SECTION 14

Renal disease at different stages of life (infancy, adolescence, pregnancy, old age)

CHAPTER 291

Growth and development

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Normal growth

Normal growth is traditionally divided into four phases: fetal, infantile, childhood, and pubertal (Fig. 291.1). Throughout each phase, the predominant influences on growth are different. During fetal life, nearly 30% of final height has already been achieved. Prematurity and low birth weight can influence subsequent growth and final height attainment. Although many otherwise normal infants born prematurely grow normally, and those who are small for gestational age (SGA) catch up in the first 6 months of life, around 10%, particularly if SGA, remain below the normal range for height into adulthood. The infantile phase is predominantly dependent on nutrition. The rate of growth at birth is as high as 25 cm per year and 170 calories per day are incorporated into new tissue. These figures remain high over the first 6 months of life, although they fall progressively to 18 cm per year and 50 calories per day respectively. Inadequate intake at this time can, therefore, have a dramatic influence on growth. The rate of growth and relative calorie requirements remain high throughout the first year, being around 12 cm per year at 1 year and 8–9 cm per year at 2 years of age and 30 and 20 calories per day are incorporated into new tissue respectively. Approximately 50% of adult height is achieved at the end of this phase.

During the childhood phase, the growth hormone (GH)–insulin-like growth factor (IGF) axis becomes the most important influence. The rate of growth continues to fall progressively, reaching a nadir at the time of onset of puberty. The pubertal phase is dependent on GH and the sex hormones acting in concert to produce the pubertal growth spurt. The age at the beginning of the increase in growth velocity is variable, but is at about 11 years in boys and 9 years in girls. The peak height velocity occurs at a mean of 13.5 years in boys and 11.5 years in girls. The rate of growth may reach as much as 13 cm per year, and this renders the individual vulnerable to the effects of poor nutrition, ill health, and hormonal derangements, resulting in a further opportunity for disruption of the genetic height potential. The average growth spurt lasts 24–36 months and contributes around 20% of the final height (Rees and Shaw, 2007).

Epidemiology of chronic kidney disease in children

Around half of children with chronic kidney disease (CKD) are diagnosed antenatally. The other half may go undiagnosed until they present in the late stages of CKD when symptoms have developed. For this reason, registries under-report CKD and the true incidence is unknown. However, data from European countries are fairly consistent, at around 11–12 per million of the age-related population (pmarp) for CKD stages 3–5, and 8 pmarp for CKD stages 4–5. Prevalence ranges from about 55 to 75 pmarp. The commonest cause is congenital abnormality of the kidneys and urinary tract (CAKUT), particularly in younger children and males (Harambat et al., 2012). The majority of children on renal replacement therapy (RRT) have a renal transplant. For example, in the United Kingdom in 2010, there were a total of 870 children and young people < 18 years of age on RRT. Of these, 75% were transplanted, and 85% had a transplant at transfer to adult services (Pruthi et al., 2010). The reported incidence of patients initiating RRT is higher in the United States and seems to be increasing, rising from 14 to 15 per million population over the 8 years up to 2008. It is not clear however if this is a true increase in CKD or increased acceptance of patients onto RRT programmes (United States Renal Data System, 2010).

Effect of chronic kidney disease on growth phases

International, national, and individual country registries and some single centres provide information on the height achievements of children with CKD. There is less data on growth in conservatively managed CKD, a group that is less well defined, than children on RRT. All such registries report mean height standard deviation score (the number of standard deviations from the mean for the normal population of the same age, HtSDS) below normal. However, although remaining below average, the height prognosis is improving over the years (Hartung and Furth, 2013). This is despite a more challenging population, as children of all ages (including neonates) and with complex co-morbidities are now accepted for RRT in the developed world.

Growth in infancy

Infants born with CKD are the group that is most vulnerable to an inadequate rate of growth, and this can have a permanent effect on ultimate height potential. Because the rate of growth is so high, rapid losses of as much as 2 HtSDS can occur in the first 6 months of life. Although in all reports throughout the world < 2 year olds have the lowest HtSDS of all ages, they have the best response to intensified nutrition and post-transplantation catch-up growth. Some catch up may continue during the childhood phase of growth but there is a further decline during puberty so that final height potential is less than would have been predicted. This is illustrated in Fig. 291.2A, which shows the HtSDS at birth, 6 months of age, and then annually for up to 20 years in a group of children with

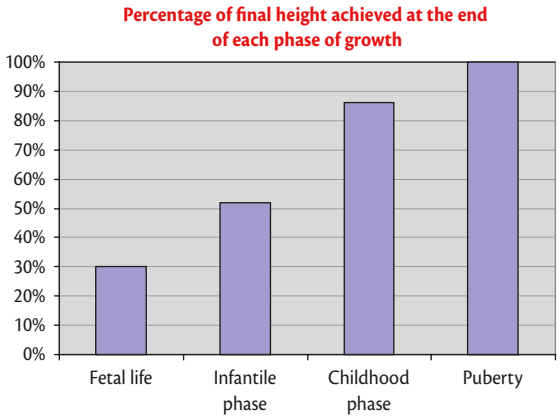
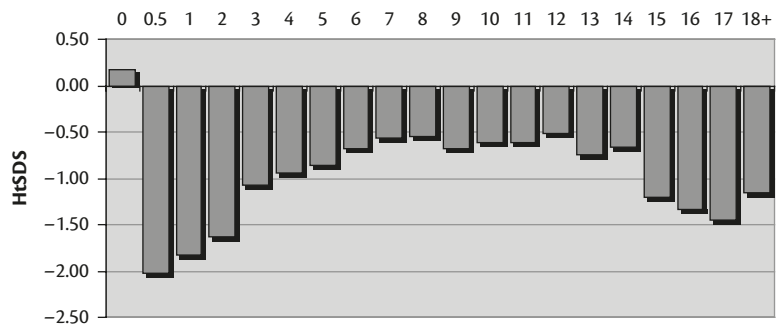


Fig. 291.1 The four phases of growth and the percentage of final height achieved at the end of each phase.

CKD stage 4/5 at birth with no other co-morbidities that might affect growth (Mekahli et al., 2010).

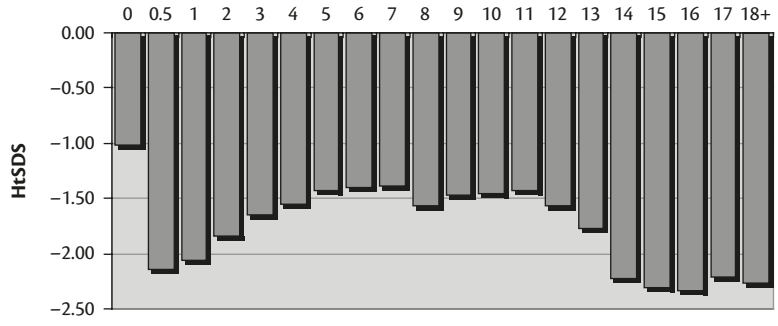
What can also be seen, however, is that, not unexpectedly, children with associated co-morbidities grow less well than children who are otherwise normal (Fig. 291.2B). A third of patients have one or more reported co-morbidities: renal abnormalities often coexist with syndromes and chromosomal abnormalities. Most of such infants will be SGA, and it can be seen in Fig. 291.2B that the HtSDS is already below normal at birth. Several studies have shown that both prematurity and low birth weight are common in young children with CKD. The incidence is particularly high in infants on dialysis but perhaps more surprisingly is high in children with less severe CKD too. Registry data does not always distinguish between infants who do or do not have co-morbidities, but it has been shown that of 429 children with a mean glomerular filtration rate (GFR) of 43 mL/min/1.73m^2 in the US CKD registry (52% of whom presented at birth), low birth weight (LBW, < 2500 g) occurred in 17%, prematurity (gestational age < 36 weeks) in 12% and SGA (birth

(A)



Age	0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+
N	20	33	38	39	38	37	35	33	33	30	29	31	27	28	23	23	17	17	12	17
BMI	14	12	12	14	14	15	16	16	17	18	20	21	20	22	23	23	23	23	22	25

(B)



Age	0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+
N	20	24	34	37	35	34	32	32	33	32	30	31	26	24	21	23	23	23	19	15
BMI	12	13	13	14	14	15	15	16	17	19	19	20	21	22	23	22	22	22	23	25

Fig. 291.2 (A) Height SDS and BMI in children without co-morbidities. (B) Height SDS and BMI in children with co-morbidities.
Reproduced with permission from Mekahli, D., Shaw, V., Ledermann, S.E., *et al.* (2010). Long term outcome of infants with severe CKD. *Clin J Am Soc Nephrol*, 5, 10–17.

weight < 10th percentile for gestational age) in 14%. Interestingly, 40% had needed intensive care at birth. The comparable overall incidence of abnormal birth history in the US population is 7–8%. LBW, prematurity, SGA, and requirement for intensive care were all risk factors for poor growth outcomes, independent of renal function (Greenbaum et al., 2011).

The principal reason for a progressive decline in HtSDS after birth is that the infant with CKD is characteristically difficult to feed because of anorexia and vomiting. There are many reasons for this. Appetite may be decreased due to the need for multiple medications, deceased clearance of cytokines that affect appetite and satiety, and because the most common diagnosis in infants with CKD is CAKUT. Such infants often have obligatory losses of salt and water and therefore have a preference for salty foods and large volumes of water. Vomiting is common, due to the fact that the infant diet is liquid and therefore high volume, and because gastro-oesophageal reflux is frequent and elevated polypeptide hormones result in abnormal gastrointestinal motility. Urological surgery or episodes of sepsis may result in periods of fasting. Struggling with feeds may result in family stress and this may exacerbate the situation. The infant on peritoneal dialysis (PD) is vulnerable to raised intra-abdominal pressure, which may affect both appetite and cause vomiting, and a fluid restriction may result in the need for specialized, hyperosmolar feeds in order to provide adequate nutrition. Peritoneal dialysate losses of protein and sodium may be high. Finally, co-morbidities may cause poor feeding in their own right (Rees and Brandt, 2010).

There is some evidence that the prognosis for growth in young children is improving with time: a study from the United States found that the mean HtSDS of children starting dialysis before 18 months of age between 1983 and 1995 was −3.0. This had increased to −1.4 between 1996 and 2008 (Hijazi et al., 2009).

What can be done to improve growth in infancy?

Because growth in infancy is so dependent on nutrition, all efforts have to be focused on the provision of an optimum intake. This is often difficult without the use of supplementary feeding. Prokinetic, antacid, and antireflux drugs may be of benefit but if there is a decline in the rate of growth the early use of enteral feeding can prevent any further deterioration. The aim is to pre-empt the development of malnutrition rather than treat it after it has happened. Frequent review and the involvement of a renal dietician are essential: a baby entirely dependent on a prescribed enteral feed needs the volume, energy, and protein increased on a weekly basis or they will rapidly become underfed (Rees and Jones, 2013). The International Paediatric Peritoneal Dialysis Network (IPPN) registry of the International Pediatric Dialysis Network has provided some interesting data from around the world, enabling review of 153 infants on PD. On analysis of feeding type, dialysis intensity, biochemical, and haematological control, only gastrostomy feeding was associated with improved preservation of linear growth; demand or nasogastric feeding did not show any benefit (Rees et al., 2011).

The childhood and pubertal phases of growth

The rate of growth during the childhood phase is usually normal, although catch-up growth is uncommon. There is very little data on the onset and development of secondary sexual characteristics, and most studies are based on the timing and duration of the pubertal growth spurt. Historically these have demonstrated that a delayed and diminished pubertal growth spurt and a reduction in total height gain was common, although growth continued into late adolescence. However, more recent data from children on RRT between 1998 and 2009 have shown a substantial improvement in all aspects of growth and development, such that bone age delay is less pronounced, onset of puberty is less delayed, age at menarche is almost normal, and the height gain during puberty has increased, with a clear pubertal growth spurt (Franke et al., 2013).

Causes of poor growth in chronic kidney disease

Nutrition

Although it is generally recognized that nutritional supplementation can induce catch-up growth during the infantile phase of growth (as described above), whether it can do so during the childhood and pubertal phases is controversial (Rees and Jones, 2013). However, improvement in nutritional state is important to prevent morbidity and decrease mortality. Hypoalbuminaemia, a surrogate marker of protein energy wasting, has been associated with mortality in children initiating dialysis, such that each −1 g/dL difference in serum albumin between patients was associated with a 54% higher risk of death. On the other hand, a higher albumin (> 4 g/dL) in adolescents on haemodialysis (HD) was associated with a 57% reduced risk of death, as well as fewer hospitalizations. Given the known deterioration in nutritional intake that occurs as CKD progresses, early nutritional intervention is important for both long-term survival and linear growth (Rees and Mak, 2011).

Haematological and biochemical parameters

Acidosis and chronic sodium depletion, particularly in infants with CAKUT who are frequently salt and bicarbonate losers, are easily correctable causes of poor growth. The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) CKD database identified that a haematocrit < 33% was an independent risk factor for short stature, and treating anaemia early does seem to be associated with an improvement in growth. The optimum range for parathyroid hormone (PTH) levels is controversial, but certainly severe hyperparathyroidism is associated with impaired growth, and growth can be normal with PTH levels within the normal range, even in children on dialysis (Rees and Jones, 2013).

The GH–IGFI axis

Children with CKD have normal to high levels of circulating GH despite poor growth indicating a degree of resistance to it. This is due to decreased tissue expression of the GH receptor, abnormalities in post-GH-receptor signalling, and decreased bioactivity of IGF-1 due to an excess of circulating IGF-binding proteins (Rees and Mak, 2011).

Recombinant human growth hormone (rhGH) has been used for many years to improve growth in children with growth failure due to CKD. A Cochrane meta-analysis concluded that 1 year of 25 IU/m^2/week rhGH administration in children with CKD results in an average height increase of 3.88 cm over the first year of treatment, with decreasing effect thereafter (Hodson et al., 2012). The response in prepubertal children and/or stage 3 or 4 CKD exceeds that in pubertal children and/or stage 5. RhGH administration may result

in an increase in final adult height but there are no randomized controlled trials. RhGH therapy is also associated with higher muscle mass in children with CKD stage 5 (Foster et al., 2011).

Steroid therapy

Steroid therapy has a detrimental effect on growth. Clearly dose has the most important effect, but duration of therapy is another important factor that can cause delayed bone maturation, delayed onset of puberty, and therefore a delayed, attenuated pubertal growth spurt, which can extend into early adult life (Rees and Mak, 2011). The use of steroid-sparing regimens has been beneficial on growth post transplant (Klare et al., 2012).

