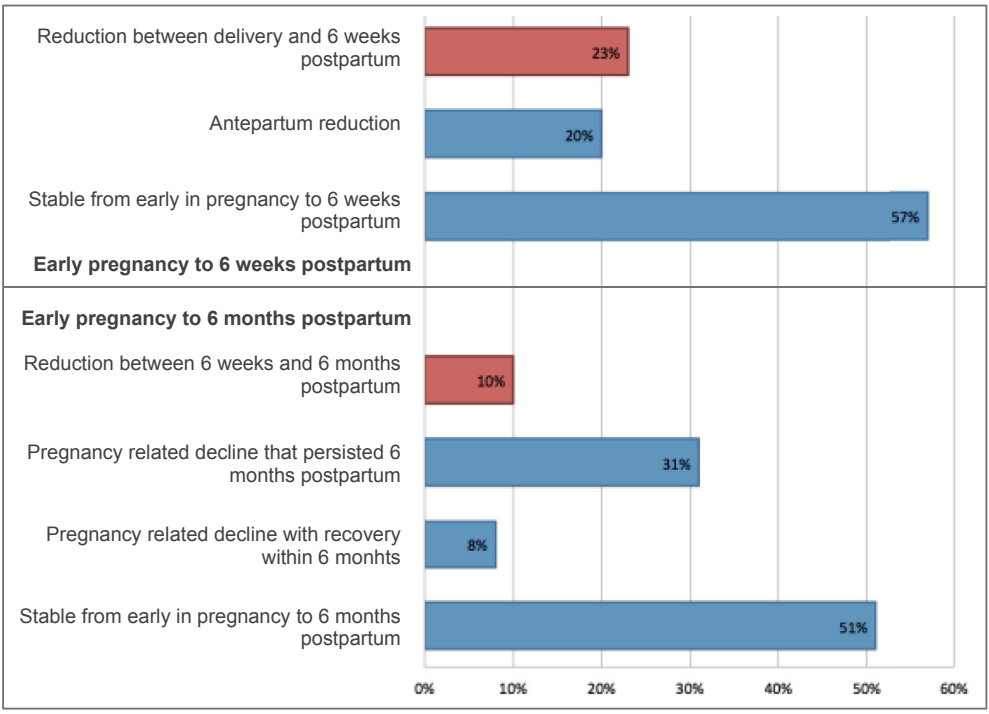

Fig. 1. Changes in glomerular filtration rate in women with primary renal disease before and after delivery (Adapted from Jones and Haylett) [18]. Columns in red represent initial deterioration in the postpartum period.

The mainstay of nephrological care for most glomerulonephropathies and other rare renal diseases should optimise common comorbid complications to include hypertension, proteinuria and diabetes. Joint obstetric and nephrology review should be undertaken by 6 weeks and coordinated at earlier stages of the postpartum period where required. Regular review and changes to drug regimens incorporating contraceptive, anti-hypertensive and immunosuppressant medications should be undertaken with new mothers.

Hypertension-related disorders

Diagnosis

A total of 3–5% of women with CKD will have pre-existing chronic arterial hypertension (essential or secondary to primary renal disease) [3] that deteriorates through pregnancy and may develop as a complication of gestational change or pre-eclampsia [24]. The development of hypertension postpartum is associated with a number of life-threatening complications, including eclampsia (that may occur up to 4 weeks following delivery) and intracerebral haemorrhage or cerebral vasoconstriction syndrome [25].

Hypertension postpartum should prompt a comprehensive history-taking and assessment to delineate a cause. Short-term causes of hypertension early postpartum (<6 weeks) should account for pain, concomitant use of nephrotoxic drugs (to include non-steroidal anti-inflammatory agents) and hypervolaemia compounded by parenteral fluid administration.

An assessment of secondary, systemic causes for hypertension (to include screens for endocrine, renal and neurological disease and an exclusion of nephrotoxic drug use) should be performed when hypertension persists after 6 weeks' postpartum in women who had been normotensive prior to pregnancy.

We describe a 33-year old woman (gravida 1, para 0) with a diagnosis of biopsy confirmed lupus nephritis (LN) following an earlier presentation with the nephrotic syndrome and acute kidney injury (AKI) (SCr 155 μmol/l, uPCR 623 mg/mmol, albumin 28g/L) in March 2013. Treatment included pulsed cyclophosphamide for 4 months, after which maintenance therapy with mycophenolate mofetil (MMF) and oral prednisolone was commenced. Despite achieving partial remission of her renal disease she continued to have persistent proteinuria (> 3g/day) ascribed to chronic glomerular lesions observed on histology in September 2014. Serial BP recordings were normotensive (≤ 130/80 mmHg).

