28 Pregnancy and Chronic Kidney Disease

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Before You Start: Facts You Need to Know

- CKD stages 1 and 2 affect up to 3 % of women of childbearing age and CKD stages 3–5 affect about 1 in 150 women.
- Over 95 % of the women with CKD becoming pregnant will be CKD stages 1 and 2.
- CKD stages 3–5 complicate about 1 in 750 pregnancies.
- Fertility declines with CKD progression over time.
- All women with CKD are at increased risk of pregnancy complications and adverse maternal and fetal outcomes which are related to the severity of prepregnancy kidney dysfunction, increasing further with hypertension and proteinuria and in systemic diseases, such as diabetes and SLE.
- Risk of accelerated decline and irreversible loss of kidney function during pregnancy or immediately afterwards is higher with more severe degrees of kidney dysfunction and with poorly controlled hypertension.
- Progressive hypertension with proteinuria and/or renal deterioration in late pregnancy may be difficult to distinguish from preeclampsia.
- The historically dismal maternal and fetal outcomes are improving with advances in obstetric, nephrological and neonatal care.

The provision of care for women with chronic kidney disease (CKD) contemplating pregnancy or already pregnant must involve clinicians working in a multidisciplinary team (MDT) in a tertiary centre [1, 2]. They must have an up-to-date knowledge of the changes in kidney that occur in normal pregnancy and the potential adverse effects of kidney impairment, an awareness of risks and complications with CKD, experience of modern antenatal and fetal surveillance and an ability to handle delivery care and afterwards. This chapter is based on some of the older literature, the limited evidence-based guidelines that are available, recently reported case series and personal experience [2–10]. The care of women on dialysis or with a kidney transplant will not be dealt with in this chapter.

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28.1 Prepregnancy Assessment

The basic components should be establishment of baseline parameters, analysis of risks as well as provision of health education and advice, plus any interventions that might be considered helpful, all 'cemented together' by that much used word 'counselling' (Boxes 28.1 and 28.2). Often a woman (and her partner) may bypass some important questions such as 'should I get pregnant?' and move straight into 'will my pregnancy be alright?' and 'will I have a live, healthy baby?' and possibly 'will I be alright after my pregnancy?' So the MDT must somehow ensure that all the relevant information is passed on, based on fact, not anecdote, covering the 'unasked questions' as well. Even if some of the answers are not favourable, many women will choose to go ahead for a pregnancy (or with the pregnancy) in an effort to re-establish a normal life in the face of chronic illness [7–10]. In some cases, this may cause a breakdown in communication with the MDT, and indeed, some women may not seek advice until already pregnant. This may lead to ethical dilemmas regarding clinicians' duties of care towards women who ignore advice. Attempts are being made to differentiate 'healthy' and 'pathological' levels of assumed risk and to understand the psychology of women who pursue parenthood despite substantial risk to their own health and that of their unborn child.

Thus, in the ideal world, a planned pregnancy is one that is desired before conception, occurs when contraception is discontinued in order to get pregnant and where the woman does try to achieve optimal health beforehand.

Box 28.1. Organisation of Care in CKD

- Before pregnancy, all women of childbearing age with CKD should be made aware of its implications for their reproductive health and careers.
- Women need input on contraception, modification of remedial risk factors and optimisation of and/or alterations to medication for their CKD and any associated comorbidities (such as hypertension, diabetes or SLE) in addition to explanations about the risks and rates of pregnancy complications, adverse maternal and fetal outcomes and possible impacts on long-term renal prognosis.
- The MDT must work in partnership with these women to tailor personalised prepregnancy, antenatal, delivery and postnatal care, in a centre with all the necessary facilities for dealing with high-risk patients and their babies.
- This 'active preparation for pregnancy' should involve the woman's partner.
- Some women may not seek advice until already pregnant.
- Undiagnosed CKD may be suspected/diagnosed for the first time during pregnancy when a complication or an adverse event occurs.

Box 28.2. Prepregnancy CKD Assessment Criteria

- Cause of CKD (±systemic disease such as SLE or diabetes).
- Stage of CKD (eGFR).
- Presence or absence of significant proteinuria (≥300 mg/24 h).
- Normotension or 'well-controlled hypertension' with diastolic BP ≤80 mmHg.
- Past obstetric history.
- Genetic counselling may be required for familial CKD.
- Assessment of diet, BMI, nicotine and alcohol intake.
- Some advise counselling for CKD 1 and 2 only if there are adverse risk factors.

28.2 Normal Pregnancy

The renal tract undergoes marked anatomical, haemodynamic, tubular and endocrine changes as part of the systemic upheaval of maternal adaptation

to pregnancy. The kidneys enlarge because both vascular volume and interstitial space increase but there is no accelerated renal growth nor morphological alterations akin to compensatory renal hypertrophy. The calyces, renal pelves and ureters dilate markedly, invariably more prominent on the right side, seen in 90 % of women, mimicking outflow obstruction. The relevant functional changes are listed in Box 28.3.

28.3 CKD and the Prospects for Pregnancy

A woman may lose up to 50 % of her kidney function and still maintain S_{cr} below 125 μmol/L (1.4 mg/dL), because of hyperfiltration by the remaining nephrons; however, if kidney function is more severely compromised, then further small decreases in GFR will cause S_{cr} to increase markedly. In women with CKD, whilst the pathology may be both biochemically and clinically silent, the internal milieu may already be disrupted. Most individuals remain symptom-free until GFR declines to less than 25 % of normal, and many serum constituents are frequently normal until a late stage of disease. However, degrees of functional impairment that do not appear to disrupt homeostasis in nonpregnant individuals can jeopardise pregnancy (Box 28.4).