Dialysis dose

The dialysis dose that would optimize dietary intake, nutritional status, and growth is unknown. However, the greatest success in inducing catch-up growth has been seen in children on intensified HD programmes, including short sessions of haemodiafiltration (2–3 hours, five or six times per week) (Fischbach et al., 2010), and nocturnal HD (Müller et al., 2008). This is likely to be due to improved clearance of toxic molecules, reduction of inflammation, and improved appetite and/or nutritional intake.

Epidemiology of growth in chronic kidney disease

It might be expected that over the years there would be an improvement in the HtSDS of children entering RRT programmes. The use of gastrostomies, newer feed supplements and treatments for anaemia, better understanding of the effects of acidosis and renal bone disease on growth, and the use of rhGH would be expected to contribute to this. In Germany, the overall mean HtSDS has improved over the past 20 years from −3.03 to −1.80. Interestingly, this improvement seemed to be predominantly in the peripubertal years: until the age of 6 years, the difference in HtSDS was not significant, whereas it improved significantly in adolescence from −3.40 to −1.52 with a decrease in the delay of the pubertal growth spurt, age at menarche, bone maturation, and body mass index (BMI) (Franke et al., 2013).

Conservatively managed CKD

Even moderate reduction of GFR has been reported to result in impaired growth. The principal registry providing data on the epidemiology of growth in conservatively managed CKD is the NAPRTCS. The 2006 report covers the 10 years between 1994 and 2004 and includes a very large cohort of > 5000 children with GFRs of up to 75 mL/min/1.73 m^2. As expected, the most growth retarded were the youngest children, with a mean HtSDS for < 2 years of age of −2.3, but mean HtSDS was reduced at all ages (−1.7, −1.4, −1.0 at 2–6, 6–12, and > 12 years respectively), with over one-third overall being below the third centile for height. HtSDS worsened with progression of CKD, so that there was a strong correlation between creatinine clearance and HtSDS (−3.2, −1.9, −1.5, and −0.9 for GFR < 10, 10–25, 25–50, and > 50 mL/min/1.73 m^2 respectively) (Seikaly et al., 2006). This means that many children, and particularly the very young, are already short at the time of entry to RRT programmes. NAPRTCS data for 2005 found that the mean HtSDS at the start of dialysis in 3910 children was −1.66, that is, well below that of the normal population, in whom the mean HtSDS would be 0 (NAPRTCS, 2005).

Dialysis

Short stature is even more common in children on dialysis. The United States Renal Data System (USRDS) is another registry collecting data on patients on RRT programmes in the United States. The 2007 report shows that the height and weight of approximately half of children on dialysis were below the 20th centile for the normal population (United States Renal Data System, 2008, pp. 296–7). The British Association for Paediatric Nephrology (BAPN) reports that in 2006, of 105 dialysis patients, 61% were below the 10th percentile, and 44% below the 2nd centile for height (Lewis et al., 2011). The IPPN collects data from > 1800 children on PD from around the world, and is, therefore, able to provide comparisons of all aspects of PD according to region in a large cohort of children on PD to date. Currently, the mean HtSDS at commencing PD is −2.35 SD, and is below normal worldwide, but there is a large variation, ranging in 21 countries from −1.3 in the United Kingdom, to −3.5 in Brazil. The mean BMI SDS is −0.01, and does not parallel the HtSDS, however, with less variation from normal. BMI has a wide range throughout the world, varying from a high incidence of obesity in the United States, where the mean BMI SDS is 0.8, to malnutrition, the lowest BMI being in India, where it is −1.4 (IPPN, 2012). Regional variations in resources are likely to contribute to these differences (Rees and Mak, 2012).

A declining rate of growth on dialysis is described in most studies, including three registries that report on longitudinal growth on dialysis: namely NAPRTCS, the IPPN and the BAPN. The NAPRTCS (2006) reports a decrease in HtSDS from −1.64 to −1.71 after 1 year and −1.84 after 2 years (NAPRTCS, 2006), and in the 2011 report, the mean HtSDS of 3292 children commencing chronic PD was −1.71, and was −1.77 after 2 years in 781 children still receiving PD. Weight deficit was not as bad as height deficit, at a mean of −1.13 SD (NAPRTCS, 2011). Younger children and those with the lowest BMIs were most likely to have an increase in weight SDS. Of 407 HD patients, the mean change in HtSDS/year was −0.10. Growth retardation was most pronounced in patients who were young, male, had longer durations on HD, and higher nPCR and baseline HtSDS (Gorman et al., 2008). Patients in the IPPN showed a decrease in HtSDS that correlated with time on PD (IPPN 2012). In the United Kingdom between 1999 and 2008, HtSDS remained remarkably stable, at a median of −1.4 to −1.9 SD. Weight, too, remained stable, at −0.9 to −1.6 SD (Hussain et al., 2010). There is no evidence that growth differs with dialysis modality (NAPRTCS, 2006). Given our knowledge that in the majority of reports HtSDS declines with increasing time on dialysis, the obvious key to prevention of growth deterioration is pre-emptive transplantation.

Post transplant

Catch-up growth may occur post transplant but is dependent on age, transplant function, and immunosuppressive regimen. The NAPRTCS database for 2005 described the mean HtSDS at transplant and over the next 6 years according to age. This data demonstrates the importance of height achievement before transplant, because only children below the age of 6 years showed any improvement in growth post transplant (NAPRTCS, 2005).

NAPRTCS data also suggests that HtSDS at the time of transplant has improved over the years, from a mean HtSDS of −2.4 in 1987, to −1.4 in 2007 (Fine et al., 2010). BAPN data has shown that between 1999 and 2008, HtSDS has remained stable, at a median of −1.2 to −1.4, that is, similar to NAPRTCS later values (Hussein et al., 2010). However, reports from children managed with steroid-free immunosuppression suggest that much better growth can be obtained (Klare et al., 2012).

Overall, children on dialysis are shorter than their transplanted peers, although both groups are below the heights of the normal age-matched population. Some children can be very short: BAPN data showed that 48% of transplant patients were below the 10th percentile with 39% being below the 5th percentile and 27% below the 2nd percentile. The corresponding figures for dialysis patients were 61% below the 10th percentile, 54% below the 5th percentile and 44% below the 2nd percentile (Lewis et al., 2007).

Final height

Most reports of final heights do not discriminate according to the patient characteristics, and in particular registries do not separate out children with co-morbidities that affect growth. Also, inevitably, they reflect treatment that commenced at least 18 years ago. Furthermore some patients may have been in CKD stage 5 from birth whereas others may already be well grown before they develop CKD in later childhood. Patients may have been managed with dialysis, transplant, or, most likely, both. They may or may not have received steroids. With this in mind, mean final heights vary from 148–158 cm for females to 162–168 cm for males (2nd percentiles 151 and 163 cm respectively), with over half of patients attaining an adult height within the normal range. There is very little difference to be seen whether treated with rhGH or not (Rees and Jones, 2012).

There is evidence that over the years, final height post transplantation is improving (Fine et al., 2010). This is likely to be due to a combination of factors such as better growth attained prior to transplant, pre-emptive transplantation thus avoiding dialysis, and to the development of protocols that minimize the use of corticosteroids. European data show an improvement in final height from −2.06 SDS in children who reached adulthood in 1990–1995 to −1.33 SDS among those reaching adulthood in 2006–2011. Older age at start of RRT, starting RRT more recently, cumulative time with a transplant, and greater height SDS at initiation of RRT were independently associated with a higher final height SDS. Most impressively, recent results of the avoidance of post-transplant steroids altogether has reported excellent results, with mean final heights of 177 and 175 cm in males transplanted prepubertally and postpubertally respectively with similar figures of 165 and 162 cm for females (Klare et al., 2012)

Obesity

Obesity is emerging as a new problem for children with CKD, and seems to parallel the incidence around the world in the normal population. The IPPN database demonstrates this regional variation in BMI, from a mean BMI SDS of 0.8 in the United States to −1.4 in India in children of all ages (IPPN, 2012); and of infants, 26% were obese in the United States and 50% malnourished in Turkey (Rees et al., 2011). In the European Society for Paediatric Nephrology (ESPN)/European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) registry including 25 countries, of 5199 patients below the age of 18 years the prevalence of underweight was 4.3%, while 19.6% and 11.2% were overweight or obese respectively. Receiving steroid therapy and living with a renal transplant were independent risk factors for overweight. In North America, the frequency of obesity is increasing in the CKD population both before and at CKD stage 5 (Rees and Jones, 2012).

Obesity is a particular problem after renal transplantation. This has been studied in the NAPRTCS database in a retrospective cohort study of 4326 children transplanted between 1995 and 2006, and followed up to January 2007. Median BMI increased by 11% at 6 months but with no substantial changes thereafter (Foster et al., 2010). The use of steroid-sparing regimens may mitigate post-transplant obesity (Klare et al., 2012).

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CHAPTER 292

The adolescent with renal disease: transition to adult services

Stephen D. Marks

Introduction

Transition to adult care can cause anxieties and concerns for young adults with any nephrological condition with normal or abnormal renal function (chronic or end-stage kidney disease). It is rightly perceived to be a high-risk time for young adults with chronic diseases, but it is also widely recognized that risk-taking behaviour is common in healthy individuals at this age. Transition may sometimes be blamed for behaviours that were liable to happen anyway; on the other hand, there is persuasive evidence that the risks can be reduced.

Transition programmes are designed to phase the move to adult services and reduce the risk of loss of confidence in the services. They may begin any time from about 11–13 years of age and are aligned to either transitioning from a paediatric service to an adult service; or a paediatric service to a transition clinic to an adult service; or a paediatric service to an adolescent service to a young adult service to a general adult service.

Living with a chronic illness is difficult for patients of any age, but is more complex with the developing mind and body of adolescents trying to find their identity. Most adolescent patients expect, or are expected, to become independent and manage their own healthcare needs and take over their healthcare responsibilities from their legal guardian(s) or parent(s). This includes being responsible for obtaining and self-administration of medications, reaching fluid targets (or not exceeding fluid limits), diet, catheterization, attending outpatient clinics, and complying with investigations and adhering to treatments. Some adolescents have complex healthcare needs (some of whom may have developmental delay) and may have different paediatric subspecialty consultants, which require to be transferred to adult specialists.

Medical, surgical, and nursing practices have changed over the years and many children are now surviving into adult life with conditions that were once unknown to adult nephrologists (such as primary hyperoxaluria or cystinosis). Issues around transition also affect those not susceptible to end-stage kidney disease such as frequently relapsing nephrotic syndrome.

Adherence

Many professionals discussing the difficulties of managing adolescents with chronic disease will highlight the importance of adherence to recommended therapy.

International registries report reduced patient and renal allograft survival in young renal transplant recipients. Each year, young adults lose their precious kidney transplants and dialysis patients die from complications as a result of non-adherence. Understanding risk-taking behaviour as a normal part of the adolescent developmental process is key to dealing with complex situations and discussions, such as the experimentation of recreational drugs. Young adults need to learn about the causes of their renal condition and the importance of medications (especially immunosuppressive medications for renal transplant recipients) if they are to maintain adherence to therapy as they adopt responsibility for it. It is important for young adult patients with renal disease to adhere to their medications, diet, fluid allowance or target, lifestyle, catheterization, and management of stomas and dialysis where appropriate as well as clinic appointments and investigations.

Renal transplant recipients need to know that non-adherence to immunosuppressive medications may result in renal allograft loss and the requirement for dialysis (although the young adult may never have had dialysis or may not remember their dialysis treatment if this was in their early childhood).

A key issue is that if patients do not feel well cared for (or cared about) in their new environment, this education may be wasted.

Timing of transfer

Timing of transfer of care should take into account chronological age and maturity, adolescent readiness, medical stability, psychosocial issues, and the views of the adolescent and their parents or guardians.

In the United Kingdom, transfer to adult services usually occurs between 16 and 18 years of age. However, this is interpreted flexibly in some areas, although practice varies internationally and some adult units do not have trained staff to manage young adults before their 18th birthday. The American Society of Adolescent Medicine very reasonably recommends that services should be appropriate for both the chronological age of the patient and development attained.

Historically, young adults were transferred to adult nephrological care at a single point in time with movement to a new healthcare setting, provider, or both, without a preceding transition process. A preparation period and education programme may help the young patient to acquire the necessary knowledge and skills to

function in an adult service, largely independent of parents and staff, before they are transferred.

Where should they attend?

Asking adolescents where they would like to be seen in clinics may be valuable. Clinic attendance may be hampered by young adults being surrounded by much older, sicker patients, but also by being in an environment that was clearly created for young children in mind, as is often the case for paediatric facilities.

Visits to and meeting staff and/or patients from the adult unit can help to allay fears during the preparation for transfer.

The transition process itself depends on the modality of renal therapies and requirement for nephrological follow-up. This may be relatively simple for patients with chronic kidney disease, or more complex for adolescents with end-stage kidney disease who require in-centre haemodialysis (waiting for a slot to dialyse in an adult satellite unit), or home haemodialysis or peritoneal dialysis. There may be a tension between providing local care and attendance at a specialist clinic such as a transplant clinic, or one for a specific group of diseases, or indeed a transition or young adult clinic.

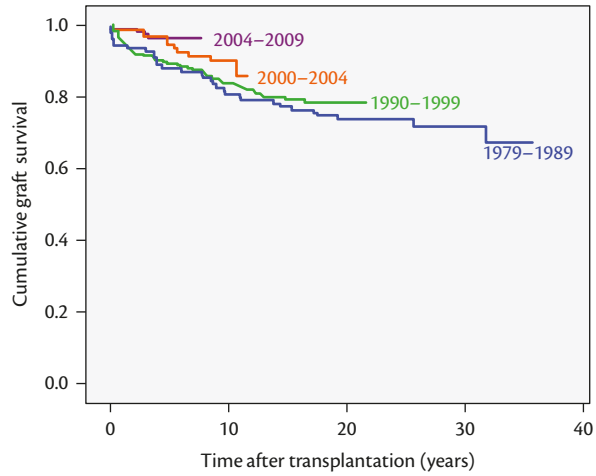
Transition programmes

Modern transition programmes view transfer as only one component, with transition as an anticipated, coordinated process of movement from child-centric to adult-oriented healthcare systems over a prolonged period of time. This smooth transition of care for adolescents with renal disease between paediatric and adult nephrology services should involve a preparatory phase, the transfer event itself and post-transfer phase.