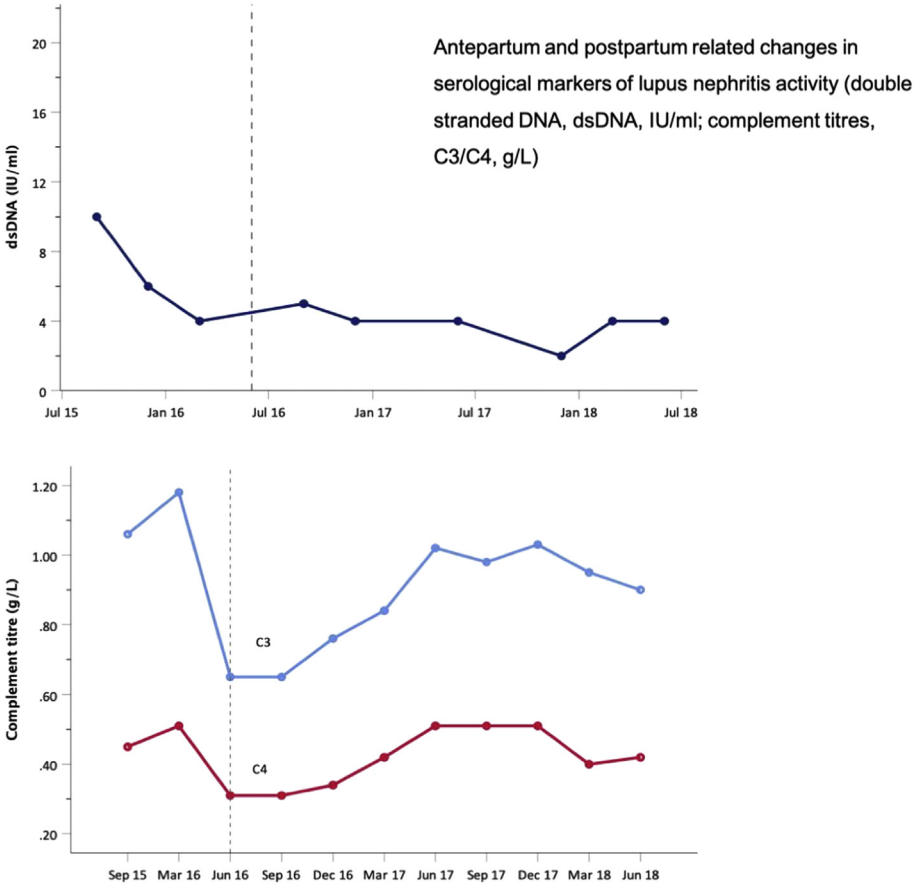

Fig. 2. Case study. Changes to maternal renal function (eGFR, SCr, albumin, uPCR) and lupus disease activity (dsDNA, C3 and C4 titres) prior to, during and 2 years postpartum.

Deteriorations in parameters of renal function during pregnancy are outlined in the graphs (opposite). BP remained normotensive independently of anti-hypertensive treatment. An emergency caesarean section was performed in June 2016 at 36+2 weeks for worsening foetal intra-uterine growth restriction and maternal renal function. Maternal biochemistry (antepartum): SCr 115 μmol/l, eGFR 47 ml/min/1.73m^2, albumin 26 g/L . Hypovolaemic shock as a result of a 2.5 litre blood loss at the end of delivery occurred.

Continuous haemo veno-venous filtration (CVVHF) was commenced for AKI and oligoanuria after delivery and discontinued by day 3 of the puerperium.

By six months, maternal renal function had not recovered to antepartum values (SCr 147 μmol/l, eGFR 36 ml/min/1.73m^2). MMF was recommenced at one year postpartum and further modifications to anti-hypertensive medications initiated in view of persistent, nephrotic range proteinuria. Lupus serological markers (dsDNA and C3/C4 titres) have remained at normal levels. A decline to CKD 3bA3 disease (SCr 160 μmol/l, eGFR 32 ml/min/1.73m^2) was observed at two years.

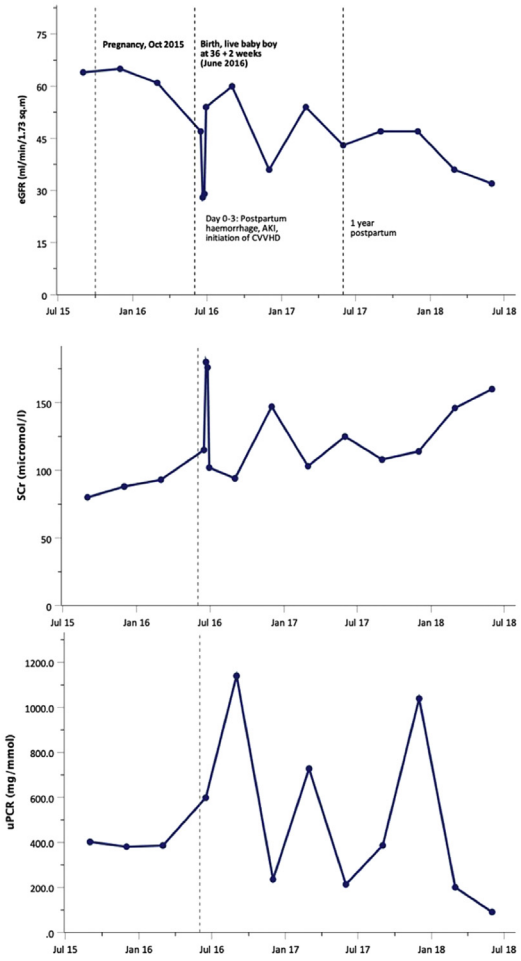

Fig. 2. (*continued*)

Postpartum pre-eclampsia should be suspected with new-onset significant hypertension or accelerations in pre-existing hypertension ($\geq$160/110 mmHg) in the presence of severe headache, visual disturbances or other focal neurological signs.

A strategy informing the short-term and long-term investigation and management of women with hypertensive disorders in the postpartum period is outlined in Fig. 3 (see below).