The traditional approach [7], with CKD defined as *mild*, *moderate* and *severe*, based on S_{cr} has been replaced by a system based on the current CKD classification that is part of the US National Kidney Foundation (NKF) K/DOQI clinical practice guidelines, endorsed by the UK National Service Framework for Renal Services, and now widely adopted. Estimated GFR (eGFR) is estimated from the Modification of Diet in Renal Disease (MDRD) formula and its refinement CKD-EPI formula. Prepregnancy eGFR has a better sensitivity in detecting

Box 28.3. Normal Pregnancy and Renal Physiology

- Normal cardiovascular function and healthy renal system, with optimal adaptation to increasing demands of pregnancy, are prerequisites for successful obstetric outcome.
- Glomerular filtration rate (GFR) increases to 50 % above prepregnancy values, primarily due to increased renal blood flow (RBF) rather than a rise in intraglomerular pressure, so there is unlikely to be hyperfiltration sclerosis.
- Serum creatinine (S_{cr}) in the 1st, 2nd and 3rd trimesters averages 60, 54 and 64 μmol/L (0.66, 0.59 and 0.70 mg/dL), respectively, with measured creatinine clearances (C_{cr}) of 151, 154 and 129 mL/min, respectively, with return to S_{cr} baseline (70 μmol/L/0.75 mg/dL) by 3 months postpartum. As well as gestational age-specific values, some units now use ethnicity-specific normal ranges as, for example, nonpregnant Afro-Caribbean women have higher S_{cr} levels than Caucasians.
- Serum urea (S_{urea}) averages 3 mmol/L (7 mg/dL) throughout pregnancy, a fall from the nonpregnant value of 5 mmol/L (12 mg/dL).
- Values of S_{cr} of 80 μmol/L (0.9 mg/dL) and S_{urea} of 6 mmol/L (14 mg/dL), which are acceptable in the nonpregnant state, are definitely suspect in pregnancy.
- 24-h urinary total protein excretion (TPE) increases throughout the trimesters in normal pregnancy and up to 300 mg per 24 h can be regarded as normal.
- Serum albumin (S_{alb}) decreases progressively from mean of 38 g/L at 12 weeks gestation to 32 g/L by 36 weeks. Corresponding cholesterol levels are 4.5 mmol/L and 6.6 mmol/L, respectively. Occasionally, S_{alb} may decrease by up to 10 g/L and with bigger increments than usual in serum cholesterol, plus oedema, usually in late pregnancy; nephrotic syndrome may be simulated.

Source: Data from Refs. [2, 7, 10–14]

Box 28.4. CKD and Physiological Adaptation to Pregnancy

- Women with CKD have impaired ability to make physiological adaptations during pregnancy.
- Pregnancy GFR increments may be blunted, even absent, especially in CKD stages 3–5, with the likelihood of further GFR decline as pregnancy progresses.
- Failure of S_{cr} to decrease in the first trimester is suggestive of future complications.
- CKD may be associated with inability to boost renal hormones, leading to normochromic normocytic anaemia, reduced plasma volume expansion and vitamin D deficiency.
- In CKD, so-called significant proteinuria (TPE > 300 mg per 24 h) may correlate with a protein concentration of 30 mg/dL in a 'spot' urine sample, but given the problems with dipstick testing, a 24-h or some timed quantification may be preferred and/or use of 'spot' protein/creatinine ratio, with 30 mg/µmol (0.3 mg/mg) or more being significant.
- Increased TPE up to 3 g/24 h can occur in CKD patients; an exaggeration of the physiological increase in healthy women and even the cessation of renoprotection from antiproteinuric drugs alone rarely indicate functional deterioration.
- Early in pregnancy BP can decrease and in CKD may mask mild hypertension that has been present but undiagnosed before pregnancy.

Source: Data from Refs. [2, 7, 9–11, 13–15]

subclinical renal dysfunction and its influence on pregnancy outcome (if not CKD progression) as compared to S_{cr} alone [5, 9, 10]. The literature is still primarily retrospective. No attempt has yet been made to revisit the older literature on *mild*, *moderate* and *severe* dysfunction and to assess whether or not conversion of those data to CKD staging is even possible from a practical point of view; however, S_{cr} values <125, >125 and >180 µmol/L (<1.4, >1.4 and >2.0 mg/dL) – *mild*, *moderate* and *severe* impairment – respectively, correspond approximately to CKD stages 1, 2 and 3A, 3B, and 4 and 5, respectively. In the longer term, confirmation of outcomes and prognoses and even development of guidelines require adequate prospective trials [6, 7].

28.4 Pregnancy in Women with CKD

Assessment of the CKD patient presents two basic and often conflicting issues: fetal prognosis (the effect of CKD on pregnancy) and the maternal prognosis, both during pregnancy and in the long term [11, 15]. Across the spectrum of CKD, there is a stepwise increase in the likelihood of complications and adverse outcomes such as hypertension, preeclampsia, deteriorating maternal renal function (often persistent), proteinuria, anaemia, urinary infections, fetal growth restriction and fetal loss. Aside from these obvious unfavourable outcomes, there are increases in 'surrogate' outcomes too (compared to normal pregnancy) including preterm delivery, caesarean section and the need for neonatal intensive care unit access, clearly evident between CKD stages 1 and 2, underlining the importance of even minor decreases in kidney function [6, 10, 16] (Box 28.5 and Table 28.1).

CKD Stages 1 and 2 Normotensive women with intact or only mildly decreased but stable kidney function generally do very well, with more than 97 % live births, about 75 % of which are appropriate for gestational age. There is an increased incidence of superimposed preeclampsia or late-pregnancy hypertension as well as increased proteinuria exceeding the nephrotic

range (3 g per 24 h) in 50 % of women in the second half of pregnancy. Pregnancy does not appear to adversely affect the course of the CKD [6, 7].