Transfer of care can be a stressful time for patients and their parents. Parents may be reluctant to leave familiar staff and clinic surroundings and resist attempts by the adult service to enhance the self-advocacy of their child, if not adequately prepared. The development of young adult clinics in adult nephrology may help to bridge the gap between paediatric and adult services and enhance the education and preparation of young adults from a parent-focused to patient-focused service.

A good transition programme should individualize care on a background model of transitioning young adults with renal disease. The framework should involve adolescent trained physicians, surgeons, nurse specialists, pharmacists, and allied health professionals, including the psychosocial team and other multidisciplinary team members, such as youth workers. Ideally both paediatric and adult professionals provide ongoing care in a joint clinic from adolescence through to adulthood, the duration of which can be individualized. Patients then benefit both from experts in paediatric diseases and the appropriate management of more pertinent adult issues, such as sexual health, fertility issues, and cardiovascular disease.

This model is used in the transitioning of adolescent renal transplant recipients at Great Ormond Street Hospital for Children NHS Foundation Trust, London, where the joint clinic lasts for around 2 to 3 years (Fig. 292.1). Young adults and their families attend a special joint transition clinic at 3-monthly intervals in addition to both regular and adolescent clinic appointments during the preparatory phase of transitioning, setting an individualized time in the future for transfer of care to adult healthcare services, supported by youth workers and a buddy system to foster peer support. During these specialist clinics, educational sessions are available for both patients and their parents, who have informal visits to the adult hospital setting and its inpatient and outpatient clinic facilities where they see adult staff previously introduced to them by the paediatric staff. This facilitates familiarity with the new adult team prior to embarking on formal outpatient clinic attendances with investigations, such as blood tests (which may be an issue for some adolescent patients).



1979–1989	115	111	90	81	20
1990–1999	235	229	192	25	
2000–2004	98	96	35		
2004–2009	130	129			

Fig. 292.1 Transition programme for adolescents with renal disease. Improvement of cumulative graft survival with more recent transition programmes.

Improved patient outcomes

Transition programmes are set up to improve patient-related outcome measures as well as patient experiences. However, improving patient outcomes can only be achieved by careful preparation and management. Renal allograft outcomes are improving (Fig. 292.2) and transition programmes may be contributing to this.

Adolescents may be reluctant to leave friends and healthcare personnel. They may lack maturity, have adherence issues, and an ongoing dependence on parents or guardians. Their parents or legal guardians may not accept relaxing the reins as they have taken the lead in their child's care, potentially for years in the paediatric clinic. They need to work towards a good long-term outcome, which depends on the young adult managing their own care in a safe and reliable manner.

Barriers

There may be barriers to successful transition from the healthcare system, which may be related to personnel or time and financial constraints of services. However, unsuccessful transfers can be very expensive in hospital admissions, lost allografts, and lost lives.

There should be communication links between paediatric and adult services, with transfer of documentation (including inpatient and outpatient medical and nursing notes, operation notes,

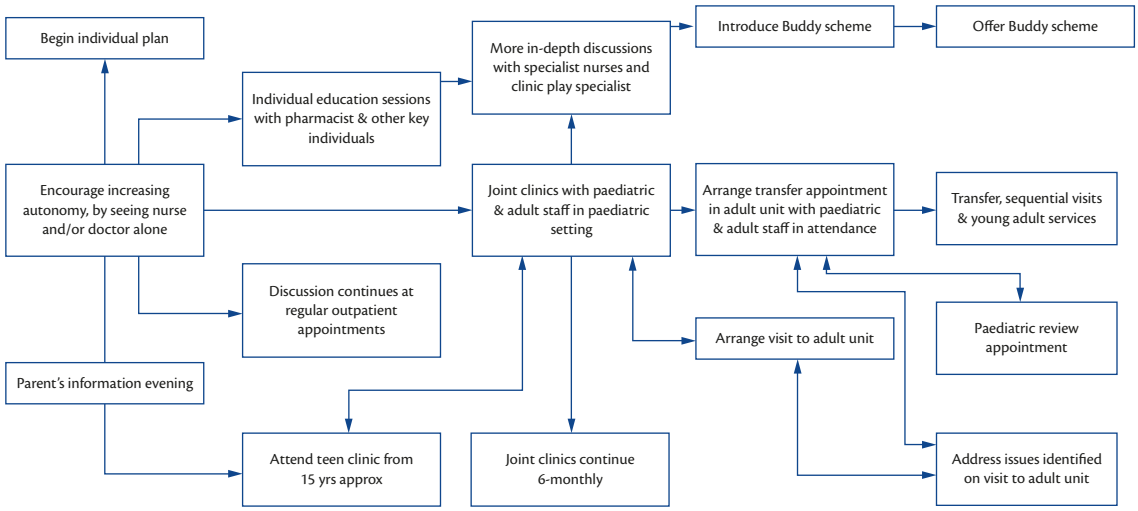


Fig. 292.2 Improvements in renal allograft survival over time.

longitudinal laboratory data, including histopathology and radiology results, and specialist reports). Paediatric medical and nursing staff may have an emotional attachment to patients and lack confidence in the potential care given by health professionals in the adult clinic due to differences in the attitudes and priorities of adult services—or simply because they do not know the staff there.

Adult medical and nursing staff may lack confidence in managing adolescents. They may be concerned regarding different dynamics of consultation (such as the presence of parents in consultations). They may also lack confidence in paediatric staff if aware of differences in the attitudes and priorities of paediatric services (such as feeling that the paediatrician has not managed the patient correctly or transferred either too early or too late).

Many of the attitudinal barriers can be lowered by involving a limited group of staff in transfers and ensuring good communication in both directions via this team.

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CHAPTER 293

Contraception in patients with kidney disease

Kate Wiles and Catherine Nelson-Piercy

The importance of reproductive health issues in the renal population

It is estimated that family planning programmes worldwide prevent 187 million unintended pregnancies, 105 million abortions, 60 million unplanned births, 2.7 million infant deaths, and 215,000 maternal mortalities (Amy and Tripathi, 2009). Conclusive evidence that contraceptive counselling improves use of, adherence to, or continuation of contraceptive practices is difficult to obtain, particularly in the context of heterogeneous randomized trial data (Lopez et al., 2008). However, consensus opinion is that contraceptive counselling improves patient choice, patient satisfaction, and more sustained use of correct contraception (Amy and Tripathi, 2009). Contraception counselling in relation to renal disease includes the ability to provide accurate and appropriate information for those with chronic kidney disease (CKD) of varying aetiology and severity, as well as for the renal transplant population.

CKD is estimated to affect 3% of women of childbearing age (Coresh et al., 2007) and population trends of older primiparity and increasing obesity are likely to cause this to rise. The severity of pre-pregnancy CKD is the major determinant of the increased risk to pregnancy in terms of fetal growth restriction, preterm delivery, pre-eclampsia, and perinatal death; as well as conferring a proportional risk of persistent deterioration in maternal renal function post partum (Williams and Davison, 2008). The teratogenic properties of angiotensin converting enzyme inhibitors and angiotensin receptor antagonists need to be remembered in this population for whom they are widely prescribed. In a small UK study, only 48% of women aged 20–45 with CKD had discussed contraception, 45% did not know the risks of pregnancy, 39% were unaware of potentially teratogenic medication, and 29% had had an unplanned pregnancy (Baines et al. 2011).

Although end-stage renal disease confers a fertility rate 10 times lower than the general population, conception and high-risk pregnancy can occur with 3.3 pregnancies per 1000 patient-years in more recent cohorts (Shahir et al., 2013). However, apparently few nephrologists discuss fertility issues with their dialysis patients (Kimmel and Patel, 2003).

Following transplantation, fertility increases and ovulatory cycles can begin as early as 1 month after renal transplantation (Watnick and Rueda, 2008; Faculty of Sexual and Reproductive Healthcare, 2009; Deshpande et al., 2011). Pregnancies in patients following renal transplantation are associated with more complications than women with matched native renal function (Stratta et al., 2006; Bramham et al., 2013). In addition, the teratogenicity of maintainance immunesuppresion, specifically mycophenolate mofetil, needs to be considered (Pisoni and D'Cruz, 2008). In the United Kingdom, 100–500 per million women aged 20–44 years have renal transplants (UK Renal Registry, 2011) and data in the United Kingdom suggest that over one-third of patients with a renal transplant have unplanned pregnancies (Bramham et al., 2013). In the United States, 5–12% of renal transplants occur in women of childbearing age of whom 50% have unintended pregnancies (Yildirim and Uslu, 2005). These data are mirrored around the world with 29% of pregnancies being unintended in kidney transplant recipients in Iran, 92% of whom were using coitus interruptus as the only method of contraception (Ghazizadeh et al., 2005). In China, 15% of transplant patients reported unwanted pregnancies with 34% of these women having two or three unwanted pregnancies. Of these, 56% were not using any method of contraception largely due to a failure to realize that reproductive potential is restored after transplantation (Xu et al., 2011). Less than 50% of a Brazilian transplant population was found to have received contraceptive advice following renal transplantation and 92.9% of pregnancies in this group were unplanned (Guazzelli et al., 2008).

Risks of contraceptive use in renal patients

There are very few studies that have specifically examined the safety of different contraceptive methods in patients with renal disease as most trials deliberately exclude subjects with medical comorbidity. Evidence from 'healthy' populations is therefore used to determine the suitability of different contraceptive methods in those who have renal disease. The *UK Medical Eligibility Criteria for Contraceptive Use* offers evidence-based and expert consensus guidance for contraceptive use in the presence of different medical conditions (Faculty of Sexual and Reproductive Healthcare, 2009). Although renal disease is not considered as a separate entity within this guideline, advice on specific presentations that apply to women with renal disease is offered. Relevant for nephrologists is the guidance on hypertension, lupus, diabetes, venous thromboembolism (VTE), and vascular risk. These issues are discussed for each of the contraceptive methods below.

In providing contraceptive counseling to renal patients, it must be remembered that the effectiveness of any contraceptive method depends on both the acceptability of the method to the patient and subsequent compliance. Although absolute contraindications to particular contraceptives can exist in certain clinical settings, the

Table 293.1 Summary of the advantages and disadvantages of contraceptive methods for women with renal disease

Contraceptive method		Advantages	Disadvantages
Combined contraceptives	Combined oral contraceptive (COC)	Reduced ovarian and endometrial cancer risk	Failure rate 0.3–8% Increased VTE risk (~ ×2 background) Blood pressure rise Increased arterial thrombosis risk Increased cervical cancer risk
	Transdermal combined patch (Evra®)	Not affected by vomiting or malabsorption	Failure rate 0.3–8% Oestrogen risk as for COC Higher risk of VTE than COC
	Vaginal ring (Nuvaring®)		
Progesterone-only contraceptives	Progesterone-only pill (POP)	Safe for those for whom oestrogens are contraindicated including VTE and hypertension	Small compliance window (excluding desogestrel preparations)
	Intramuscular depot (Depo-Provera®)	Not affected by vomiting or malabsorption Effective for 12 weeks	Increased break-through menstrual bleeding Adverse lipid profile (increased LDL, reduced HDL) Reversible decrease in bone-mineral density
	Implant (Nexplanon®)	Not affected by vomiting or malabsorption Effective for 3 years	Increased break-through menstrual bleeding
	Intrauterine system (Mirena®)	Failure rate < 1% Not affected by vomiting or malabsorption Effective for 3 years Reduced menstrual bleeding	
Copper IUD		Failure rate < 1% Not affected by vomiting or malabsorption Can be used as emergency contraception Effective for 10 years	Increased break-through menstrual bleeding
Barrier methods	Male condom	Convenient Protection against sexually transmitted disease Not affected by vomiting or malabsorption	Significant failure rate with typical use (15–32%) Increased UTIs Genital ulceration and HIV risk with spermicide use
	Female condom		
	Cervical cap		
	Diaphragm		
	Sponge		
Sterilization		Effective	Irreversible Operative risk for female renal patient
Fertility awareness methods			Failure rate 25% Signs and symptoms affected by medication
Lactational amenorrhoea		Benefits of breastfeeding for infant	Difficult to 'diagnose' post-partum amenorrhoea Finite time span

'safety' of a particular method is often not a discrete 'yes–no' variable but exists on a spectrum from recognized safety to contraceptive risk potentially outweighing benefit. Acceptability must be considered in this context. In addition, contraceptive decision-making must be weighted against the risk of an unplanned pregnancy in renal disease, particularly in the contexts of unstable renal function and the use of tetratogenic medication.

Table 293.1 provides a summary of the advantages and disadvantages of different contraceptive methods, with specific reference to those with renal disease. Important drug interactions which are relevant to nephrological practice are outlined in Table 293.2.

Combined oral contraceptives

The combined oral contraceptive (COC) contains an oestrogen, most commonly ethinylestradiol, and a progestogen, which act to inhibit ovulation. The effectiveness of the COC can be measured in terms of 'typical use' with a failure rate of 8 per 100 women per year. This is recognized to be lower than with 'perfect use,' which has a failure rate of only 0.3 per 100 women per year (Trussell, 2004).

The amount of oestrogen in the pill has fallen over time due to the epidemiological link between oestrogen and breast cancer and the association of oestrogen with adverse thromboembolic,

Table 293.2 Interactions between renal drugs and contraception

Class of drug	Effect/interaction	Effect on contraceptive efficacy	Recommendations
Antihypertensives	Hypotensive effect may be antagonized by combined hormonal contraceptive	None expected	Monitor
Diuretics	◆ Oestrogens may antagonize diuretic effect ◆ Theoretical risk of hyperkalaemia when potassium sparing diuretics are used with drospirenone	None expected	Monitor
Statins		Minor to moderate increase in ethinylestradiol. Clinical significance unknown. Effect likely to be small	
Antidiabetic drugs	Oestrogens and progestogens antagonize hypoglycaemic effect		Monitor
Immunosuppressants	◆ Plasma levels of tacrolimus possibly increased by ethinylestradiol, gestodene, and norethisterone ◆ Ciclosporin levels possibly increased by oestrogens and progestogens—unconfirmed and uncertain clinical significance	Tacrolimus theoretically inhibits metabolism of oestrogens and progestogens. Clinical significance unknown. Effect likely to be small	Monitor tacrolimus and ciclosporin levels Monitor liver function.
Reflux medication: proton-pump inhibitors and H_2 receptor blockers	Increased gastric pH theorectically reduces absorption of ulipristal acetate (selective progesterone receptor modulator used as emergency contraception)	Reduced efficacy of ulipristal acetate	Concomitant use of ulipristal acetate and PPI/H_2 blockers is not advised

Adapted from Faculty of Sexual and Reproductive Healthcare (2012). *Drug Interactions with Hormonal Contraception*. London: Royal College of Obstetricians and Gynaecologists.

cerebrovascular, and cardiovascular events. Today's COCs contain approximately 30 micrograms of oestrogen compared to a historical 50 micrograms. Studies of COCs with a 20-microgram oestrogen component have failed to demonstrate vascular risk reduction (Lidegaard et al., 2002) but do show increased menstrual cycle disruption and trial discontinuation due to menstrual bleeding disturbances (Gallo et al., 2008).