Management

Previous and recent systematic reviews have identified a paucity of data to guide the treatment of postpartum hypertension [26]. This has differed in accordance with organisational recommendations. National Institute of Care and Excellence (NICE) guidance mandates frequent monitoring of blood pressure (BP) every one to two days in the first two weeks postpartum after pre-eclampsia, and at least once in the first three to five days following gestational hypertension [27]. Initiation of anti-hypertensive treatment is mandated at a target BP of $\geq$150/100 mmHg postpartum, which is also in line with recommendations outlined by the American College of Obstetrics and Gynaecology (ACOG) [28]. However, since publication of the international CHIPS Trial (Control of Hypertension In Pregnancy Study) [29], consensus has moved in the favour of target BP < 140/90 during pregnancy and

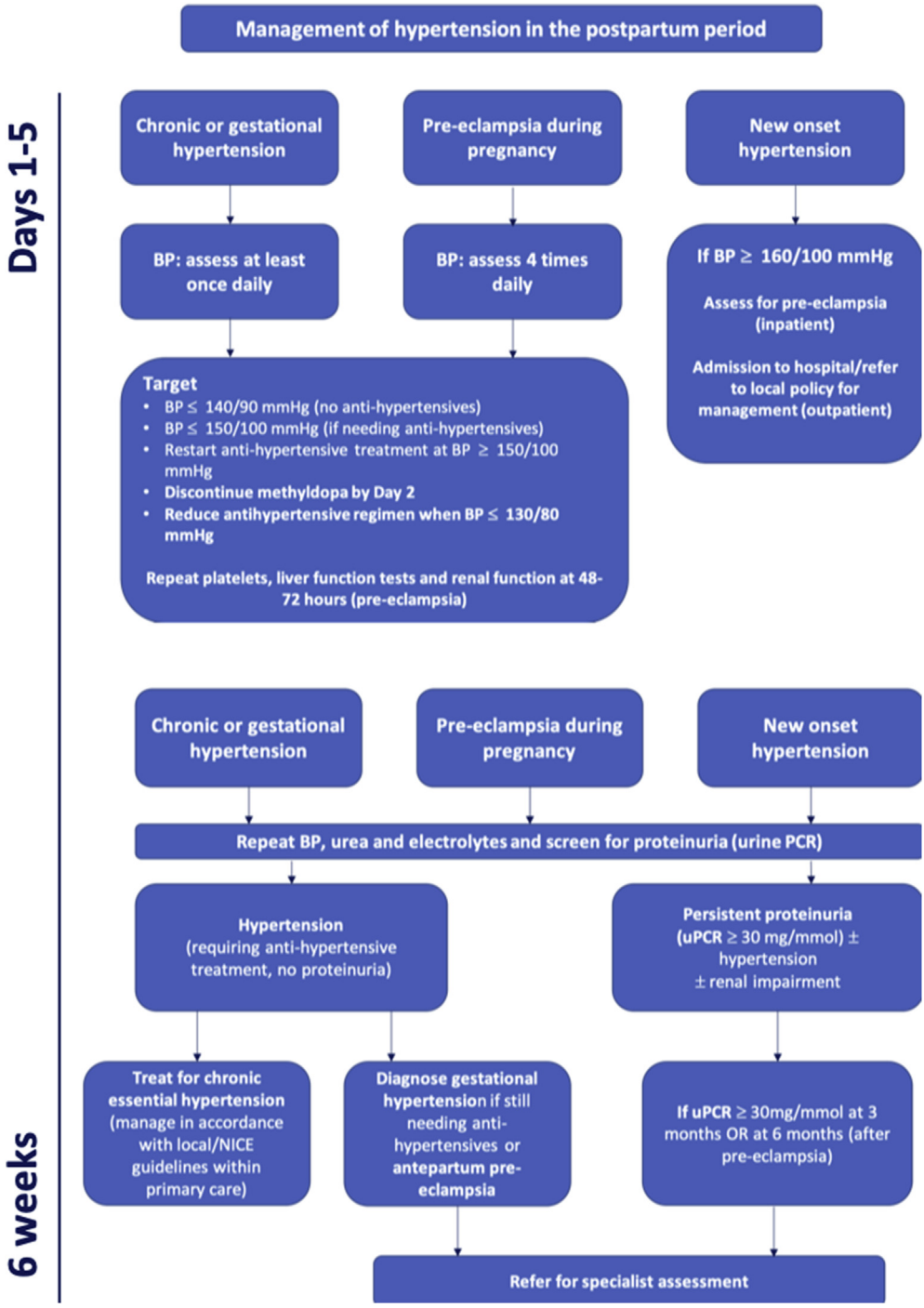

Fig. 3. A recommended approach to the inpatient and outpatient management of hypertension diagnosed in the postpartum period in accordance with UK national guidance (NICE CG107 Hypertension in pregnancy: diagnosis and management) [25,26].

postpartum; among 987 women (74.6% of whom had chronic hypertension) randomised to 'tight-control' or 'less-tight control' (target diastolic BP of 85 mmHg and 100 mmHg respectively), women in 'tight-control' (vs. 'less-tight') had fewer incidences of severe hypertension, low platelets and elevated liver enzymes with symptoms.