There are exceptions as certain types of CKD appear more sensitive to pregnancy, including lupus nephropathy [15, 20] and perhaps membranoproliferative glomerulonephritis. In addition, women with scleroderma and periarteritis nodosa do poorly (especially when there is marked kidney involvement and associated hypertension) and thus should be counselled to avoid pregnancy. Furthermore, there is some disagreement about whether pregnancy adversely influences the natural history of IgA nephropathy, focal segmental glomerulosclerosis and reflux nephropathy [7]. It seems likely that prognosis with these renal lesions is actually similar to that of women with mild impairment in general, provided prepregnancy function is preserved and high blood pressure absent.

Box 28.5. Influences on Maternal and Fetal Outcomes in CKD

- Level of prepregnancy kidney impairment: CKD stage (eGFR).
- Satisfactory prepregnancy BP: spontaneous or therapeutically achieved normotension and its optimal control throughout pregnancy. Relative risk of fetal death is 10 times higher when prepregnancy mean arterial pressure (MAP) ≥105 mmHg, compared with normotension. Absence of hypertension, almost regardless of kidney impairment, predicts best outcomes.
- Degree of proteinuria.
- Cause of CKD and the presence of a systemic disease/comorbidities.
- In addition, CKD itself has independent and significant effects on fetal outcome.
- Adverse past obstetric history.

Source: Data from Refs. [3, 7, 8, 11, 14, 15]

CKD Stages 3 and 4 Prognoses are poor but live births still approach 90 %. Preeclampsia, fetal growth restriction and/or preterm delivery occur in well over 50 %. Many women experience renal functional loss more rapidly than would be expected from the natural course of their CKD, and poorly controlled hypertension is a harbinger of poor outcome. Best overall outcomes occur when prepregnancy eGFR is 40–60 mL/min and TPE ≤1 g/24 h. Poor outcomes are associated with eGFR <40 mL/min and TPE > 1 g/24 h, this combination resulting in worse outcomes than either feature alone [4].

CKD Stage 5 (*But Not on Dialysis*) Although there is a paucity of data for analysis, it is obvious that the outlook is markedly curtailed. Preeclampsia/hypertension is common by term

Table 28.1 Prepregnancy CKD stage and estimates of obstetric complications/outcomes and renal prognosis

							Loss of >25 % RF		
CKD stage	Prepregnancy eGFR	S_{cr} (μmol/L)	FGR	Preterm delivery	PE	Perinatal death	During pregnancy	6 months PP	ESRF 1–2 year PP
Normal 1	≥90	<110	14	28	13	2	2	0	0
Mild 2	60–89 (<90)		30	35	40				
Mod 3	30–59 (<60)	>110	40	65	55	5	35	15	2
Severe 4	15–29 (<30)	>180	65	90	60	8	65	50	30
Estab RF 5	<15 (but not on dialysis)	>250	>80	95	>70	15	90	60	45

Estimates are based on Refs. [4–10, 13, 14, 17–19] and from 62 women/93 pregnancies which attained at least 24 weeks gestation (Davison, unpublished data from 1993–2006)

Aim is to provide 'at a glance' information to facilitate counselling and management, whilst not belittling much more detailed coverage and analyses (with their own inherent weaknesses too) in those publications utilised

All estimates expressed as a percentage

FGR fetal growth restriction, S_{cr} serum creatinine, *PE* preeclampsia, *RF* renal function, *PP* postpartum, *ESRF* end-stage renal failure, *eGFR* estimated glomerular filtration rate (mL/min/1.73 m^2)

(>70 %) as is significant proteinuria (60 %), as well as deterioration in kidney function, which is at times, rapid, substantial and irreversible. Although infant survival rates are good (>80 %), rates of preterm delivery (95 %) and fetal growth restriction (FGR) (>80 %) underscore the very high potential for obstetric complications in these women. Many of these women are amenorrhoeic and subfertile but keep trying for a pregnancy since kidney function will keep on declining with time and dialysis is not necessarily 'going to help' and a kidney transplant may involve a many year wait. Furthermore, some women may even seek assisted conception in the face of their infertility.

28.5 Antenatal Strategy and Decision-Making

These patients must be seen as early as possible [1, 2, 21]. Thereafter assessments should be at 2–4 week intervals until 32 weeks' gestation and then every 1–2 weeks, depending on the clinical circumstances. In most cases, the basic principle is to manage the associated clinical features rather than the type of CKD.

1. Assessment of kidney function by S_{cr} or timed C_{cr} and by protein excretion, either as 24-h excretion or a spot protein/creatinine ratio. *The use of eGFR from MDRD or CKD-EPI formulae is not valid in pregnancy*, *as actual GFR is underestimated* [5]. If eGFR is used, it might erroneously signal to the clinician an exaggerated deterioration in kidney function and might prompt unnecessary delivery. *Cystatin C as a GFR marker is of no use because there is placental production of Cystatin C*, *especially prominent in the third trimester*.
2. Careful blood pressure monitoring for early detection of hypertension (and assessment of its severity) and preeclampsia. There are debates about so-called tight control, the accuracy of automated devices and the role of ambulatory blood pressure measurements.
3. Early detection and treatment of anaemia, usually by oral/intravenous iron therapy. Some recommend use of recombinant human erythropoietin if haematocrit is 20 % or less, but caution is needed as hypertension can be caused or aggravated. Blood transfusion may need to be considered.
4. From early pregnancy prophylactic low-dose aspirin is advisable. Definitive thromboprophylaxis will be required when proteinuria exceeds 3 g/24 h or S_{alb} <25 g/L, the dose of low molecular weight heparin depending on the level of kidney impairment [11, 15, 22].
5. Early detection of covert bacteriuria or confirmation of urinary tract infection (UTI) and prompt treatment; if there are recurrent UTIs, then antibiotic prophylaxis should be given throughout pregnancy.
6. Biophysical/ultrasound surveillance of fetal size, growth, development and well-being is mandatory, with timing of the scans and decision-making depending on the evolving clinical situation. Doppler studies can be used to assess placental function as well as helping to predict potential complications such as preeclampsia and fetal distress. Not all women, however, with abnormal uterine artery Dopplers will develop complications, and such tests must not be used in isolation.