The non-contraceptive benefits of the COC include a 20% reduction in the relative risk of ovarian cancer for every 5 years of use in addition to a measured protective effect against endometrial cancer (Amy and Tripathi, 2009). Cancer prevalence in users of the COC has relevance to the renal transplant population in whom, as a product of immunosuppressive burden, there is an increased lifetime risk of cancer. Although use of the COC could theoretically reduce the transplant patient's twofold risk of ovarian cancer, the clinical concern is that the fivefold risk of cervical cancer that transplantation confers, may be augmented by the use of the COC (Watnick and Rueda, 2008).

The use of COCs increases the risk of VTE from an incidence of 3.01 per 10 000 women years in never or former users to 6.29 per 10,000 women years in current users (Lidegaard et al., 2009). A higher oestrogen content and the use of the progestogens desogestrel, gestodene, and drospirenone are associated with increased risk. Of note, this doubling of VTE risk occurs even when patients taking medication for diabetes, heart disease, hypertension, and hyperlipidaemia are excluded from the study. The VTE risk of COCs is unacceptable for patients with a history of VTE and for patients with lupus and either positive, or unknown, antiphospholipid antibodies. Nephrotic syndromes are not included as a discrete entry in either UK or international contraceptive guidelines, presumably due to their rarity in the young female population. However, given the nature of coagulation abnormalities in nephrosis, including urinary losses of anticoagulants and increased hepatic synthesis of procoagulants stimulated by hypoalbuminaemia (Kanfer, 2008), the added thrombotic risk of COCs with either sustained or remitting proteinuric disease needs to be remembered and alternative contraceptive methods prescribed.

Use of the COC is associated with a rise in blood pressure and, although the mechanism for this is not clearly understood, the increase in blood pressure can exceed diagnostic thresholds for hypertension (Chasan-Taber et al., 1996; Williamson et al., 1996). This is relevant to the renal population where rates of arterial hypertension are much higher than in the general population. In a study of oral and transdermal combined hormonal contraceptive methods in a renal transplant population, > 80% of patients were hypertensive at study entry and modifications in the type and doses of antihypertensives were required when these contraceptive methods were introduced (Pietrzak et al., 2007). COCs have been found to influence the renal haemodynamic response to salt. Salt loading in patients taking COCs produces an increased filtration fraction, which is hypothesized to be due to the effects of exogenous oestrogen on the renin–angiotensin system, nitric oxide, and prostaglandins (Pechère-Bertschi et al., 2003). These haemodynamic data come from women without concomitant renal disease, but generates concern that there could be an adverse impact on disease progression.

The arterial thromboembolic risk of COCs is very relevant to the renal population. Reduction in glomerular filtration rate and proteinuria are both independent vascular risk factors and the excessive cardiovascular mortality associated with end-stage renal disease is well described (Baigent et al., 2000; Go et al., 2004; Di Angelantonio et al., 2010). Even patients who have undergone renal transplantation carry an excessive vascular disease burden (Watnick and Rueda, 2008). COCs add to vascular risk and increase rates of thrombotic stroke and myocardial infarction 1.3–2.3-fold compared to non-COC users (Lidegaard et al., 2012a). The vascular

risk of COCs means they are contraindicated in established vascular disease. In addition, the risks of COC use outweigh any advantage in obesity (body mass index (BMI) > 35 kg/m^2), cigarette smokers, diabetes with microvascular complications, and even patients with controlled, treated hypertension.

Other combined hormonal contraceptives

Just like the COC, both the transdermal combined patch (Evra®) and the vaginal ring (Nuvaring®) utilize a combination of an oestrogen and progestogen to inhibit ovulation. In addition, these non-oral methods will suppress endometrial growth and increase cervical mucous viscosity thereby inhibiting sperm migration to the uterus. The combined patch adheres to the skin and is changed weekly. The ring is placed into the vagina with hormonal transport across the vaginal wall into the bloodstream. The vaginal ring is worn for 3 weeks followed by a 1-week break. Both of these contraceptive methods can be considered equivalent to the COC in terms of efficacy and additionally will not be affected by nausea, vomiting, or gastrointestinal malabsorption. The use of the vaginal ring has been described in renal patients following transplantation without consequence to BMI, blood pressure, biochemical parameters, or immunosuppressive drug levels (Paternoster et al., 2010).

Adverse effects of these combined methods mirror those of the COCs. Therefore contraindications to the use of a transdermal combined patch or vaginal ring in patients with renal disease are the same as for COCs. In addition, cohort data suggest an even higher risk of VTE with the combined patch and vaginal ring than with COCs (Lidegaard et al., 2012b). Myocardial and thrombotic stroke data are limited by the small number of users of these methods and the rarity of these events in the populations studied. However, as vascular risk increases with age, women aged > 50 are advised to switch from these methods to progesterone-only or non-hormonal contraceptive methods. Based on that premise, the individual patient's premature vascular risk due to concomitant renal disease should be assessed and potentially prompt the same clinical recommendation. Long-term data including cancer association are not yet available.

Progesterone-only methods

Progesterone-only methods of contraception include the progesterone-only pill (POP) as well as parenteral and intrauterine methods of progesterone delivery. Parenteral methods include both an intramuscular injection of a long-acting progestogen (Depo-Provera®), which is repeated at 12-weekly intervals, and a surgically placed implant (Nexplanon®) effective for 3 years. Intra-uterine progesterone delivery is provided by an intrauterine system (IUS) with a slow-releasing progestogen reservoir of levornorgestrel (Mirena®) causing reversible atrophy of the endometrium, effective for 5 years.

Efficacy varies between these progesterone-only methods. Most POPs act primarily by thickening the cervical mucous and ovulation is not always inhibited. These preparations are dependent on daily compliance within a 3-hour window and therefore 'typical use' efficacy is less than with the COC (Weisberg, 1999). The exception to this is the desogestrel pill (Cerazette®, Cerelle®, Nacrez®, Aizea®) which will inhibit ovulation in most cycles and therefore has a 36-hour window within which to re-dose. Injectable and intrauterine methods which do not rely on daily compliance have lower failure rates than both combined and progesterone-only pills and therefore represent the most effective reversible contraceptive methods available (Amy and Tripathi, 2009). Use of the levornorgestrel IUS carries an unintended pregnancy rate of 0.2% in the first year of use, and use of a progestogen-based implant, 0.05% (Trussell, 2011).

The advantage of progesterone-only preparations is their safety profile in patients for whom oestrogens are contraindicated. In the renal population they can be used in patients with VTE, thrombophilia, and in the context of nephrotic syndrome, hypertension, smoking, and obesity. A cohort study of two potent progesterone-only oral contraceptive agents has been performed on 187 patients with systemic lupus of whom 22.9% had renal disaese and 8.5% were nephritic. This study demonstrated that the POP is an effective, well-tolerated contraceptive method (Chabbert-Buffet et al., 2011). Of note, use of the POP in this study population did not increase the incidence of either generalized disease flares or flares of lupus nephritis.

Although there are no absolute contraindications to their use, it is recognized that all currently used synthetic progestogens decrease circulating high-density lipoproteins (HDLs) and there is a well-recognized link between low HDL levels and ischaemic heart disease (Jamil and Siddiq, 2012). In addition, injectable contraceptives have been found to increase low-density lipoprotein (LDL) cholesterol, which although transient, does persist for up to 6 months after discontinuation (Berenson et al., 2009). For that reason, the theoretical risks of long-term progesterone-only formulations in the context of ischaemic heart disease, stroke, and antiphospholipid antibody positive lupus need to be considered. The use of depot formulations in vascular disease and complicated diabetes is not recommended in UK guidance (Faculty of Sexual and Reproductive Healthcare, 2009).

Of all the progesterone-only methods, only depot medroxyprogesterone (Depo-Provera®) has been shown to be associated with a decrease in bone mineral density, which is reversible with discontinuation of treatment (Walsh et al., 2008; Harel et al., 2010). Although an increased fracture risk has not been demonstrated, this may be a consideration in renal patients taking high-dose or long-term steroid therapy.

A final consideration is the effect of progesterone-only preparations in altering menstrual bleeding patterns. Although the Mirena® IUS reduces bleeding by 74–97% (Hubacher and Grimes, 2002), the other POP contraceptive methods can cause an increase in break-through menstrual bleeding. This spectrum of effects will need to be considered in the context of anticoagulation, lupus patients with associated thrombocytopenia, and for those who experience bleeding in association with uraemia.

Intrauterine devices

In addition to the progestogen-releasing IUS (Mirena®) described above, copper-bearing intrauterine devices (IUDs) also provide reliable contraception. The copper IUD works due to immobilization of sperm and inhibition of fertilization. It is effective for 10 years. A copper IUD represents the most cost-effective contraception method available in terms of efficacy provided, with first-year failure rates of 0.6–0.8%% (Trussell, 2011).

In contrast to the Mirena® which reduces menstrual bleeding, the main side effect of the copper coil is that it can increase menstrual flow by 30% and cause dysmenorrhea (Amy and Tripathi, 2009). In the renal population, this is relevant for patients with anaemia, thrombocytopenia, patients who are anticoagulated, and for those who are at risk from uraemic bleeding. A Cochrane review has recommended the use of non-steroidal anti-inflammatories for IUD-associated menorrhagia and dysmenorrhoea (Grimes et al., 2006) but this treatment will be contraindicated for many with renal disease.

Potential concerns have been raised with the use of both progesterone and copper IUDs in renal transplant recipients. Firstly, there is worry that they will be less effective in a patient who is maintained on immunosuppressive therapy. This concern is based on the premise that part of the mechanism of action of an IUD includes a local inflammatory response in the uterus and that this may be attenuated by immunosuppressive medication rendering the IUD less effective. IUD failure was reported in two renal transplant patients in 1981 (Zerner et al., 1981). However, evidence suggests that it is macrophages that play the most important role in the uterine milieu (Ortiz and Croxatto, 2007) and therefore would not be affected by the T-cell inhibitory actions of calcineurin inhibitors, antimetabolites, or biological agents such as basiliximab and daclizumab. In addition, corticosteroids can, in fact, increase macrophage activity via activation of macrophage migration inhibiting factor (Van Molle and Libert, 2005). Importantly, there are no reports of IUD failure in renal transplant recipients in contemporary literature. Although no studies have been performed to specifically examine this issue, there is no clinical evidence to suggest an excess of IUD contraceptive failure in the transplant population (Krajewski et al., 2013). IUDs are one of the most effective contraceptive methods available that should not be denied to renal transplant recipients on the basis of flawed biological theory (Estes and Westhoff, 2007).

A second theoretical concern regarding the use of IUDs in the transplant population is one of infection. However, small, retrospective studies of renal transplant patients have failed to show any cases of either pelvic infection or unplanned pregnancy in a 38-month follow-up period. Large-scale studies have not been carried out in solid organ transplant recipients but data from patients who are immunesuppressed due to human immunodeficiency virus (HIV) show no correlation between infectious complications of IUDs and immune competence as measured by CD4 count (Morrison et al., 2001). Observational evidence indicates that IUDs do not increase the risk of pelvic inflammatory disease unless they are inserted in women with pre-existing, untreated infection (Amy and Tripathi, 2009). Although universal screening for gonorrhoea and chlamydia is not recommended prior to IUD insertion, screening has been suggested for immune-suppressed populations (Estes and Westhoff, 2007).

The use of IUDs in the peritoneal dialysis population remains understudied. Current advice is poorly informed by isolated reports of peritonitis in association with IUD use in patients undergoing peritoneal dialysis (Plaza, 2002). A sensible balance needs to be made between such anecdotal data and the real risks of both alternative contraceptive methods, and unwanted pregnancy, in a dialysis population (Dimitriadis and Bargman, 2011).

Barrier methods

Barrier methods of contraception offer convenience, avoid drug interactions, and prevent transmission of sexually transmitted infections. Barrier methods include condoms, cervical caps, diaphragms, and sponges. Their effectiveness depends upon consistent and correct use by the patient. Therefore, failure rates are variable and it is important to consider 'typical use' effectiveness as well as 'perfect use'.

Both male and female condoms are available with 'typical use' failure rates of 18% and 21% respectively (Trussell, 2011). For this reason, for women for whom an unintended pregnancy would be unacceptable either on health or personal grounds, sole use of a barrier method is not the most appropriate contraceptive choice. Male and female condom use should not be combined due to an increased chance of slippage of both devices (Estes and Westhoff, 2007).

Diaphragms are thin, dome-shaped devices, which lie diagonally between the posterior fornix and pubic bone. Cervical caps are smaller than diaphragms and sit directly over the cervix. Both caps and diaphragms are sized for the individual patient and must stay in place for 6 hours after intercourse. Use of both of these methods should be combined with a spermicide in order to achieve acceptable levels of efficacy (Estes and Westhoff, 2007). The contraceptive sponge covers the cervix in a similar manner to the cap but can be used without prior pelvic examination and individualized fitting. It is impregnated with a spermicide that is activated when water is applied before use. Efficacy of these female barrier methods, even with 'perfect use', varies between 80% and 94% with increased parity being a negatively contributing factor. 'Typical use' is even less effective with 12–24% of women experiencing an unintended pregnancy in the first year (Trussell, 2011).

An increased frequency of urinary tract infection (UTI) has been associated with both diaphragm use (Fihn et al., 1985) and the use of spermicide-coated condoms (Fihn et al., 1996). This may have relevance for patients who experience frequent UTIs particularly in the context of immune suppression following renal transplantation. In addition, the only licensed spermicide marketed in the United Kingdom contains nonoixnol-9 which carries an increased risk of genital ulceration and a higher rate of HIV acquisition compared to placebo (Wilkinson et al., 2002).

Sterilization

Voluntary sterilization can be offered to all persons who understand the nature of the procedure including its low failure rate and therefore effective irreversibility, in combination with a certainty that they do not want any more children. This may not be easy for either the patient or consulting clinician to determine. The probability of regret following sterilization has been found to be higher for women sterilized before the age 30 compared to those older than 30 (Hillis et al., 1999). However, life events can also become sources of regret in family planning decisions (Amy and Tripathi, 2009). Such life events can be prevalent in the complex disease journey of the renal patient who transitions from disease stability to disease decline, renal replacement, and potentially, in and out of transplantation.