There is a lack of good-quality evidence informing which anti-hypertensive drugs should be prescribed postpartum. Practice has been informed by maternal and infant safety data, and effectiveness demonstrated in randomised trials and prospective and retrospective cohort studies of short-term BP control. Calcium channel blockers, beta-receptor antagonists and vasodilators (hydralazine) all lower postpartum BP in the absence of clear evidence to substantiate which drug class is more effective. NICE guidance recommends the discontinuation of methyldopa, a central-acting alpha-adrenoreceptor antagonist within the first 48 h of delivery, due to concerns about a theoretical negative impact on maternal mental health [27].

Angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin-II receptor antagonist (ARB) drugs can be used in CKD if serum potassium and renal function are stable. In the absence of neonatal safety data, the consensus of the Medicines and Healthcare Products Regulatory Agency (MHRA) precludes safe use of ACE-I or ARB drugs in breastfeeding mothers within the first few weeks postpartum [30] and following the delivery of pre-term babies; however, this recommendation is made on limited clinical data, and in practice, the use of enalapril, captopril or quinapril has no reported neonatal adverse effects and is deemed acceptable to use whilst breastfeeding [26].

Proteinuria

Significant proteinuria during pregnancy is indicated by urinary protein excretion $\geq$300 mg per 24 h ($\geq$30 mg/mmol on 'spot' urine PCR testing). Women with CKD are often observed to develop heavy proteinuria in the third trimester of pregnancy, which has progressed from moderate urinary protein excretion.

Physiological increases in urinary protein excretion observed during pregnancy may take up to 3 months to resolve, and proteinuria after severe pre-eclampsia can persist for up to 6 months postpartum [18]. Identifying the cause of significant proteinuria is also challenged by the indistinct overlap with hypertension, AKI and thrombocytopenia in the late third trimester to early postpartum period due to relapses of glomerular disease or pre-eclampsia superimposed on primary renal disease. Nephrology assessment (focussed on specific underlying disease) of affected women should be initiated within 6 weeks of the post-natal period where diagnostic uncertainty remains.

Detection of proteinuria at <20 weeks of pregnancy in the absence of infection can be indicative of underlying renal disease. In those pregnancies complicated by pre-eclampsia, repeat assessments should be performed at 6 months postpartum (when the glomerular injury of pre-eclampsia has resolved) and prompt referral to nephrology services for follow-up should be done if significant proteinuria persists [31].

Women with underlying nephrotic syndrome (urinary protein excretion > 3.5 g per 24 h, hypoalbuminaemia) are at higher risk of venous thromboembolism. Working obstetric and nephrology practice recommends the continuation of low-molecular-weight heparin (LMWH) prophylaxis to 6 weeks postpartum in affected patients [32]. The utility of LMWH prophylaxis with moderate to nephrotic range proteinuria is less clear but has been recommended in women with glomerular disease with a urine PCR >250 mg/mmol [33].

Diabetic nephropathy

Diabetic nephropathy, affecting 30% of patients with diabetes mellitus is the most common cause of ESRD in the Western World, complicates 5–25% of pregnancies of women with Type 1 diabetes mellitus [31]. It is hallmarked by the development of moderate albuminuria (uACR 30–300 mg/24 h), hypertension and a progressive reduction in eGFR. Resultant nephropathy of type 2 diabetes mellitus is observed less frequently in pregnant women or those of child-bearing age.

The long-term outcomes on renal survival subsequent to pregnancy in the setting of diabetic nephropathy are infrequently described in the literature. Higher risks of deterioration in renal function and progression to ESRD during pregnancy and postpartum have been observed in women with moderate to

severe renal impairment (mean ante-partum SCr of 159 μmol/l) [18], nephrotic-range proteinuria (>3 g/24 h) and severe hypertension [33]. The development of pre-eclampsia, prevalent in pregnancies complicated by diabetic nephropathy is in part ascribed to higher proteinuria, HbA1c and hypertension in early pregnancy [32] and can worsen pre-existing moderate to severe renal impairment.

Achievement of the best maternal and renal outcomes in the postpartum period should entail a multidisciplinary obstetric, nephrology and diabetes medicine specialty-based approach. Optimisation of BP postpartum and vigilance for accelerated hypertension indicative of pre-eclampsia should be implemented (see Fig. 3 – hypertension flow chart). Specific guidance corresponding to glycaemic control in CKD is lacking. Increased risks of postpartum hypoglycaemia compounded by pre-existent or worsened renal impairment and breastfeeding should be supported with appropriate adjustments to insulin doses and supplementation of dietary content [34]. Glibenclamide and metformin can be reinitiated whilst breastfeeding where renal function permits this at the lowest dose required to attain adequate glycaemic control, whereas other oral antidiabetic drugs should be avoided to circumvent hypoglycaemia in the infant. Postpartum thromboprophylaxis may need to be considered in those with persistent heavy proteinuria for up to 6 weeks.

Lupus nephritis

Systemic lupus erythematosus (SLE) is preponderant in women of child-bearing age. Though not clearly understood, the impact of active renal and extra-renal disease involvement on pregnancy is associated with catastrophic adverse pregnancy-associated outcomes. This has been evidenced in earlier meta-analysis and systemic review where active lupus conferred a 2-fold increase in the risks of pre-eclampsia (RR 1.19, 95% CI 1.44–2.53, $p = 0.0001$) and hypertension (RR 1.99, 95% CI 1.54–2.56) and to a 3-fold increase in the risk of pre-term delivery (RR 3.05, 95% CI 2.56–3.63) [35].