The clinical 'watchpoints' associated with specific types of CKD are summarised in Table 28.2.

The following guidelines apply to all CKD patients:

28.5.1 Kidney Function

If there is significant deterioration at any stage of pregnancy, then think in terms of 'prerenal, renal or post-renal' and of reversible or remediable causes such as UTI, diarrhoea, over-strict water and salt restriction, subtle dehydration or electrolyte imbalance (occasionally precipitated by inadvertent diuretic therapy), temporary renal tract obstruction or nephrotoxic drugs. Near term, as in normal pregnancy, a decrease in function of 15–20 %, which affects S_{cr} minimally, is permissible. Failure to detect a reversible cause of a significant decrement is grounds to end the pregnancy by elective delivery.

Table 28.2 CKD and pregnancy

CKD	Clinical watchpoints
Chronic glomerulonephritis and focal glomerular sclerosis (FGS)	Can be high blood pressure late in pregnancy but usually no adverse effect if renal function is preserved and hypertension absent before pregnancy. Some disagree, believing coagulation changes in pregnancy exacerbate disease, especially IgA nephropathy, membranoproliferative glomerulonephritis and FGS
IgA nephropathy	Some cite risks of sudden escalating or uncontrolled hypertension and renal deterioration. Most note good outcome when kidney function is preserved
Chronic pyelonephritis (infectious tubulointerstitial disease)	Bacteriuria in pregnancy and may lead to exacerbation
Reflux nephropathy	Some have emphasised risks of sudden escalating hypertension and worsening of kidney function. Consensus now is that results are satisfactory when prepregnancy function is only mildly affected and hypertension is absent. Vigilance for urinary tract infections is necessary. Screening of baby as soon as possible after birth, if not already detected in utero
Urolithiasis	Ureteral dilatation and stasis do not seem to affect natural history, but infections can be more frequent. Stents have been successfully placed and sonographically controlled uterostomy has been performed during gestation
Systemic lupus erythematosus (SLE)	See Boxes 28.6 and 28.7
Diabetic nephropathy	No adverse effect on the renal lesion. Increased frequency of infections, oedema or preeclampsia. Advanced nephropathy can be a problem
Human immunodeficiency virus with associate nephropathy (HIVAN)	Renal component can be nephrotic syndrome or severe impairment. Scanty literature. Should be considered when nephrotic proteinuria occurs suddenly, especially in immunocompromised patients
Adult PCKD	This autosomal dominant disorder is the most common single-gene genetic disease of humans with an incidence of 1 in 400–1,000. May request DNA probe screening of fetus. Functional impairment and hypertension are usually minimal in childbearing years. Most do not have clinical manifestation until fourth or fifth decade; only 17 % diagnosed by age of 25. Patients do well if renal impairment is minimal. One in four has late-pregnancy hypertension
Periarteritis nodosa Scleroderma	Fetal prognosis is poor. Maternal death can occur. Therapeutic abortion should be considered if disease onset during pregnancy shows rapid overall deterioration. Reactivation of quiescent scleroderma can occur during pregnancy and after delivery
Previous urologic surgery	Depending on original reason for surgery, there may be other malformations of the urogenital tract. Urinary tract infection is common during pregnancy and renal function may undergo reversible decrease. No significant obstructive problem, but Caesarean section might be necessary for abnormal presentation or to avoid disruption of the continence mechanism if artificial sphincters or neourethras are present
After nephrectomy, solitary and pelvic kidneys	Pregnancy is well tolerated. Might be associated with other malformations of the urogenital tract. Dystocia rarely occurs with a pelvic kidney

Source: Modified from Davison and Lindheimer [7]

Do not allow acute kidney injury (AKI) to accelerate to such an extent that not even terminating the pregnancy will reverse the decline [2, 23]. When proteinuria occurs and persists, but blood pressure is normal and renal function preserved, pregnancy can be allowed to continue under closer scrutiny. Thus, increased proteinuria in isolation is not used to time delivery.

28.5.2 Temporary Dialysis

This may be judged necessary during pregnancy especially when S_{urea} is much in excess of 20 mmol/L (48 mg/dL), when intrauterine fetal death is more likely [2]. Refractory hyperkalaemia, severe metabolic acidosis, pulmonary oedema responding poorly to diuretics and danger

of volume overload with heart failure may also prompt consideration of dialysis.

It is essential to watch for dialysis-induced uterine contractions, and tocolytic agents can be used with care if indicated. Dialysis-induced hypotension must be avoided too, and also remember that, in the supine position, the patient's enlarged uterus may reduce venous return and aggravate the situation. Even when volume fluctuations are minimised, however, umbilical artery Doppler velocimetry still indicates that haemodialysis temporarily causes considerable fetal haemodynamic alterations.

Dialysis may increase the chance of successful outcome by 'buying time' for fetal maturation, but it does not arrest the inexorable decline in kidney function, ultimately to end-stage failure. In trying to avoid extreme prematurity in this way, it has to be asked whether such potential life-threatening effects on the mother's renal prognosis can be justified.

28.5.3 Blood Pressure

The conventional dividing line for obstetric hypertension is 140/90 mmHg and the aim should be to keep it between 120/70 and 140/90 [11, 12, 15, 17, 21, 24–26]. Inappropriately low blood pressure is associated with fetal growth restriction (FGR) and high blood pressure with renovascular damage. Most of the specific risks of hypertension appear to be related to superimposed preeclampsia in women with CKD but the diagnosis cannot be made with certainty on clinical grounds alone as hypertension and proteinuria may be manifestations of the underlying CKD. Also, chronic hypertension alone has an increased preeclampsia risk fourfold that of normotensive pregnant women. Treatment of mild hypertension (diastolic blood pressure less than 95 mmHg in the second trimester or less than 100 mmHg in the third) is not necessary during normal pregnancy, but many treat women with CKD more aggressively, believing that this preserves kidney function [7].