Female sterilization is higher risk for the renal patient, compared to vasectomy. The requirement for an operative procedure means that hypertension, diabetic control, bleeding time, and vascular risk are important considerations in being able to provide an appropriate level of anaesthetic and perioperative care. Anaemia management should be optimized. Pre- and postoperative fluid balance is important in the prevention of a superadded pre-renal insult

to those with pre-existing renal disease. The availability of renal replacement may be a factor for patients with advanced CKD who undergo sterilization procedures.

Fertility awareness methods

Fertility awareness-based methods of contraception require identification of the fertile days of the menstrual cycle through either monitoring of cycle days, cervical secretions, or basal body temperature. This is then combined with either abstinence or barrier methods within the fertile window. Such methods are estimated to result in 24% of women experiencing an unplanned pregnancy within 1 year (Trussell, 2011) although studies of these methods are not methodologically robust and are poorly reported (Grimes et al., 2004). Drugs which affect cycle regularity, cycle hormones, and fertility signs and symptoms will further reduce the contraceptive efficacy of these methods. For the renal patient, relevant drugs include steroids, cytotoxic medications, antidepressants, and lithium. Couples using fertility awareness-based methods should be counselled about the lack of evidence on efficacy and other contraception options should be offered.

Lactational amenonorrhea

Lactational amenorrhoea utilizes a physiological birth spacing tool. Breastfeeding an infant reduces gonadotrophin release thereby suppressing ovulation. Three criteria must be met in order to ensure a sufficient contraceptive effect. The baby must be exclusively breastfed and the mother should be amenorrheic, both within 6 months of childbirth. When applied correctly, this is estimated to be 98% effective as a contraceptive method (Amy and Tripathi, 2009). However, this contraceptive approach is largely promoted in countries where other forms of contraception are not available. As a form of contraception, it is limited both by the inherent difficulties in 'diagnosing' amenorrhoea in the post-partum period and by its finite timespan. A Cochrane review of lactational amenorrhoea for family planning concluded that a wiser approach to the post-partum period would be to encourage breastfeeding and, in addition, to motivate the mother to use an alternative form of contraceptive, other than lactational amenorrhoea, if contraception is required (Van der Wijden et al., 2003).

Emergency contraception

The most widely used emergency contraceptive uses levonorgestrel at either a single high dose of 1500 micrograms, or two doses of 750 micrograms taken 12 hours apart, within a 72-hour window of unprotected sexual intercourse. As a progesterone-only preparation there are no contraindications to use in renal disease, hypertension, coagulopathy, and lupus. In addition, there is no evidence of an increase in cardiovascular complications (Faculty of Sexual and Reproductive Healthcare, 2009).

The copper IUD can also be used as an effective emergency contraceptive device up to 5 days post coitus to prevent implantation (Amy and Tripathi, 2009).

Drugs

Patients with renal disease can be prescribed a variety of different long-term and short-term medications. The interaction between these drugs and the patient's contraceptive choice needs to be appreciated by all prescribing clinicians. Drug interactions of particular relevance to the nephrologist are listed in Table 293.2.

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CHAPTER 294

Pregnancy and renal physiology

Kate Bramham and Catherine Nelson-Piercy

Kidney size, physiological hydronephrosis, and urinary symptoms in pregnancy

Kidney size and hydronephrosis

Elevated renal plasma flow and increased interstitial fluid results in an increase of up to 70% in kidney volume and length, measured by ultrasound, increases by 1–2 cm in pregnancy (Baylis and Davison, 2011). There is also marked dilatation of the pelvicalyceal systems and ureters and hydronephrosis is present in 80–90% of women by the third trimester (Cietak and Newton, 1985; Brown, 1990). The left renal pelvicalyceal system reaches a maximum diameter of 8 mm (90th centile) by 20 weeks' gestation, whereas the right renal pelvis diameter continues to increase by 0.5 mm per week from 6 to 32 weeks reaching a maximal diameter of 20 mm (90th centile) which persists until delivery (Faundes et al., 1998). It is proposed that predominance of right-sided hydronephrosis is due to dextrorotation of the uterus, and/or the left ovarian vein crossing the right ureter at the pelvic brim. The left ureter is more protected by the sigmoid colon. This partial obstruction is exacerbated by standing or the supine position, and is recognized by the 'iliac sign' on an intravenous urogram (IVU) in later pregnancy, whereby no contrast passes into the distal ureter beyond the pelvic brim (Fig. 294.1).

Pelvicalyceal dilatation has usually resolved by 6 weeks post partum but one report suggested that two out of 20 women have persistent ureteric dilation (Fried et al., 1982), and another described pregnancy-associated changes evident on IVU at 16 weeks post partum (Rasmussen and Nielsen, 1988).

Though these changes can create diagnostic challenges they are asymptomatic and of no significance, but urinary stasis increases the risk of bacteriuria, and pyelonephritis in pregnancy. It is speculated that 24-hour urine collections may be affected by incomplete emptying of the ureters, and recommended that women should lie on their side for an hour before and after the end of a collection, but practically this is challenging.

Urinary symptoms in pregnancy

Women commonly report increased urinary frequency in early pregnancy associated with nocturia, which may be due to the effects of progesterone, and increased fluid intake (FitzGerald and Graziano, 2007). In later pregnancy, the distension of the bladder is physically limited by pelvic crowding, and urinary frequency may recur.

Renal physiology in women of reproductive age and pregnancy

Changes in renal physiology with the menstrual cycle

Small studies have demonstrated fluctuations in creatinine clearance during the menstrual cycle with an increase of 20% during the luteal phase (Davison and Noble, 1981), and have been confirmed by measurement of glomerular filtration rate (GFR) and renal plasma flow with inulin clearance and para-aminohippurate respectively (Chapman et al., 1997) (Fig. 294.2). The mechanisms underlying these changes in glomerular filtration are unclear, but may be associated with the peptide hormone relaxin released by the corpus luteum, levels of which increase in the luteal phase (Stewart et al., 1990) and with progesterone following ovulation (Chesley and Tepper, 1967).

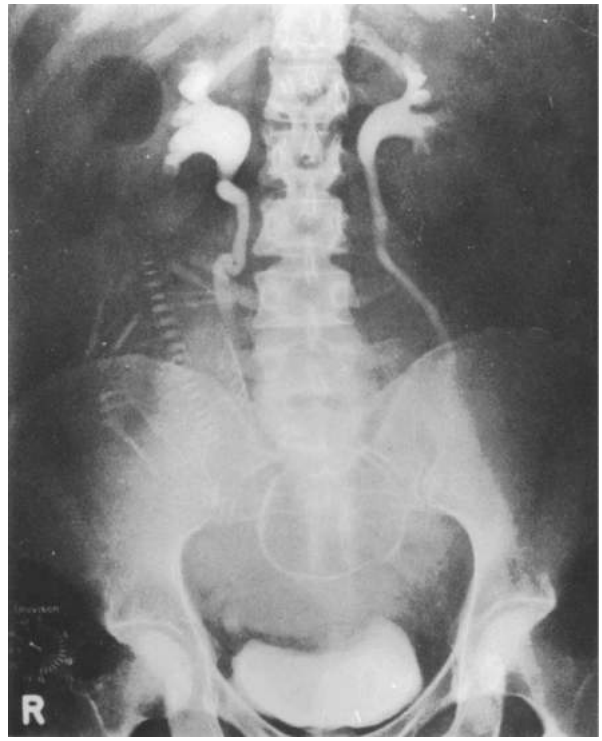

Fig. 294.1 Intravenous excretory urogram showing ureteral dilatation of pregnancy. The right ureter is abruptly cut off at the pelvic brim where it crosses the iliac artery (the so-called iliac sign).

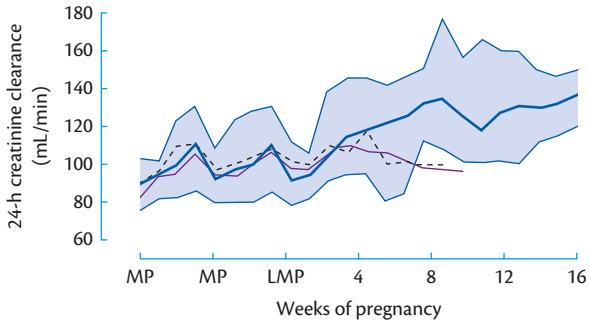

Fig. 294.2 Changes in 24-hour creatinine clearance measured weekly before conception and through to uncomplicated spontaneous abortion in two women (red solid and stippled lines). The solid line represents the mean and the stippled area the range for nine women with successful obstetric outcome. LMP = last menstrual period; MP = menstrual period.

Reproduced from Davison, J. M., Vallotton, M. B., and Lindheimer, M. D. (1981). Plasma osmolality and urinary concentration and dilution during and after pregnancy: evidence that lateral recumbency inhibits maximal urinary concentrating ability. *Br J Obstet Gynaecol*, 88, 472–9 with permission.

Changes in systemic physiology after conception

Marked physiological adaptations occur during pregnancy (Fig. 294.3), resulting in systemic vasodilation. Despite increased cardiac output there is an overall reduction in mean arterial blood pressure. Substantial changes in systemic and renal vasodilation have occurred by 6 months (Chapman et al., 1998), and blood pressure starts to rise to pre-pregnancy values towards the end of pregnancy. In addition there is an increase in plasma volume of up to 50% of non-pregnant values, which is maximal during the second trimester. It is unclear if reduced relative plasma volume secondary to systemic vasodilation elicits a renal response, including sodium and water retention, or whether the primary event occurs in the kidney, and systemic vasodilation is a secondary effect.

Changes in renal physiology after conception

Renal plasma flow

Following conception, there is a marked and sustained increase in renal plasma flow measured by para-aminohippurate clearance,

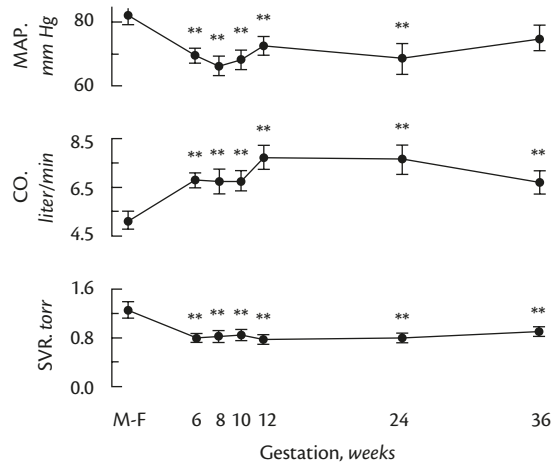

Fig. 294.3 Systemic haemodynamic changes throughout early and late human pregnancy (Chapman et al., 1998).

MAP: mean arterial pressure; CO: cardiac output; SVR: systemic vascular resistance.

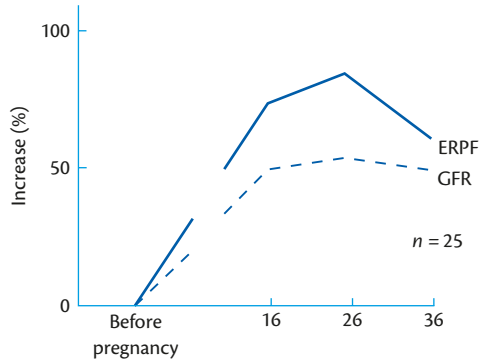

Fig. 294.4 Relative changes in renal haemodynamics during normal human pregnancy.

Calculated from the data of Davison and Hytten (1975), Dunlop (1976), Ezimokhai et al. (1981), and Davison (1985b).

with a peak at 80% compared to pre-pregnancy values. Towards the end of pregnancy, most but not all studies (Assali et al., 1959), suggest that flow falls towards pre-pregnancy levels, but still remains elevated until after delivery (Dunlop and Davison, 1987; Roberts et al., 1996; Chapman et al., 1998) (Fig. 294.4). It is unknown if renal vasodilation, hence increased blood flow, occurs independently of systemic vasodilation, but compared to other organs the kidney has one of the largest pregnancy redistributions of blood flow.

Glomerular filtration

In parallel with increased renal blood flow, GFR increases during pregnancy by up to 25% during the 4 weeks after the last menstrual period (2 weeks post conception), measured by 24-hour creatinine clearance (Davison and Noble, 1981). The earliest formal assessment in pregnancy with inulin clearance by Chapman et al. at 6 weeks after the last menstrual period (4 weeks post conception) also confirmed a very early increase in GFR. Several other studies measuring GFR with inulin have reported an increase up to 50% greater than pre-pregnancy values by 16 weeks' gestation (Dunlop and Davison, 1987; Roberts et al., 1996; Chapman et al., 1998) which is maintained until delivery (Fig. 294.4), although one report suggested a fall towards term, and may be a more true reflection of gestational changes (see 'Creatinine in pregnancy') (Assali et al., 1959).

The driving force for the majority of the increase in glomerular filtration is the elevation in renal plasma flow. A small additional increase in GFR is secondary to a reduction in plasma protein concentration, which reduces effective glomerular oncotic pressure, and has been demonstrated by neutral dextran studies in healthy pregnant women (Roberts et al., 1996).

Creatinine in pregnancy

Creatinine production by skeletal muscle remains relatively unchanged in pregnancy (Kuhlback and Widholm, 1966) therefore serum creatinine concentrations fall in parallel with increased GFR. A normal range of creatinine in pregnancy has not been established in large studies, with reports including only 5–26 subjects (Dunlop and Davison, 1987; Roberts et al., 1996; Chapman et al., 1998). An attempt to define a normal range in a larger study of healthy women reported upper thresholds (95th centile) of 85, 80, and 90 μmol/L for first, second, and third trimesters respectively, but ethnic differences in creatinine were not compared (Girling, 2000).

Estimates of GFR using creatinine in pregnancy

Estimates of GFR using Modified Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration compared to formal measurements of GFR by inulin clearance or creatinine clearance underestimate GFR by up to 20% and therefore should not be used in pregnancy (Smith et al., 2008; Alper et al., 2011). Twenty-four-hour creatinine clearance has been assessed and validated as a comparable measure to inulin clearance of GFR in pregnancy (Davison and Hytten, 1974; Chapman et al., 1998). However, creatinine is secreted into the renal tubule, and may give an overestimate of GFR by up to 10% during pregnancy (Davison and Hytten, 1974). Furthermore, incomplete emptying of dilated ureters in late pregnancy may give falsely low clearance.