Assessing the effects of pregnancy on renal survival and relapse risk in LN are two areas central to counselling women and guiding clinical care to avoid lupus flares and preserve renal function, both during and after pregnancy. This has been complicated by the heterogeneity of existing criteria defining disease activity [36] either by the magnitude of changes in parameters of proteinuria, albumin and creatinine and/or the time course for confirming disease relapse. Current practice in non-pregnant cohorts observes the definitions outlined by the European League Against Rheumatism (EULAR) in which a renal flare is defined by an increase in proteinuria, serum creatinine, active (abnormal) urinary sediment and reduction in creatinine clearance [37]. Specifically, a proteinuric flare is characterised by a sustained increment in proteinuria to >0.5–1.0 g/24 h after previous complete remission or a doubling of proteinuria to >1 g daily following a previous partial response to treatment [38].

For the purposes of evaluating pregnancy-related outcomes in patients with SLE, a large meta-analysis of 37 longitudinal studies of 2751 pregnancies in 1842 women [39] defined active LN by the presence of: (i) proteinuria >500 mg/24 h with or without an active urinary sediment or (ii) one of an increase in serum creatinine at conception, lupus flare during pregnancy, or a new diagnosis of LN during pregnancy. More recently, longitudinal data from the multi-centre prospective Progress in Understanding Pregnancy Complications in Patients with SLE (PROMISSE) study have assessed risks of disease relapse in a multi-ethnic cohort of pregnant women with inactive, stable nephritis or no history of renal disease [40]. The proportion of patients sustaining a disease flare from complete or partial remission of pre-existing LN was small (13/118, 11.0%) with few new diagnoses of LN made in those patients with no prior renal involvement (4/225, 1.6%). However, those women with preceding quiescent LN were more likely to develop active disease from complete (OR 6.88, 95% CI: 1.84–25.71, $p = 0.004$) or partial remission when adjusted for age and ethnicity (OR 20.98, 95% CI 4.69–93.98, $p = 0.001$) than those without preceding kidney disease [40]. These findings are reassuring for the negligible risks of new onset renal disease in the absence of prior renal involvement and few severe flares with otherwise uncomplicated pregnancies. However, the substantially higher risks of disease relapse in those patients with inactive disease are an important reminder of the vigilance needed to communicate and manage active disease risk and prompt treatment during late pregnancy and postpartum.

The postpartum care of patients with pre-existing LN within the first 6 weeks should adopt a multi-disciplinary specialty obstetric, nephrology and rheumatology approach focusing on the following: maintenance of disease modification; avoidance of acute kidney injury through a review of nephrotoxic

drug use (particularly non-steroidal anti-inflammatories) and monitoring for the development of hypertensive-related disorders in the puerperium where renal impairment may have deteriorated. Importantly, disease-specific assessments of prothrombotic risks should also be accounted for.

Prescription for women with SLE

SLE disease activity may flare during pregnancy or in the puerperium. From available observational data, the flare rate is variable, ranging from 27 to 70% in a total of seven comparative studies [41]; four did not identify a difference in flare rate when compared with non-pregnant controls and three studies reported an increase in disease relapse activity during pregnancy.

Corticosteroids are an integral part of both induction and maintenance treatment regimens for active LN. Conversion to intravenous hydrocortisone at the time of delivery should be initiated to avoid corticosteroid insufficiency prior to the physiological stresses of labour and delivery in those patients with preceding chronic requirements for prednisolone. Doubling of oral steroids for the first 24–72 h in the event of an anticipated complicated labour or delivery is also recommended [42]. In the event of disease flare, increasing oral steroids or administration of intravenous pulsed methylprednisolone is deemed safe in the puerperium and not contraindicated in breastfeeding [43].

Hydroxychloroquine has immunomodulatory effects that are important for reducing the risk of disease flares and thrombosis and has demonstrated improved long-term renal survival (ref). It also has a demonstrable reduction of congenital heart block in women who are seropositive for anti-Ro antibody to 50% [40]. and is considered safe in breastfeeding.

Disease modification with anti-inflammatory, anti-proliferative drugs to include MMF and methotrexate is commonly used to treat LN. In the view of the high profile of teratogenic side effects within the first trimester, these drugs would have been discontinued at 3 months prior to conception, and subject to thiopurine methyltransferase (TPMT) testing, initiation of azathioprine at 2 mg/kg/day would have been initiated. New mothers should be informed and reassured that this remains safe to continue postpartum and during the lactation period.

Recommencement of mycophenolate mofetil can be initiated for severe renal disease relapse. Prior to commencement, women should receive contraception counselling with initiation and continuation of MMF. Due to the lack of safety data corresponding to the use of MMF in breast-feeding mothers, avoidance of this treatment during lactation is recommended [43].

Calcineurin-inhibitors (CNI), including tacrolimus and ciclosporin, are safe to use postpartum and during lactation for the treatment of LN. In the absence of long-term, randomised controlled data, tacrolimus has shown efficacy for reducing proteinuria and minimising steroid use when used concomitantly with prednisolone [44]. Given the narrow therapeutic index before the onset of acute drug-related toxicity (to include nephrotoxicity and infection risk) and individual patient pharmacokinetic variability associated with CNI agents, cautious, appropriately timed therapeutic drug monitoring is mandated. A return to pre-pregnancy dosing after delivery is recommended to avoid toxicity postpartum.