Medications such as methyldopa, calcium channel blockers, labetalol and hydralazine are safe in pregnancy [24, 25]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers should not be prescribed *during* pregnancy. When patients are taking either of these before pregnancy, however, because of the significant renoprotection effect, there is a view emerging that changing to a safer drug or drugs can wait until the patient becomes pregnant.

28.5.4 Role of Kidney Biopsy in Pregnancy

Experience with kidney biopsy in pregnancy is limited, mainly because clinical circumstances rarely justify the risk of the possible complications, which are much higher in pregnancy than postpartum, 7 and 1 %, respectively, the latter akin to the rate in nonpregnant subjects [27]. Thus, kidney biopsy is usually deferred until after delivery, provided hypertension is well controlled and coagulation indices are normal.

Whilst pregnancy is considered by most to be a relative contraindication, there are a few generally agreed indications such as when severe nephrotic syndrome develops in early pregnancy or when the suspicion is of a rapidly progressive glomerular disease, for example, SLE in the second trimester, severe enough to warrant specific treatment [16].

28.5.5 Timing of Delivery

Decisions need to be individualised and involve the MDT [1], taking into account gestational age, current fetal and maternal well-being and prognosis as well as the risks of neonatal consequences of early delivery against the risks of complications of continuing the pregnancy [17, 26]. Indeed, if complications do arise, the judicious moment for intervention will inevitably take into account fetal status and perhaps a decision about the use of maternal corticosteroids for fetal lung maturation. In the absence of maternal and/or fetal deterioration, delivery should be at or near term (>37 weeks gestation). Planned

preterm delivery may be necessary if there is impending warning of intrauterine fetal death, if kidney function deteriorates substantially, if uncontrollable hypertension supervenes or eclampsia occurs [17, 23, 25, 26]. Obstetric considerations should be the main determinant for delivery by caesarean section. There is certainly an increased risk of emergency caesarean section in labour, spontaneous or induced, for either maternal or fetal complications.

During labour, kidney function and BP must be assessed frequently as well as undertaking continuous monitoring of the fetus. Strict fluid balance must be maintained. If appropriate, prophylaxis with magnesium sulphate to prevent eclampsia must be considered. During active management of the third stage of labour, use oxytocin not syntometrine. Where there is a prerenal insult such as haemorrhage, HELLP or acute fatty liver of pregnancy (AFLP), on top of worsening CKD and/or preeclampsia, which can further acutely threaten maternal kidney function, nephrotoxic drugs must be avoided and the maternal circulation restored with careful fluid management as such patients are prone to fluid overload [17, 26, 28, 29].

28.6 Postpartum Care

Immediately after delivery, there is potential for instability in BP control and fluid balance as well as further deterioration in maternal kidney function, so close surveillance is still needed [1, 17, 26, 28, 29]. Be vigilant in avoiding NSAIDs for postdelivery analgesia because in many units these are routinely prescribed, with patient self-administration.

Decisions will be needed about changing back to prepregnancy medication(s), especially renoprotective drugs, if required, but this may be delayed if mother wishes to breastfeed, dependent on any contraindications [24, 25]. With nephrotic syndrome, prophylactic heparin should be continued for 6 weeks after delivery [11].

If required, renal ultrasound should be arranged for the baby. Remember to arrange a postnatal review appointment with the MDT, both to reassess the patient and to debrief her and her partner about their pregnancy experience (which may have been complicated and worrying), their obstetric and renal future as well as contraception [2].

28.7 Systemic Lupus Erythematosus (SLE)

SLE is worthy of special mention because, even in a multidisciplinary setting, the physician and the obstetrician really must have proper experience with SLE and awareness of the extensive literature [2, 15, 16, 18]. SLE may be present with or without other connective tissue diseases (the overlap syndrome) and the complex clinical problems are due to its profound immunological disturbances, its multi-organ involvement and the complicated immunology of pregnancy itself. Prepregnancy assessment and the clinical 'watchpoints' for pregnancy management and afterwards are outlined in Boxes 28.6 and 28.7.

28.7.1 SLE and the Fetus

As well as miscarriage and FGR, SLE confers other big risks on the fetus [16]. Congenital heart block (CHB) is associated with maternal anti Ro and anti La autoantibodies and occurs in up to 4 % of the fetuses in these women, with a 15 % recurrence risk in subsequent pregnancies. It develops between 18 and 20 weeks gestation, so if suspected (from a fixed fetal heart rate of 80 bpm), then fetal echocardiography is essential. Sometimes, hydrops fetalis may develop in utero, occasionally severe, and even those babies born unscathed, half will need pacing in the first year of their lives. Neonatal lupus rash, usually on the scalp and face, and classically akin to adult subcutaneous SLE lesions, can occur soon after delivery and up to 6 months thereafter. These very rarely coexist with CHB and may take several months to subside.

Box 28.6. Prepregnancy SLE Assessment and Counselling

- Prediction of good outcome is related to disease activity and remission, as well as optimal and stable medication(s) in preceding 6 months. Degree of renal impairment, level of hypertension, if any, and low complement levels are also important.
- As well as lupus nephritis, the presence of other comorbidities, such as antiphospholipid syndrome (APS), must be considered.
- Pulmonary hypertension is an absolute contraindication to pregnancy.
- Thromboprophylaxis must be carefully reviewed if considering a past history of thrombosis, nephrotic syndrome and/or preeclampsia.
- Past obstetric history has also to be considered for any other adverse features.
- SLE increases the risk of spontaneous miscarriage, which can be as high as 30 %.
- Four out of five pregnancies will be successful when SLE is in complete remission, even if originally there were severe histopathological changes on biopsy and heavy proteinuria.
- Maternal death rate is 20-fold higher than the normal population.