Cystatin C in pregnancy

Cystatin C is freely filtered at the glomerulus and assays have been proposed to be a better way of estimating GFR in non-pregnant individuals. There is no correlation between fetal and maternal cystatin C measurements (Cataldi et al., 1999), nor has the utero-placental unit been shown to contribute to changes in maternal cystatin C (Kristensen et al., 2007), so it was hoped that it could provide useful guidance in pregnancy. However, concentrations seem to be consistently increased in the second trimester, at the time of highest GFR (Strevens et al., 2002; Bramham et al., 2009; Larsson et al., 2010) excluding cystatin as a useful marker of GFR in pregnancy.

Changes in GFR during late pregnancy and positional changes

GFR measured by inulin clearance is maintained until term; however, 24-hour creatinine clearance has been shown to fall in studies of healthy women in the third trimester, with an associated rise in serum creatinine (Davison and Hytten, 1974; Davison et al., 1980; Girling, 2000). Inulin provides an assessment of GFR over a limited number of hours, whereas 24-hour creatinine clearance is recorded over a longer period, and may be more accurate in the third trimester when postural changes may have significant influences over renal function.

A 20% reduction in both renal plasma flow, and GFR, measured by inulin clearance has been reported in women in the third trimester, when women were supine (Chesley and Sloan, 1964; Pippig, 1969), and both plasma flow and GFR have also been shown to fall on standing (Assali et al., 1959). However, other authors have also observed a reduction in renal plasma flow and creatinine clearance even when women are in lateral recumbency (Ezimokhai et al., 1981), suggesting that positional changes are not exclusively responsible for the fall in GFR in late pregnancy. It is likely that glomerular filtration does fall in the third trimester, in parallel with a reduction in renal plasma flow (resulting in a rise in serum creatinine), which is reduced further by positional changes in GFR.

Other glomerular changes in pregnancy

The 'filtration equilibrium' is reached when glomerular pressure is neutral. This may occur within the capillary before it exits the glomerulus, and therefore functional reserve/redundant filtration surface area exists. In this circumstance, further increases in renal plasma flow can elicit increases in glomerular filtration, until neutral pressure is reached further along the glomerular capillary. If the filtration equilibrium is not reached within the glomerulus, increased renal plasma flow can only result in a minimal rise in glomerular filtration.

Amino acid infusion in both pregnant rats and women results in an increase in renal vasodilatation and glomerular filtration, suggesting that despite pregnancy-associated elevated renal plasma flow, additional filtration capacity exists in normal pregnancy (Baylis, 1988; Sturgiss et al., 1996; Milne et al., 2002), that is, filtration equilibrium is still within the glomerular capillary. The proportional increases in GFR in pregnant women following amino acid infusion were comparable to non-pregnant individuals suggesting that renal vasodilatory responses in pregnancy remain intact. Pregnancy-associated increases in GFR are also observed in women with renal transplants and single kidneys despite reduced nephron number and hyperfiltration, although the response is moderately reduced (Davison, 1985a, 1978).

It might be expected that the glomerular filtration should rise precisely in parallel with increased renal plasma flow, but maximal changes in GFR are less pronounced (i.e. 80% renal plasma flow vs 50% GFR). Therefore there is a reduction in filtration fraction during the first half of pregnancy (filtration fraction = glomerular filtration/renal plasma flow). Towards the end of pregnancy, renal plasma flow returns to pre-pregnancy values, but GFR is maintained, hence filtration fraction increases. The reduction in systemic oncotic pressure, due to plasma volume expansion and reduced plasma albumin towards term, appears to have only a minimal effect on net glomerular filtration, due to a simultaneous reduction in other plasma proteins (Roberts et al., 1996; Conrad et al., 2009).

Filtration fraction is also determined by total glomerular capillary surface area and permeability of the glomerular wall. Autopsy series of pregnant women report that glomerular size, but not cellularity increases during pregnancy (Sheehan, 1980), and a study of renal biopsies in healthy pregnant women has confirmed this finding (Strevens et al., 2003).

Whilst evidence is limited, it appears that the glomerular filtration barrier also undergoes dynamic changes with gestation, which are likely to influence the filtration fraction. In a study of 11 healthy pregnant women, polydisperse neutral dextrans were infused, and their excretion observed to create dextran sieving curves which allow modelling of glomerular haemodynamics and are a surrogate indicator of changes in filtration. Fractional dextran clearances, particularly smaller dextrans, were lower in early pregnancy and decreased further in late pregnancy compared to post-partum clearances suggesting gestation related changes in glomerular porosity occur (Roberts et al., 1996). A subsequent dextran infusion study also reported an increase in breadth of distribution of glomerular pore size (Milne et al., 2002).

Mechanisms underlying hyperfiltration in pregnancy

There are few animal models amenable to the study of renal physiology in pregnancy. The rat is most frequently studied, with a gestation time of 22 days. There are several similarities to human pregnancy-associated changes including a 30–40% increase in glomerular filtration, elevated renal plasma flow, and plasma volume expansion, which falls to non-pregnant levels after delivery (Conrad, 1984; Baylis, 1987). However, experimental increases in renal plasma flow result in incremental rises in glomerular filtration in rats at much wider ranges than human pregnancy, suggesting that the filtration equilibrium (neutral pressure) in normal

pregnant rats is reached early in the glomerulus, and that a larger proportion of filtration surface area remains unused and is able to respond to increased plasma flow (Baylis, 1980).

Single nephron micropuncture studies in Muich-Wistar rats have confirmed there is no net increase in glomerular pressure despite an increased renal blood flow (Baylis, 1994). Remarkably, glomerular pressure remains constant between pregnant and non-pregnant states (Baylis, 1994). This is due to a simultaneous reduction in both afferent and efferent arteriole pressure. Similarly, dextran studies in human pregnancy also suggest that there is no increase in glomerular pressure, suggesting that increased plasma flow is predominantly responsible for hyperfiltration in pregnancy, not hydrostatic forces (Roberts et al., 1996).

Changes in autoregulation of GFR in pregnancy

In the non-pregnant state, the tubuloglomerular feedback mechanism detects increased glomerular filtration in the macular densa, as a raised sodium load in the thick ascending limb/distal tubule junction, resulting in local release of paracrine substances and causes afferent arteriolar constriction and therefore a reduction in glomerular filtration. Rat models suggest that the tubuloglomerular feedback mechanism in pregnancy is reset (in order to tolerate higher rates of filtration (Barron et al., 1989)), although overall autoregulation of renal blood flow at greater volumes remains intact (Reckelhoff et al., 1992). Nitric oxide synthesis is elevated in pregnancy and is likely to mediate vasodilation (see below). It also reduces tubuloglomerular feedback sensitivity and may be a moderator of the 'threshold resetting' to allow pregnancy-associated increases in GFR.

Other renal adaptations to hyperfiltration are associated with raised glomerular pressure and progression of chronic kidney disease (CKD) (Helal et al., 2012); however hyperfiltration in normal pregnancy has no detrimental effect on renal function. This has been confirmed by examination of renal cortical tissue from multigravid rats, who have no demonstrable difference in glomerular structure compared with virgin controls (Baylis, 1999). Similarly in humans there is no decline in renal function despite multiple pregnancies, and pregnancy-associated changes in GFR occur regardless of an individual's parity.

Relaxin

It is well recognized that the initiator of renal changes in pregnancy is unlikely to be the fetal-placental unit, which is not developed until 10–12 weeks' gestation, whereas increased glomerular filtration occurs several weeks before. Furthermore, pseudo-pregnant rats exhibit the same renal physiological adaptations as pregnant animals, including increased renal plasma flow, glomerular filtration, and plasma volume despite the absence of a placenta (Baylis, 1982; Slangen et al., 1997).

A key component to renal physiological changes appears to be the ovarian hormone relaxin. It is released after ovulation by the corpus luteum, and levels are associated with rises in glomerular filtration during the luteal phase of the menstrual cycle (Chapman et al., 1998; Smith et al., 2005). Relaxin secretion increases dramatically following conception, and is paralleled by elevations in renal plasma flow (Sherwood, 1994).

Further evidence for the role of relaxin comes from animal studies. Neutralizing antibodies to relaxin given to pregnant rats blunted a pregnancy-associated rise in renal plasma flow, glomerular filtration, and renal vascular resistance compared to pregnant controls at day 11 (Novak et al., 2001). No differences were seen in non-pregnant animals. Ovarectomy, and therefore relaxin secretion, in pregnant rats removes the renal vasodilatory response (Novak et al., 2001). Chronic relaxin administration to rats produces an increase in renal plasma flow, and GFR, which is also evident in ovarectomized animals (Danielson et al., 1999), and male rats (Danielson et al., 2000), suggesting the role of relaxin is independent of the presence of progesterone and oestrogen. Exogenous relaxin has also been found to be associated with a blunting of the vasoconstrictor response to angiotensin II (Ang II) (Danielson et al., 1999, 2000), a reduction in the myogenic response in medium sized arteries (Novak et al., 2001), and a reduction in plasma osmolality (Danielson et al., 1999) which are all recognized features of pregnancy (Novak et al., 1997).

Studies of relaxin in humans are consistent with animal models, but leave some unanswered questions. Relaxin levels rise dramatically in early pregnancy which is temporally consistent with the rise in GFR (Sherwood, 1994). Women who have had assisted conception with ovum donation do not have the expected increase in glomerular filtration, nor do they have measurable relaxin levels (Smith et al., 2006b; Conrad and Baker, 2013). However, there is a rise in GFR despite the absence of relaxin, suggesting that the response is not exclusively relaxin-mediated. Furthermore, when relaxin release was stimulated by the administration of human chorionic gonadotropin to non-pregnant females there was no associated increase in renal plasma flow (Smith et al., 2005), although this may be a reflection of relaxin concentrations achieved not being as high as those observed in pregnancy. The same authors also studied the response to intravenous recombinant relaxin given to healthy non-pregnant females and males, and observed a significant rise in renal plasma flow (50%) but glomerular filtration was unchanged, suggesting that additional mediators are required for changes in filtration fraction, and/or a shift in filtration equilibrium (Smith et al., 2006a).

The role of relaxin in later pregnancy is unclear. Relaxin concentrations are elevated in the first trimester, fall and plateau until 36 weeks' gestation when they fall by approximately 40%, then return to pre-pregnancy values post partum (Bell et al., 1987; Ogueh et al., 2011). Relaxin concentration in later pregnancy has been shown to correlate with renal artery resistance indices (Ogueh et al., 2011), but not with worse pregnancy outcomes (Szlachter et al., 1982; Bell et al., 1988; Lafayette et al., 2011). The role of relaxin in women with reduced renal function has not been explored.

Progesterone

Progesterone is also a potential mediator of increased renal plasma flow and GFR, and has been shown to produce moderate rises in both when administered to non-pregnant women or men (Chesley and Tepper, 1967; Atallah et al., 1988). Furthermore, if the placenta is removed from mid-term rats, a reduction in GFR and renal plasma flow is observed suggesting placental factors may be of importance in later pregnancy (Matthews and Taylor, 1960). Further study of the role of progesterone is needed.

Nitric oxide

Following initiation by relaxin and other unknown factors, pregnancy-associated renal vasodilation involves a nitric oxide-dependent pathway. Again evidence comes from rat models, which have demonstrated a reduction in GFR in gravid but

not non-pregnant rats following acute administration of nitric oxide synthase (NOS) inhibitors (Danielson and Conrad, 1995). Furthermore, chronic administration of NOS inhibitors in rat models result in a blunted renal response to pregnancy (Baylis and Engles, 1992; Cadnapaphornchai et al., 2001). Non-pregnant rats with an elevated GFR due to exogenous relaxin, also have a reduction in GFR following NOS inhibitors (Danielson et al., 1999). NO appears to be endothelial in origin, as endothelial removal abrogated pregnancy-associated reduced myogenic activity in small renal arteries of mid-term rats (Gandley et al., 2001). Several NOS isoforms have been isolated but their individual contribution remains to be validated.

Further indirect evidence comes from the study of oxidative products of nitric oxide (inorganic nitrite and nitrate—NOx) and cyclic guanosine monophosphate (cGMP), a secondary messenger of nitric oxide. Increased plasma and urine levels of NOx and cGMP have been reported in pregnant rats compared with non-pregnant controls (Conrad and Vernier, 1989; Deng et al., 1996). Similarly, raised levels of plasma and urine cGMP have been described in human pregnancy compared with non-pregnant subjects (Kopp et al., 1977). However, unlike renal adaptations, cGMP levels were sustained post partum. It is hypothesized that cGMP levels may also reflect atrial natriuretic peptide (ANP) signalling, which is raised post partum (Gregoire et al., 1990).

A limitation of the study of excretion of NO oxidative products is the unknown contribution of NO-containing food. Accurate assessment can only be performed with controlled intake, and only one study has been successfully performed, which failed to demonstrate a rise in NO oxidative products between pregnant and non-pregnant women (Conrad et al., 1999b). However, plasma and urine levels of NO oxidative products may not reflect regional NO production and further study is required.

Endothelin type B receptor

Endothelin type B (ET_B) receptors in the endothelium mediate the release of vasodilators including NO, prostacyclin, and endothelium-derived hyperpolarizing factor, and may play a role in endothelin-1 clearance (a potent vasoconstrictor). ET_B receptor blockade in rats blunts a pregnancy-associated rise in renal plasma flow, and glomerular filtration (Conrad et al., 1999a). Furthermore, ET_B receptor blockade in relaxin administered rats also prevented an appropriate renal adaptive response (Danielson et al., 2000; Novak et al., 2002), and removed pregnancy-associated attenuated myogenic activity in mid-term rat renal arteries (Gandley et al., 2001), thus suggesting that ET_B signalling may be a mediator of relaxin-induced NO-mediated vasodilation in pregnancy.

Matrix metalloproteinase 2

Matrix metalloproteinase 2 (MMP2) can convert endothelin into an active form, has been shown to be upregulated by relaxin in fibroblasts (Palejwala et al., 2001), and is increased in small renal arteries of mid-term pregnant rats and relaxin treated non-pregnant rats (Jeyabalan et al., 2003). Inhibition of MMP2 in pregnant rats, and relaxin-treated non-pregnant rats resulted in a reduction in renal plasma flow, glomerular filtration, and increased myogenic reactivity in renal arteries (Jeyabalan et al., 2003). Furthermore, in ET_B receptor deficient rats there was markedly increased MMP2 activity supporting the role of MMP as a mediator of pregnancy-associated renal vasodilation upstream from ET_B receptor and NO mechanisms.

Further understanding of the primary stimulus and mechanisms underlying renal adaptations in pregnancy is needed, and could be used to modulate the pathological changes associated with hyperfiltration mediated renal disease.