The risk of venous thromboembolic events (VTE) is heightened postpartum and greater in women with SLE. In a large observational study of pregnancies in women with SLE had a 34-fold increase in the risk of thrombophilia (described by antiphospholipid antibody seropositive status and other ICD classified disorders of hypercoagulability) when compared with non-SLE pregnancies (percentage of SLE pregnancies affected by thrombophilia, 4.0%; percentage of non-SLE pregnancies affected by thrombophilia, 0.04%, OR: 34.7, 95% CI 27.7–43.3, $p < 0.001$) [45].

An assessment of anticoagulation should be made in the postpartum period. Therapeutic unfractionated or low-molecular-weight heparin commensurate to renal impairment should be initiated prior to commencement of warfarin in the event of a confirmed VTE (deep venous thrombosis or pulmonary embolism). It should also be considered specifically as a part of treatment for severe, nephrotic renal disease relapse, hypoalbuminaemia (<20–25 g/l) and heavy proteinuria (>10 g/24 h) [46].

Thrombotic microangiopathies

Thrombotic microangiopathy (TMA) is used to describe a constellation of clinical disorders hallmarked by microangiopathic haemolytic anaemia, thrombocytopenia and end-organ damage resulting

from the pathological formation and aggregation of thrombi, fibrin and platelets within arteriolar and capillary walls. Organ involvement is mostly renal or cerebrovascular.

TMAs are rare in pregnancy, affecting 1 in 25,000 pregnancies, but are considered a medical emergency whereby diagnostic delays and the resulting treatment delays can be life-threatening [47]. The most common TMA in the puerperium is HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, which occurs in 10%–20% of cases of pre-eclampsia; treatment is delivery of the baby and placenta. It is vital to distinguish this from atypical haemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP), which are rare TMA-associated disorders occurring during pregnancy, and the puerperium in which an overlap between clinical features of haemolysis and thrombocytopenia are observed (see Table 2 – differential diagnoses of TMAs) but that do not warrant immediate delivery, thus avoiding risks associated with iatrogenic prematurity for the neonate.

Thrombocytopenic purpura (TTP)

TTP develops due to acquired inhibitory antibody activity to ADAMTS-13 (a metalloproteinase and disintegrin), an enzyme that cleaves von Willebrand Factor. Absence of or a deficiency in ADAMTS-13 (less than 10%) results in the formation of large vWF multimeric proteins and platelet aggregation causing microvascular thrombosis. For women with known ADAMTS13 deficiency, pregnancy is a risk factor for relapse, with documented rates varying from 23% to 50% [49]. One important distinction between both disease entities lies in the presence of significant AKI heralded by a marked rise in SCr of more than two times the upper limit of normal. Where the clinical picture remains indistinct for either TMA-related disorder, the assessment of ADAMTS-13 deficiency is paramount to diagnosis.

Atypical haemolytic uremic syndrome (aHUS)

aHUS is a rare form of TMA characterised by a biochemical triad of microangiopathic haemolysis, thrombocytopenia and AKI. Over the last two decades, the classification of HUS has been transformed into distinct subtypes to include typical HUS (precipitated by Shiga-toxin production from *Escherichia coli* and confirmed by polymerase chain reaction testing of stool) and atypical HUS (aHUS). A total of 10%–20% of all cases of aHUS are pregnancy related [50] when it usually occurs on a background of obstetric complications and is most common postpartum [51]. A diagnosis of aHUS should be favoured above that of postpartum preeclampsia or HELLP syndrome when there are the following clinical signs [52]:

- SCr $\geq$175 μmol/l
- LDH $\geq$ 1000U/l
- Hb < 80 g/l
- Personal or family history of aHUS
- Persistence of laboratory abnormalities $\geq$ 72 h postpartum.

In 60% of cases, there are abnormalities in components mediating the alternative pathways of complement (activators: factor C3, factor B; or regulators: membrane cofactor protein, thrombomodulin, factor H and factor I) [53]. Pregnancy is a known trigger, in women with this genetic

Table 2
Differential diagnoses of TMAs. Clinical features of thrombocytopenic purpura, haemolytic uremic syndrome, acute fatty liver of pregnancy, catastrophic anti-phospholipid syndrome and HELLP [Adapted from Banerjee, 2018] [48].

Conditions	TTP	aHUS	HELLP	AFLP
Incidence	1 in 25,000	1 in 25,000	10 to 20% of PET	1 in 20,000
Time of presentation	2nd trimester	¾ occur postpartum	3rd trimester & postpartum	3rd trimester & postpartum
AKI	30–80%	70% dialysis dependant	70%	3–5%
Neurologic sequalae	Common	Uncommon	Eclampsia	Encephalopathy common
Platelets ($\times 10^9$/l)	<10	<10–30	>30	<100
Coagulopathy	No	No	Yes (20%)	Yes
Elevated transaminases	No	No	Yes	Yes
ADAMPTS-13	Deficient	Present	Reduced marginally	Reduced marginally
Treatment	Plasmapheresis	Unaffected	Affected	Unaffected

predisposition. However, to complicate the diagnosis further, some experts consider that there is less clear distinction between TTP and HUS [54].