Source: Data from Refs. [2, 7, 15, 16, 18]

Box 28.7. Pregnancy in SLE Patients

- Complications are common: extrarenal flare (25 %), renal flare (most commonly after delivery) (10 %), FGR (at least 30 %), preterm delivery (50 %) and preeclampsia (at least 10 %).
- In pregnancy up to 20 % of patients have GFR decrements, progressive in 8 %.
- Preeclampsia occurs earlier and more frequently in women with lupus nephritis, even compared to women with similar impairment due to a different CKD.
- Presence of lupus anticoagulant strongly associated with development of preeclampsia.
- Lupus nephritis classes III and IV are more likely to be associated with preeclampsia than classes II and V.
- In a known SLE patient, preeclampsia may be difficult to distinguish from a renal 'flare' (even postpartum), but decreasing complement levels, urinary sediment analysis and increasing anti-dsDNA levels may be helpful as well as evidence of increased lupus disease activity in other organs.
- The most reliable arbiter for distinguishing preeclampsia from lupus nephritis is kidney biopsy, but it is rarely undertaken in pregnancy. It may be considered appropriate in 2nd trimester, if felt that result will tailor/alter management, in relation to 'buying time'.
- SLE has a predilection for the childbearing age group, and if SLE nephropathy becomes manifest for the first time in pregnancy, it may be mistaken for preeclampsia.
- Extrarenal 'flares' occur predominantly in the second half of pregnancy, with renal 'flares' more common in puerperium, a time of increased vigilance as SLE medication(s) (if any) may need adjusting as well as those for ongoing management of hypertension and for thrombosis, in line with breastfeeding considerations.

Source: Data from Refs. [2, 7, 15, 16, 18, 25]

28.8 Suspicion and/or Diagnosis of De Novo CKD During Pregnancy

For some women, pregnancy may be their first major contact with health-care services and represents a valuable opportunity to detect chronic medical conditions, including CKD. If this possibility is raised, it is essential to try and establish a diagnosis as well as a course of management that will be helpful to both mother and fetus [7]. When a patient presents with hypertension, proteinuria and/or abnormal kidney function, it is difficult to distinguish parenchymal CKD from preeclampsia [12–14, 19]. A previous history of kidney disorders, abnormal urine analysis, a family history of CKD or a history of systemic illness known to involve the kidneys is obviously very helpful, but even so CKD and preeclampsia may coexist. In 10–20 % of patients where preeclampsia is severe, of early onset and especially with heavy proteinuria, this may in fact be the first clinical presentation, indeed unmasking rather than development, of asymptomatic/undiagnosed CKD from prepregnancy, more so if the woman is multiparous [13, 14, 19].

Proteinuria alone, in the absence of urinary infection, can be an indication of kidney dysfunction. If TPE is consistently ≥500 mg/24 h, then renal impairment will be present in about half, 40 % will go on to develop hypertension, 25 % will have low birth weight babies and 50 % will deliver preterm. Some of these women may have been labelled preeclamptic in previous pregnancies, but remember that undetected CKD is very likely [7, 13, 30].

In women suspected of having CKD, their assessment and subsequent blood testing are similar to those of nonpregnant patients but the definitive diagnosis has to wait until after delivery [14, 30]. Their pregnancies should be allowed to continue if kidney function and blood pressure remain stable. Nephrology follow-up after delivery is essential for continued assessment and perhaps final diagnosis, with the aim of reducing progressive deterioration and concurrent escalation of cardiovascular and metabolic risks. Intervention with lifestyle changes and then timely pharmacological intervention with the first indication of sequelae is particularly important if there was preeclampsia, as it is a marker for remote cardiovascular, cerebrovascular, metabolic and renal problems [30–32].

28.9 Loss of Kidney Function in Pregnancy and Afterwards in Women with CKD

Pregnancy does not cause or otherwise affect the rate of progression beyond what might be expected in the nonpregnant state, provided that before the pregnancy, kidney impairment was minimal and hypertension absent or very well controlled (Box 28.8). During pregnancy of course, there is a hypercoagulable state, with an augmented coagulation cascade and decreased fibrinolytic activity which even if only slightly augmented in CKD patients, could mediate insidious AKI with thrombotic glomerular injury. Prolonged periods of protein trafficking are nephrotoxic too, with induction of proinflammatory and inflammatory cytokines causing glomerular injury along with tubulointerstitial damage. In the long-term prognosis, however, an important factor could be the sclerotic effect that prolonged, gestational renal vasodilation might have in the residual (intact) glomeruli of the kidneys of these women, especially if contributed to by an increased intraglomerular pressure. The situation may be worse in a single diseased kidney, where more sclerosis has usually occurred within the few (intact) glomeruli. Although the evidence in healthy women and those with mild kidney disease argues against hyperfiltration-induced damage in pregnancy, or any increase in intraglomerular pressure, there is little doubt that in some women with moderate, and certainly severe dysfunction, unpredicted, accelerated and irreversible renal decline does occur in pregnancy and/or afterwards [2, 6, 7, 10, 13].

Box 28.8. Worsening CKD During Pregnancy and Afterwards

- Rate of CKD progression and gradual erosion of kidney function usually relates to the level of BP control, degree of proteinuria, underlying CKD and previous rate of GFR decline.
- In pregnancy there may be accelerated and irreversible decline greater than that predicted based on previous course.
- Renal insufficiency and hypertension, especially where poorly controlled, are the major risk factors for permanent exacerbations of underlying CKD.
- Risk of decline is highest when renal insufficiency is greatest.
- Cause of CKD, other than lupus nephritis, is probably not a major determinant of worsening CKD if factored for pre-existing renal insufficiency and hypertension.
- With preeclampsia, kidney function often declines further, mimicking CKD deterioration.
- Sequential S_{cr} measurements showing escalating concentrations may be evidence of preeclampsia in absence of any other renal diagnoses.
- Addition of a prerenal insult may further reduce kidney function, such as antepartum haemorrhage (APH) and/or postpartum haemorrhage (PPH). Regular use of NSAIDs can acutely and additionally threaten maternal kidney function, as can HELLP, preeclampsia, HUS, acute fatty liver of pregnancy (AFLP) or thrombotic microangiopathies.