Pregnancy-associated renal physiological changes in women with chronic kidney disease

The adaptation to pregnancy appears to be remarkably robust, as women with single kidneys, and renal transplants, with hypertrophied and hyper-filtering nephrons also have a reduction in serum creatinine, and rise in glomerular filtration (Davison, 1978; Davison, 1985a). Women with pre-existing renal impairment who do not achieve a gestational fall in creatinine have more pregnancy complications (Jones and Hayslett, 1996; Lindheimer et al., 2001). Furthermore, a small study 24-hour creatinine clearance in the first trimester found a lack of an early rise was associated with miscarriage in two women (Davison and Noble, 1981) (Fig. 294.2). Thus an appropriate renal response to pregnancy appears to be important for successful pregnancy outcomes.

Plasma volume expansion

Throughout gestation there is substantial retention of sodium and water producing an increase of 6–9 L in total body water, 900 mEq of sodium (Conrad et al., 2009), and a net increase of 4–7 L extracellular volume (Pipe et al., 1979; Lukaski et al., 1994), which is followed by a natriuresis post partum (Lindheimer and Davison, 1995). Water retention is proportionally greater than sodium retention and there is a reduction of approximately 10 mOsm/kg in plasma osmolality. Factors affecting sodium retention are given in Table 294.1. Threshold adjustments are present in early pregnancy (Chapman et al., 1998), which may be preceded by a reduction in

Table 294.1 Influences on salt retention and excretion in pregnancy

Salt retention	Salt excretion
Hormonal influences	
Angiotensin II	Atrial natriuretic peptide (mainly post partum)
Aldosterone	Progesterone
Oestrogen	Nitric oxide
Deoxycorticosterone	Prostaglandins
Placental lactogen	
Prolactin	
Physical influences	
Reduced glomerular filtration rate associated with supine, and upright posture	Increased glomerular filtration rate
Systemic vasodilation	Decreased plasma oncotic pressure
Ureteric obstruction secondary to increased uterine size	

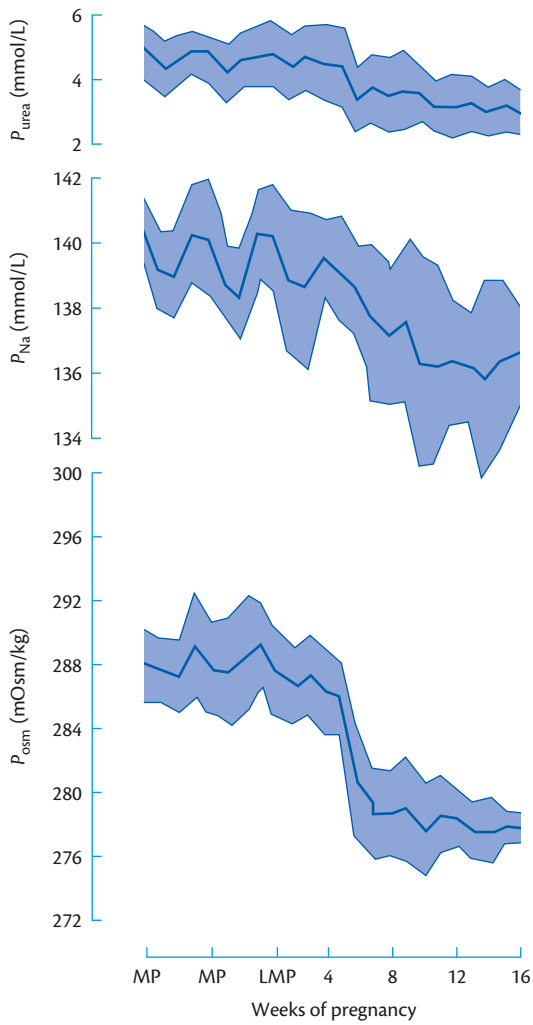

Fig. 294.5 Mean values (± SD) for plasma urea (P_{urea}), sodium (P_{Na}), and osmolality (P_{osm}) measured at weekly intervals from before conception through the first trimester in nine women with successful obstetric outcome. LMP = last menstrual period; MP = menstrual period.

Reproduced from Davison, J. M., Vallotton, M. B., and Lindheimer, M. D. (1981). Plasma osmolality and urinary concentration and dilution during and after pregnancy: evidence that lateral recumbency inhibits maximal urinary concentrating ability. *Br J Obstet Gynaecol*, 88, 472–9 with permission.

the osmolality threshold which triggers thirst, resulting in mild transient polyuria in early pregnancy (Fig. 294.5).

Despite increases in extracellular volume, blood pressure falls due to an enhanced vasodilatory response. Frequently mediators of volume expansion also have synergistic vasoconstrictor effects, and similarly natriuretic pathways are associated with vasodilatory responses, therefore there is a sophisticated resetting of volume and homeostatic vasoactive responses in order to achieve the physiological changes observed in pregnancy.

There is controversy regarding the primary mechanism of plasma volume expansion, and there are three proposed pathways:

- 'Under-fill' theory—sodium and water retention occur in response to reduced effective circulating volume secondary to systemic vasodilatation, for example, cirrhosis and heart failure.
- 'Normal-fill' theory—homeostatic mechanisms are simply reset in order for the pregnant women to perceive the new state of volume expansion as 'normal'.
- 'Over-fill' theory—systemic vasodilation occurs in response to excess sodium and water retention.

Evidence for mediators of volume expansion are presented below.

Antidiuretic hormone

Antidiuretic hormone (ADH) is usually released in response to raised osmolality and volume contraction, and therefore excretion would be expected to be downregulated in response to pregnancy-associated low osmolalities and volume expansion. However, ADH is secreted in pregnant women at lower blood pressures, resulting in a net retention of water (Davison et al., 1989). Similarly, in rat models, ADH excretion occurs at much lower plasma osmolalities and higher plasma volumes in pregnant animals than in non-pregnant controls (Barron et al., 1989), but urinary concentration and diluting capacity are unchanged (Durr et al., 1981). Urinary concentrating mechanism in humans also remain intact, although in later pregnancy maximal concentrations of urine are reduced suggesting a modified response to ADH (Lindheimer and Davison, 1995). Vasopressinase is produced by the placenta, and ADH clearance increases fourfold between early and mid pregnancy, therefore ADH is likely to be produced at even higher levels in order to achieve its effects (Davison et al., 1989).

The mechanism underlying resetting of responses to reduced osmolality had not been extensively studied; however, beta-human chorionic gonadotrophin (β-HCG) has been shown to reduce the threshold for ADH release and thirst in non-pregnant women (Davison et al., 1988) and may be contributory.

Exogenous relaxin moderates the ADH response in rats (Weisinger et al., 1993). Furthermore, women with egg donation, which is associated with reduced β-HCG and relaxin, have a blunted reduction in plasma osmolality (Smith et al., 2006b).

Atrial natriuretic peptide

An appropriate homeostatic response in the non-pregnant state to plasma volume expansion is ANP release, however Chapman et al. noted only minimal changes in ANP levels at 12 weeks' gestation, that is, after substantial increases in volume expansion have already occurred (Chapman et al., 1998), in keeping with resetting of homeostatic mechanisms—the 'normal fill' theory. A meta-analysis of studies comparing ANP levels in non-pregnant and pregnant women reported that changes in ANP during the first and second trimesters were minimal, but there was a 41% increase in the third trimester (Castro et al., 1994) which also is consistent with changes in atrial size which does not increase until the third trimester (Steegers et al., 1991). However, Irons et al. demonstrated an increased clearance of ANP which may mask elevated production (Irons et al., 1996b).

The meta-analysis of ANP in pregnancy also found mean ANP concentrations were 148% greater during the first week post partum than in non-pregnant women (Castro et al., 1994), which is in keeping with post-partum natriuresis. Post-partum renin and aldosterone concentrations in rats are immediately suppressed suggesting there is a rapid resetting of volume sensing post partum (Nadel et al., 1988).

Animal models support these findings and there is also evidence of a blunted response to circulating ANP in pregnancy. In response to saline infusion, pregnant rats have less ANP excretion than non-pregnant controls (Ni et al., 2004), and reduced natriuresis in response to increased blood pressure (Masilamani et al., 1998). Furthermore, pregnant rats given exogenous ANP have a reduced natriuretic response compared with non-pregnant controls (Omer et al., 1995; Masilamani et al., 1998).

A mechanism for blunting of tubular responses to ANP was suggested by Baylis et al. who have identified increased levels of cGMP breakdown products (ANP signals via cGMP) in the inner medullary collecting ducts of pregnant rats, an important site of ANP action (Mahaney et al., 1998). This disruption of the signalling pathway is likely to be due to the presence of increased phosphodiesterase 5 (PDE5) which has also been found to be locally increased (Ni et al., 2004). Inhibition of PDE5 restores the natriuretic response to ANP to that found in non-pregnant animals (Knight et al., 2007).

Conflicting results come from Irons et al. who infused low-dose ANP into women in late pregnancy and 4 months post partum (Irons et al., 1996a). There was a natriuretic response in pregnant women but not post partum. This unexpected finding may be due to the timing of sample collection, as the actions of ANP are rapid, and the natriuretic effect may have been missed.

Conversely, women with pre-eclampsia including those with pre-eclampsia superimposed on chronic hypertension, who have significant volume contraction hence ANP should be suppressed, have high levels of ANP compared with gestation-matched controls (August et al., 1990; Irons et al., 1996a, 1997), suggesting that ANP may by a pathophysiological mediator of abnormal volume regulation in hypertensive disorders of pregnancy.

Renin–angiotensin–aldosterone system

Activity of the renin–angiotensin–aldosterone system (RAAS) in pregnancy has been extensively studied and is complex. Local RAAS activity during pregnancy has also been identified in many organ systems (Broughton Pipkin, 2007) and more recently the role of intrarenal RAAS in pregnancy has been explored (Pringle et al., 2013). In brief, systemic RAAS is activated in early pregnancy (Weir et al., 1976; Chapman et al., 1998), resulting in sodium reuptake by direct action of Ang II on the proximal tubule, and elevated levels of circulating aldosterone. Baseline renin activity is increased, and further elevations occur in response to sodium restriction, and supine and standing positions (Lindheimer and Katz, 1985). Aldosterone in pregnancy may be even higher than those of a non-pregnant patient with primary hyperaldosteronism (Conrad et al., 2009). Aldosterone is loosely bound to plasma proteins, and increases in total levels during pregnancy are likely to represent even greater rises in free aldosterone levels as plasma protein levels fall. RAAS activation in early pregnancy supports the 'underfill' hypothesis; pregnancy-associated systemic vasodilatation elicits secondary volume expansion, although systemic RAAS activity persists after volume expansion has occurred, which is inconsistent with this theory.

Vasopressor effects of Ang II have been shown to be blunted in both rat (Conrad and Colpoys, 1986) and human pregnancy (Gant et al., 1987), but pregnant women have an enhanced release of aldosterone in response to Ang II (Brown et al., 1988) therefore the anti-natriuretic effect of the RAAS predominates. Despite this 'resetting,' appropriate RAAS downregulation has been reported in response to saline infusion, or high salt diets, and upregulation in response to salt restriction or diuretics (Conrad et al., 2009). Restoration of sensitivity to Ang II is unlikely to be responsible for renal vasoconstriction and reduced plasma flow at later gestations as Ang II receptor blockade had no effect on renal haemodynamics in pregnant rats near to term (Baylis and Collins, 1986).

In pre-eclampsia, paradoxically RAAS activity is suppressed (Broughton Pipkin, 2007) which is an appropriate secondary response to vasoconstriction, but an inappropriate response to volume contraction. This pattern is also reported in women with chronic hypertension; RAAS activity is noted in early pregnancy, but becomes suppressed with the evolution of superimposed pre-eclampsia (August et al., 2004). Agonist antibodies to Ang II receptors have been isolated from pre-eclamptic sera (Wallukat et al., 1999) which may go some way to explaining this conundrum, but further research is required to untangle the pathophysiological role of the RAAS system, particularly in individuals with pre-existing RAAS activation associated with chronic hypertension and CKD.

Other mineralocorticoids

Circulating progesterone is converted to 11-deoxycorticosterone (DOC) (21-hydroxyprogesterone) by extra-adrenal hydroxylation (Winkel et al., 1980) which is enhanced in the presence of oestrogen (MacDonald et al., 1982). DOC is a mineralocorticoid with no significant glucocorticoid activity, and circulates bound to cortisol-binding globulin. It may be displaced by elevated progesterone and cortisol in later pregnancy resulting in higher free levels. Plasma DOC concentrations during pregnancy are 4–50-fold higher than in non-pregnant controls (Winkel et al., 1980); however, the relative contribution of DOC to plasma volume expansion is not known.

Oestrogen is also associated with sodium retention and has been shown to affect amiloride sensitive epithelial sodium channel (ENaC) mRNA expression in renal collecting tubule cells *in vitro* (Gambling et al., 2004), and induces sodium retention in rats, but its influence on sodium handling in pregnancy is unknown.

Changes in renal protein handling in pregnancy

Total protein excretion increases in pregnancy and the upper limit of normal is considered to be 300 mg/24 hours (Higby et al., 1994). This is the consequence of changes in renal protein handling throughout the nephron.

Glomerular changes in protein handling

Several authors have reported that urinary levels in pregnancy of some plasma proteins are increased (α-1-antitrypsin, transferrin, beta-lipoprotein, complement fractions β1-A-C, immunoglobulin (Ig)-D, and α-macroglobulin), some are reduced (thyroxine binding pre-albumin, IgG, and IgA) and some are unchanged (hemopexin, haptoglobin, and IgM) compared to non-pregnant controls (Horne et al., 1970; Studd and Wood, 1976; Beetham et al., 1988), suggesting that selective changes in glomerular permeability occur in pregnancy. However, Roberts et al. found alterations in selectivity for dextran clearances of smaller particles, but clearance of larger particles were unchanged (Roberts et al., 1996).

It has been proposed that a gestational increase in glomerular negative charge, rather than pore size may explain differential excretion of larger molecules. Transferrin excretion increases disproportionately to albumin excretion in pregnancy (Cheung et al., 1989), despite their similar molecular size, which may be a consequence of the greater anionic charge of albumin. Similarly serum cystatin, which is also anionic, rises despite increases in GFR during pregnancy (Strevens et al., 2002). A loss of negative glomerular charge may be responsible for the increase in albumin excretion seen in pre-eclampsia (Conrad et al., 2009).