In aHUS, the complement mediator, eculizumab, has replaced plasma exchange as the gold standard and has significantly improved prognosis, thereby reducing the incidence of ESRD that develops in the majority of patients who receive only supportive care [55]. Eculizamab is a recombinant, humanised, monoclonal antibody directed against C5. However, given the rarity of aHUS, there is no high-level evidence to guide treatment, prognostic counselling or management; some literature even fails to separate the pathology of the separate TMA disorders [57]. The evidence base consists of expert opinion and case series [58]. The largest case series was 100 patients with aHUS, in which for 21 patients, it occurred during pregnancy; severe renal involvement was noted in all cases, 81% required haemodialysis, and 61% reached ESRD within 1 month [56]. However, this case series was prior to the introduction of eculizumab. Since eculizumab was introduced, there are case reports of women who have not been appropriately diagnosed and suffered significant morbidity and mortality as a result [59,60]. Eculizumab is currently only licensed for use postpartum, although there are some safety data on use in pregnancy for treatment of paroxysmal nocturnal haemoglobinuria [61]. Eculizumab renders patients susceptible to meningococcal infections warranting vaccination prior to commencement of treatment and close monitoring for early signs of meningococcal infections [62].

Chronic kidney disease identified during pregnancy

Kidney health is routinely assessed in pregnancy through ante-natal care schedules designed to screen for pre-eclampsia, a complication of pregnancy typically presenting with high blood pressure and proteinuria [63]. However, for a proportion of women, this screening will unmask a previously undiagnosed, likely asymptomatic renal condition. Indeed, proteinuria of greater than 300 mg/24 h, and/or hypertension before 20 weeks of pregnancy in a woman with no known chronic hypertension, warrant detailed assessment of kidney function in pregnancy and certainly postpartum, with a lower threshold for investigation in women with known comorbidities, especially previously undiagnosed diabetes [64]. The substantial, adaptive haemodynamic, immunological and renal tubular changes of pregnancy alter normal ranges of routine markers of kidney function, thereby making primary diagnosis of renal disease in pregnancy particularly challenging, further complicated by a lack of routine biochemical assessment of renal function resulting in no baseline or historic value. However, any significant rise in SCr will indicate a deterioration in maternal renal function and assessment of the overall clinical picture will educate the need for further investigation. The threshold recommended in London AKI Network's 'Obstetric AKI Pathway' [65] reported upper limits of normal SCr in first, second and third trimesters as 85, 80 and 90 μl/l respectively with SCr values over these thresholds as indicative of AKI acknowledging the common lack of baseline. It is now clear that these values are well above the 95th percentile [9]. Despite a lack of robust definition, pregnancy itself is a known risk factor for AKI, and given that even after complete resolution of a minor AKI [66], the risk of CKD is elevated warranting NICE to recommend monitoring for at least 2 years [67]. Furthermore, even Stage 1 AKI in women of child-bearing age is associated with a four-fold increase in risk of pre-eclampsia in a future pregnancy despite apparent renal recovery, which is proposed to be due to residual renal damage [68].

The primary aim in all suspected renal disease is to achieve a diagnosis, although this may not be possible during pregnancy due to an inability to determine the true extent of background hypertension, proteinuria or severity of renal impairment [6] or due to unacceptability of potential risks associated with necessary investigations such as imaging or renal biopsy. However, diagnosis allows appropriate management and counselling. Renal ultrasound is often performed in pregnancy to assess for scarring or renal artery stenosis, but caution is warranted in interpretation due to physiological hydronephrosis [69]. Observation of postpartum adaptation back to pre-pregnancy function is, therefore, crucial in women with suspected CKD, but without delay in possible investigation, diagnosis and treatment of renal disease through misplaced optimism for normalising blood pressure, SCr and/or proteinuria [70]. This relies on open communication with the woman and effective multi-disciplinary care ideally involving a specialist obstetrician, nephrologist, midwife and GP. Involvement of other specialists in women with relevant comorbidities such as diabetes is also beneficial.

To optimise pregnancy as a screening for CKD, it is essential that women with signs of renal disease are seen at least once postpartum by a nephrologist or specialist physician to reassess blood pressure, renal function and proteinuria with detailed understanding of the clinical picture. Postpartum proteinuria assessment should not be performed in the presence of lochia. This holistic assessment will educate a care plan including investigations to facilitate a diagnosis, long-term monitoring, treatment, including commencement of renoprotection therapy and counselling, including contraception, pregnancy spacing and risk implications for future pregnancies. Fig. 4 summarises suggested indications