Source: Data from Refs. [2, 4–7, 9–12, 16, 22–24, 29]

28.10 Preeclampsia: Diagnosis, Significance and Prognosis (Boxes 28.9 and 28.10)

Preeclampsia remains a major cause of maternal and perinatal morbidity and mortality. Interestingly, it is the commonest cause of glomerular disease worldwide. The diagnosis of preeclampsia, with the ability for appropriate intervention is based on traditional but often unreliable and nonspecific criteria of hypertension and proteinuria [12, 13, 21, 25, 26]. Evidence of involvement of one or more other organs with liver function abnormalities, thrombocytopenia, DIC and/or patient-reported symptomatology may help to establish the diagnosis. In addition, marked rises in S_{cr} (without any other explanation), ever-increasing BP and/or escalating antihypertensive requirements may imply superimposed preeclampsia. Nevertheless, preeclampsia cannot be diagnosed clinically with certainty in women with CKD [2, 12–14, 17, 19].

By elucidating the pathophysiology of preeclampsia and identifying some of the many underlying factors, their measurement might then be used as an aid in predicting preeclampsia in 'at-risk' women, like those with CKD, and/or in diagnosing preeclampsia when the diagnosis is suspected. Ideally, it might be possible to distinguish between preeclampsia and the progressive hypertension, proteinuria and renal deterioration of AKI in CKD patients. Said otherwise, there may be a clinically useful 'marker' of preeclampsia, and if presymptomatic biomarker profiling is possible, then prevention or even modification of risk might be feasible, let alone treatment [30, 31, 33, 35].

In preeclampsia the balance between proangiogenic and antiangiogenic factors is altered [13, 14, 30, 35]. This is due to disturbances in the vascular development of the placenta with underperfusion and ischaemia such that the hypoxic trophoblast secretes a wide range of antiangiogenic factors into the maternal circulation. These include placental growth factor (PlGF) as well as soluble fms-like tyrosine kinase-1 (sFlt-1) (a soluble decoy receptor for vascular endothelial growth factor (VEGF)) and soluble endoglin (sEng), both of which block VEGF-mediated signalling, which is important for normal endothelial function.

Box 28.9. Preeclampsia and CKD

- During pregnancy in CKD patients, hypertension worsens or develops in 30 %, proteinuria increases in over 50 % and decline in kidney function can often occur.
- If preeclampsia develops in CKD patients, then maternal kidney function often deteriorates further.
- In CKD, hypertension and proteinuria are not necessarily due to preeclampsia, as exacerbation of CKD can mimic preeclampsia and/or the two may coexist.
- The uncertainty of clinical diagnosis leads to difficulty in differentiating preeclampsia from not only exacerbation of CKD but also HUS, AFLP and thrombotic microangiopathies.
- Risk of developing preeclampsia in CKD is higher with more severe degrees of renal impairment (from 10 % up to 80 %), higher still in the presence of hypertension.
- Preeclampsia is the most common cause of nephrotic syndrome in pregnancy, but it may also be secondary to underlying CKD, or both.
- Clinically useful circulating 'markers' for preeclampsia are being identified and tested to assist not only with diagnosis but also with presymptomatic prediction of risk and/or complications with the potential for therapeutic intervention(s).

Source: Data from Refs. [2–4, 6, 8, 9, 12–14, 17, 19, 20, 22–24, 30, 33, 34]

Box 28.10. Prognosis After Preeclampsia

- No longer assume that preeclampsia is a condition cured by delivery.
- Although renal changes in general are believed to resolve completely after delivery ('delivery cures the disease'), there is evidence that preeclampsia may leave permanent renal impairment or add further to the deficit of already damaged kidneys.
- Damage may be direct or indirect via hypertension and/or widespread endothelial dysfunction.
- After preeclampsia there is a three- to eightfold increased risk of cardiovascular disease (including ischaemic heart disease, hypertension and stroke) as well as obesity, dyslipidaemia and end-stage renal disease.
- Preeclampsia and cardiovascular disease share risk factors such as hypertension, obesity, diabetes and hypercholesterolaemia, so preeclampsia is certainly a marker for cardiovascular risk.
- Not yet definitely known whether preeclampsia per se adds to the risk; if so, then preeclampsia would be an independent risk factor and not just a marker.
- These remote risks are greatest in those who also had preterm births, FGR and/or recurrent preeclampsia, all frequently seen in CKD women anyway.
- Preeclampsia will add to the already unfavourable cardiovascular and metabolic profile of CKD patients, as CKD patients already carry risk factors.
- Offspring of preeclamptic mothers are more likely to have a higher BP from childhood and a stroke in later life.
- There is a need to elucidate the underlying biological factors that underpin the association between preeclampsia and disease later in life.