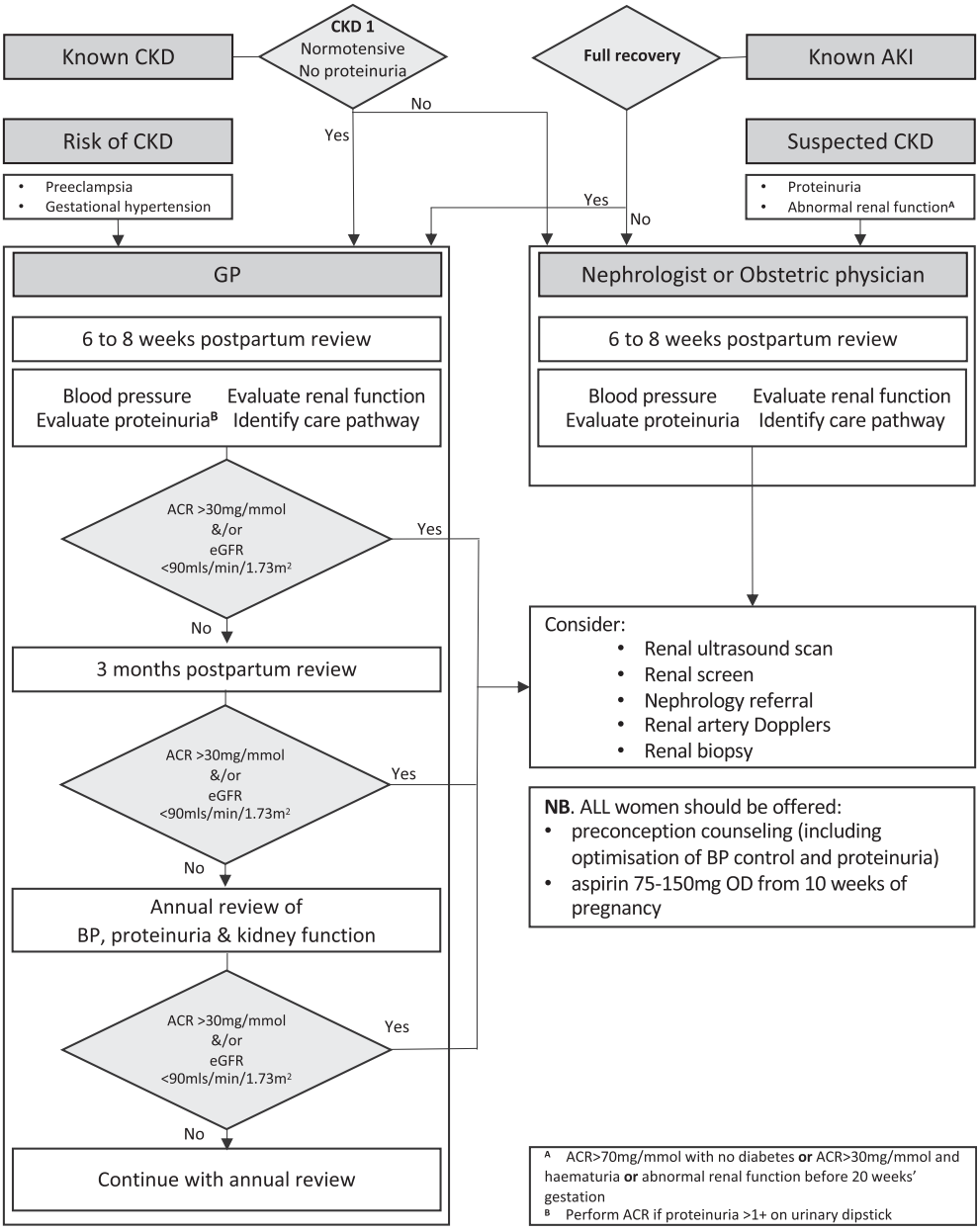

Fig. 4. Flow chart summarising postpartum review of renal function and appropriate follow-up.

and timings of referrals postpartum. It is often possible for women to have continued monitoring in a primary care setting [70] rather than directly with a nephrologist.

Consideration of any genetic contribution to the renal disease such as in the case of a diagnosis of autosomal dominant polycystic kidney disease, or vesicoureteric reflux, both of which are relatively common diagnosis in pregnancy due to presentation with mild haematuria or recurrent UTI's, proteinuria and hypertension. Women need to be appropriately counselled regarding transmission risk for her new baby and that for future pregnancies.

All women who have demonstrated impaired renal function in pregnancy, irrespective of postpartum recovery, should be informed of the increased risk of hypertension and/or pre-eclampsia in a future pregnancy. Lifestyle advice, including smoking cessation and general cardiovascular health promotion, needs to be clearly communicated. Women should be aware of the importance of ongoing monitoring of BP and proteinuria outside pregnancy with blood pressure targets of 120–139 mmHg systolic and below 90 mmHg diastolic [71] and treatment with an ACE inhibitor or angiotensin 2 receptor antagonist preferred when both hypertension and proteinuria are present [72].

Summary

The postpartum period is increasingly acknowledged as a time when appropriate care-planning and multi-disciplinary working can have substantial long-term health implications for the mother and her baby. A major challenge is the lack of robust evidence. Nevertheless, women with known CKD should receive individualised multi-disciplinary care that considers the aetiology of disease, the response of their renal function to the substantial hemodynamic changes occurring during pregnancy and postpartum, the specific risks associated with this time period including that of preeclampsia, AKI or TMAs, and prescription that is sensitive to those who are breastfeeding and considering future pregnancy plans. Such an approach is likely to improve patient experience and health outcomes. Women with newly diagnosed or suspected renal disease revealed by the renal stress-test of pregnancy should be fully investigated postpartum with the aim of reaching a diagnosis to inform a clear plan of care. Specialist input from tertiary centres should be sought freely, with such communication facilitated by the development of maternal medicine networks.

Practice Points

- Women with CKD are at risk of pregnancy-related deterioration in their kidney function up to six months postpartum, and they warrant detailed care planning on discharge from maternity services.
- Women with CKD are at increased risk of postpartum complications of pregnancy including AKI, preeclampsia and TMAs.
- The majority of medications that are used during pregnancy can be used whilst breastfeeding, but frequent review of medication dosages is warranted given the haemodynamic instability following giving birth.
- Pregnancy is an optimal time to screen for CKD and women who demonstrate persistent proteinuria or hypertension after 3 months postpartum warrant detailed investigation.

Research Agenda

- Ethnicity-specific normal ranges of serum creatinine, including expected change during the peripartum period.
- Pregnancy and postpartum specific definition of acute kidney injury.
- Effective referral and communication pathways for postpartum discharge from maternity care.

Conflicts of interest

None.

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