Source: Data from Refs. [2, 7, 8, 13, 14, 19, 20, 30–32]

Thus, there is widespread endothelial disruption, microangiopathy and a disturbed inflammatory response, potentially creating a favourable setting for autoimmunity, and the glomerulus is afflicted as part of all this, with disruption of podocyte and endothelial symbiosis. Podocyturia as well as markers of endothelial injury, such as von Willebrand factor,

Box 28.11. Relevant Guidelines

1. *American College of Obstetrics and Gynecology* (*ACOG*) *guideline*:

   Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force in Pregnancy. Obstet Gynecol 2013;122: 1122–31. [26]
2. *American College of Rheumatology guideline*:

   American College of Rheumatology Guidelines for screening, treatment and management of lupus nephritis. Arthritis Care Res. 2012;64:797–808. [18]
3. *Centre for Maternal and Child Enquiries* (*CMACE*). Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. BJOG. 2011;118(Suppl 1). [http://onlinelibrary.wiley.com/doi/10.1111/bjo.2011.118.issue-s1/issue-toc] [1]
4. *International Society for the Study of Hypertension in Pregnancy* (*ISSHP*) *guideline*:

   The definition of severe and early-onset preeclampsia: statements from ISSHP. Pregnancy Hypertens. 2014;4: 97–104. [12]
5. *National Institute for Health and Clinical Excellence* (*NICE*) *guidelines*:

   Clinical Guideline 34. Hypertension: management of hypertension in adults in primary care 2006. [www.nice.org.uk/guidance/index.jsp?action=byID&0=10986=byID&0=10986] [24]

   Clinical Guideline 73. Early identification and management of CKD 2008. [http://guidance.nice.org.uk/CG73/Guidance/pdf/English] [20]

   Clinical Guideline 107. Hypertension in Pregnancy. The management of hypertensive disorders in pregnancy 2010. [21] [www.nice.org.uk/nicemedia/live/13098/50418/50418.pdf]

   Clinical Guideline: 169. Acute kidney injury. Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy 2013. [http://guidance.nice.org.uk/CG169/Guidance/pdf/English] [23]
6. *Royal College of Anaesthetists* (*RCA*). Providing equity of critical and maternity care for critically ill pregnant or recently pregnant women. 2011. [http://www.rcoa.ac.uk/document-store/providing-equity-of-critical-and-maternity-care-the-critically-ill-pregnant-or] [28]
7. *Royal College of Obstetricians & Gynaecologists* (*RCOG*) *Guidelines*:

   Green Top Guideline 37a. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium 2009. [22] [www.rcog.org.uk/files/rcog-corp/GTG37aReducingRiskThrombosis.pdf]

   Green Top Guideline 10(A). Management of severe preeclampsia and eclampsia 2006, reviewed 2010. [http://www.rcog.org.uk/womens-health/clinical-guidance/management-severe-pre-eclampsiaeclampsia-green-top-10a] [17]

   Green Top Clinical Guideline 56. Maternal collapse in pregnancy and the puerperium. 2011. [http://www.rcog.org.uk/files/rcog-corp/GTG56.pdf] [29]

   54th RCOG Study Group: Renal disease in pregnancy 2008. RCOG Press, London, 273 p [2]
8. *Society of Obstetrics & Gynecology of Canada* (*SOGC*) *Guidelines*:

   Clinical Practice Guideline 206. Diagnosis, evaluation and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens. 2014;4:105–45 [25]

fibronectin and osteopontin, are yet to be proven clinically useful [13, 14, 19, 30].

Pathogenic agonistic autoantibodies, although not specific, are highly prevalent in preeclampsia, one of which (AT_1-AA) can activate the major angiotensin II type 1 receptor (AT_1R) [13, 30, 35]. There then can follow hypertension, hypercoagulation and glomerular dysfunction as well as FGR, secondary to AT_1-AA-induced placental damage and ischaemia and yet a further increase in sFlt-1 and sEng. Antibody titres correlate with the severity of disease and thus may be useful as a presymptomatic biomarker and their blockage and/or removal may potentially be a treatment option [35]. As sFlt-1 and PlGF reflect underlying placental and endothelial pathophysiology, their measurement may also be useful, but sensitivity and specificity issues need assessment, as does the evaluation of many new candidate biomarkers. Even though measurement of PlGF is becoming an integral component of clinical care for the diagnosis and management of suspected preeclampsia, it seems likely that a clinically useful predictive model will also need to include elements of maternal history, demographic information, standard biochemical investigations and ultrasound biophysical assessment as well as biomarkers, in order to achieve useful stratification of risk [31, 33–35].

There is little doubt that women diagnosed with preeclampsia have a substantially increased risk of cardiovascular disease, cerebrovascular disease, end-stage renal disease and metabolic problems in later life and this risk may also be associated with conditions that coexist with preeclampsia, including CKD [30–33]. Lifestyle interventions after preeclampsia may decrease the cardiovascular risks, but information is now needed about the interplay between genetic, proteomic and environmental factors so as to understand the clinical implications [31].

Before You Finish: Practice Pearls for the Clinician

- Prepregnancy assessment/counselling is a crucial yet neglected approach for best management, providing the ideal opportunity to establish baselines, to achieve optimal use of medication(s) and health education and to discuss all aspects of pregnancy.
- Once a CKD patient, always a CKD patient, and important determinants are prepregnancy renal status (CKD stage), the absence or presence of hypertension (and its management) as well as first-class fetal surveillance, timely delivery and appropriate neonatal care.
- All women with CKD are at increased risk of pregnancy complications with overall at least a two- to fourfold higher risk of adverse fetal outcome, even those with CKD Stage 1.
- Absence of severe hypertension or renal dysfunction prepregnancy is favourable for pregnancy and renal prognosis. If dysfunction is severe, there is still a fair chance that pregnancy will succeed, but risks are much greater, including AKI and its aftermath.
- Type of renal disease probably does not influence outcome but the collagen disorders, IgA and reflux nephropathies and certainly SLE need special consideration.
- Proteinuria is common during pregnancy (up to 3 g/24 h) but little is known about the longer-term implications of the increased protein trafficking within the kidney.
- Severe hypertension is a much greater adverse feature than low but stable kidney function. ‘Controlling a sign’ does not modify the basic pathophysiology underlying clinical deterioration. Preeclampsia cannot be diagnosed clinically with certainty.
- Rapidly deteriorating kidney function, however, even without hypertension, can be ominous.
- Postnatal assessment and debriefing are very important.

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