Tubular changes in protein handling

Low-molecular-weight proteins are freely filtered, and their presence in urine is likely to indicate saturation of tubular resorption. Retinol binding protein and beta-2-microglobulin excretion have been shown to be significantly elevated compared with non-pregnant controls, and increase throughout gestation (Beetham et al., 1988; Bernard et al., 1992). However, excretion remains elevated in the third trimester despite a reduction in GFR, therefore tubular capacity to reabsorb protein may also be relatively reduced in later pregnancy. Furthermore, urinary excretion of medium sized proteins including alpha-1-microglobulin (Bernard et al., 1992) and light chains, which cannot be freely filtered, are also increased in pregnancy, which suggests specific pregnancy-associated changes in tubular handling of proteins.

Urinary albumin

It is widely accepted that urinary albumin increases in pregnancy, and accounts for approximately 10–30% of total urinary protein excretion (Cheung et al., 1989; Taylor and Davison, 1997). However, a few studies report that excretion remains unchanged (Misiani et al., 1991; Brown et al., 1994; Bernard et al., 1992), or even falls (Beetham et al., 1988). Increased albumin excretion is evident by 16 weeks' gestation in normal pregnancy, and is significantly higher in the third trimester compared with pre-pregnancy, first and second trimester values (Taylor and Davison, 1997).

Nocturnal excretion of urinary albumin is lower compared to daytime excretion in both pregnant and non-pregnant controls (Douma et al., 1995). The diurnal difference between albumin excretion is reduced in pregnant women, therefore the maximal differences between pregnant and non-pregnant controls is likely to be found in overnight urine collections. The relatively higher nocturnal albumin excretion in pregnancy may be partly explained by positional changes in GFR (Assali et al., 1959). The influence of position on proteinuria was explored by comparing urinary albumin excretion in pregnant and non-pregnant women on strict bed-rest (Douma et al., 1995). Interestingly, non-pregnant women still maintained a diurnal variation in excretion, but some pregnant women did not, suggesting that orthostatic changes in albumin excretion in pregnancy may be important.

Despite a fall in serum albumin in late pregnancy there is no change in rate of synthesis or catabolism of albumin between pregnant and non-pregnant women, therefore a combination of increased urinary loss and increased plasma volume must be the principal cause of lower serum albumin and there must be a reduced threshold for stimulation of synthesis (Honger, 1968). It has been proposed that this effect may be oestrogen or progesterone mediated (Honger, 1968).

Restoration of pregnancy-related changes in proteinuria to non-pregnant levels varies between studies and appears to take longer than alterations in GFR to non-pregnant values. Taylor and Davison found urinary albuminuria returned to pre-pregnancy values by 12 weeks post partum (Taylor and Davison, 1997), whereas others suggest persistence for even longer (Lopez-Espinoza et al., 1986; Wright et al., 1987) with resolution by 12 months (Roberts et al., 1996).

Tubular changes in pregnancy

Glucose

Glycosuria is variable in pregnancy but can reach quantities 10-fold higher than that found in non-pregnant individuals (Baylis, 2011), despite no change in plasma concentrations. It is present at early gestations and is likely to reflect reduced proximal tubular reabsorption (Davison and Hytten, 1975), and increased filtered load of glucose (Sturgiss et al., 1994). Impaired tubular reabsorption of glucose may persist after pregnancy in those with severe gestational glycosuria (Davison and Hytten, 1975).

Amino acids

Amino acid excretion increases during pregnancy, probably due to reduced reabsorption and distinct patterns of urinary amino acids at different gestations have been reported (Hytten and Cheyne, 1972). Total levels may reach up to 2 g/24 hours (Baylis, 2011).

Uric acid

Renal handling of uric acid changes during pregnancy. It is freely filtered by the glomerulus, and the majority is reabsorbed in proximal tubule, with further resorption along the nephron, resulting in approximately 10% excretion of the filtered load. In early pregnancy plasma concentrations fall by up to 25% (Lind et al., 1984), possibly due to reduced net tubular resorption of uric acid (Dunlop and Davison, 1977). Plasma levels rise in later pregnancy due to enhanced reuptake of filtered uric acid by the tubule or due to reduced GFR. Higher plasma concentrations occur in the morning, compared with evening (Boyle et al., 1966). Caucasians have lower levels in the absence of pathology compared with non-Caucasians, although further work is needed (Barry et al., 1992). It has been recognized for decades that women with pre-eclampsia have significantly raised uric acid compared with normotensive controls (Schaffer et al., 1943) due to enhanced tubular resorption (Conrad et al., 2009); however, uric acid is also elevated in renal disease, and therefore should not be used as a diagnostic tool in pregnancies known to be complicated by CKD. Furthermore the limitations of uric acid in the diagnosis of pre-eclampsia in pregnancy unaffected by CKD are well recognized.

Calcium

Calcium excretion increases two- to threefold during normal pregnancy, that is, greater than predicted by increased GFR, such that supersaturation of urine occurs (Maikranz et al., 1989). However, the combined effects of increased acid glycoprotein excretion, including Tamm–Horsfall protein and nephrocalcin, inhibits stone formation and pregnancy is not associated with increased renal calculi (Butler et al., 2000). Increased production of 1,25-dihydroxyvitamin D_3 (calcitriol) occurs during pregnancy, and

is also associated with hypercalciuria. Parathyroid hormone (PTH) levels are lower in pregnant women, compared with post partum (Pedersen et al., 1984), which may be the consequence of calcitriol suppression. Lower PTH may also suppress calcium reabsorption in the ascending limb of the loop of Henle (Maikranz et al., 1994).

Fractional excretion of calcium is reduced in women with pre-eclampsia, but appears to occur by a mechanism independent of PTH (Pedersen et al., 1984). Relative changes in 1,25-dihydroxyvitamin D_3, and calcium excretion in women with CKD in pregnancy compared to women with normal renal function are unknown.

Potassium

Approximately 300 mEq of potassium is gained during pregnancy, due to a net reduction in potassium excretion, but it is redistributed throughout fetal and maternal tissues, hence serum concentrations in pregnancy remain normal or lower than non-pregnant values. The anti-mineralocorticoid action of progesterone is thought to be responsible, despite high circulating levels of aldosterone (Lindheimer et al., 1987).

Acid–base balance

Pregnancy is associated with a mild chronic respiratory alkalosis due to increased minute ventilation, despite overall increased production of hydrogen ions secondary to raised basal metabolic rate and increased food consumption. Blood concentrations of hydrogen ions decrease by 2–4 mmol/L in early pregnancy, resulting in a rise in average arterial pH to 7.44 (Lucius et al., 1970). Serum bicarbonate levels fall to 18–22 mmol/L to compensate for reduced carbon dioxide partial pressures.

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CHAPTER 295

Pregnancy in patients with chronic kidney disease and on dialysis

Kate Bramham and Catherine Nelson-Piercy

Introduction

The prevalence of chronic kidney disease (CKD) is increasing in women of child-bearing age, and CKD may present for the first time in pregnancy. Whilst most women have successful outcomes, pregnancy in those with CKD is associated with an increased risk of both maternal and fetal adverse events. This chapter describes general management of women with CKD before, during, and after pregnancy, and details of complications specific to CKD aetiology.

Epidemiology

CKD stages 3–5 is currently estimated to affect up to 2% of women aged between 16 and 54 years old in the United Kingdom (Health and Social Care Information Centre, 2010), and up to 3% of women aged 20–39 years old in the United States (Coresh et al., 2007). Risk factors associated with CKD are increasing in women of child-bearing age including hypertension (Bateman et al., 2012), obesity (Kelly et al., 2008), diabetes (NICE, 2008) and advancing maternal age (Mathews and Hamilton, 2009). It is expected that more pregnancies will be complicated by CKD in future decades. A considerable part of antenatal care is devoted to the detection of pre-eclampsia. Monitoring of blood pressure and proteinuria may allow the identification of CKD for the first time during pregnancy, and any woman with proteinuria before 20 weeks' gestation should be investigated for renal disease, after infection has been excluded.

Measuring glomerular filtration in pregnancy

During pregnancy, glomerular filtration increases by 50% (see Chapter 294). Estimates of glomerular filtration rate (GFR) using Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration formulas underestimate GFR by up to 20% compared to formal measurements of GFR by inulin clearance or creatinine clearance (Smith et al., 2008; Alper et al., 2011), and therefore should not be used in pregnancy. Serial creatinine concentrations give an assessment of an individual's renal adaptations during pregnancy, and 24-hour creatinine clearance provides the only assessment of GFR during pregnancy that is practical and readily available; however, limitations in the accuracy of 24-hour urine collections are well recognized.

Published reference ranges for creatinine during pregnancy are based on small numbers of women, but it is generally acknowledged that creatinine reaches a nadir in the second trimester and starts to rise towards term (Girling, 2000). Widely used reference ranges for pregnancy are given in Table 295.1. Historically, pregnancy outcomes have been classified by serum creatinine prior to pregnancy (Williams and Davison, 2008), but more recent publications have categorized outcomes according to pre-pregnancy CKD stage (Piccoli et al., 2010)

Pre-pregnancy counselling

In 1975, a review of renal disease in pregnancy published in *The Lancet* reported that 'Children of women with renal disease used to be born dangerously or not at all—not at all if their doctors had their way' (Anonymous, 1975). Advances in the management of women with CKD prior to, and during pregnancy and their infants over recent decades have improved outcomes and consequently the majority of women with CKD have successful pregnancies. However, all women with CKD remain at increased risk of complications compared with healthy controls (Nevis et al., 2011).

The latest Confidential Enquiry into Maternal Deaths in the United Kingdom recommended pre-pregnancy counselling for women with chronic medical conditions (Centre for Maternal and Child Health Enquiries, 2011). Ideally all women with CKD should be offered pre-pregnancy counselling in order to discuss the following:

- The effect of renal disease on pregnancy, including maternal and fetal complications
- The effect of pregnancy on renal disease
- Safety of medication.

In addition, pre-pregnancy counselling affords an opportunity to advise women to take folic acid supplements for at least 3 months before attempting to conceive, in order to reduce the risk of neural tube defects (MRC Vitamin Study Research Group, 1991), and to recommend starting aspirin (75 mg) by 12 weeks' gestation for

Table 295.1 Normal laboratory values in pregnancy/non-pregnancy

	Pre-pregnancy	First trimester	Second trimester	Third trimester
Urea (mmol/L)	2.5–7.5	2.8–4.2	2.5–4.1	2.4–3.8
Creatinine (μmol/L)	65–101	52–68	44–65	55–73
Creatinine clearance (mL/min)	70–140	140–162	139–169	119–139
Na (mmol/L)	135–145	130–140	130–140	130–140
K (mmol/L)	3.5–5.0	3.3–4.1	3.3–4.1	3.3–4.1

Adapted from Nelson Piercy (2010).

the prevention of pre-eclampsia and fetal growth restriction (Duley et al., 2007). Renal function and blood pressure control should be optimized, rubella immunity confirmed, and smoking cessation discussed. Pregnancy and renal outcomes are described below according to severity of renal disease.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor antagonists must be stopped as soon as pregnancy is confirmed because of the severe fetopathy associated with exposure in the second and third trimesters. Women taking ACEIs should be counselled about the risks of these drugs in pregnancy, and women who may conceive should discuss whether or not they should remain on this class of drugs or discontinue them as soon as pregnancy is suspected (see Chapter 296).

Factors affecting pregnancy outcomes

Predictors of adverse events in pregnancy include:

- Severity of renal disease
- Presence/severity of proteinuria
- Presence/severity of hypertension
- Development of pre-eclampsia/superimposed pre-eclampsia
- Previous poor obstetric history.

Proteinuria

Several authors have identified proteinuria as a risk factor for worse pregnancy outcomes in women with CKD (Imbasciati and Ponticelli, 1991; Jungers and Chauveau, 1997; Rashid and Rashid, 2003; Piccoli et al., 2010). Pre-existing proteinuria is enhanced during pregnancy due to increased renal blood flow and altered renal handling of protein and occurs in all women with CKD (Piccoli et al., 2010). Furthermore, cessation of ACEIs exacerbates glomerular proteinuria. Up to 30% of women with CKD without proteinuria excrete significant amounts of protein (300 mg/24 hours, or 30 mg/μmol creatinine) during pregnancy which progresses with gestation (Stratta et al., 2006).

Pregnancy and proteinuria are associated with hypercoagulability and increased venous thromboembolic risk. Thresholds for the use of thromboprophylaxis are unknown but expert opinion suggests the use of low-molecular-weight heparin (e.g. 40 mg enoxaparin) if proteinuria is >2 g/24 hours and albumin <20 g/dL, with a dose reduction in women with more severe renal impairment (Williams, 2010).

Hypertension

Chronic hypertension in the absence of CKD is becoming more prevalent in women of child-bearing age and is associated with poor pregnancy outcomes compared with normotensive controls (Bateman et al., 2012). Secondary hypertension is repeatedly reported as a risk factor for worse pregnancy outcomes in women with CKD (Katz et al., 1980; Jungers and Chauveau, 1997; Piccoli et al., 2010; Bateman et al., 2012).

Women with pre-existing hypertension secondary to CKD may have a reduction in blood pressure due to systemic vasodilation in early pregnancy, and antihypertensives may be withheld or reduced for several weeks. However, most women with CKD experience an increase in blood pressure towards term, and those who have previously been normotensive are more likely to develop gestational hypertension than healthy controls (Nevis et al., 2011). Target blood pressures for CKD in pregnancy have not been validated, but reduced fetal growth is increased in women treated with antihypertensives and diastolic blood pressure < 70 mmHg (von Dadelszen et al., 2000), and systolic blood pressures > 160 mmHg are associated with intracerebral haemorrhage (Martin et al., 2005). Expert study group recommendations are a target of 120–139/70–85 mmHg for all women with CKD (Bramham et al., 2015).

Pre-eclampsia

Diagnosis of pre-eclampsia is challenging in women with CKD as the hallmark features—hypertension and proteinuria—are also frequently present in the absence of pre-eclampsia, or may develop due to pregnancy-associated physiological changes towards term. Superimposed pre-eclampsia occurs in women with pre-existing hypertension or proteinuria. Research definitions of superimposed pre-eclampsia specify that additional features are required, including clinical symptoms or changes in other parameters, for example, liver function tests or a fall in platelet count (Brown et al., 2001). In practice, additional features may be absent but women with CKD may have a rapid rise in blood pressure or dramatic increase in proteinuria, coupled with non-specific clinical features, for example, oedema or headache. Frequently women with suspected superimposed pre-eclampsia may require inpatient admission for maternal and fetal assessment. A decision to deliver is made by a multidisciplinary team evaluating the risk of deterioration of renal disease in the mother against neonatal complications of preterm delivery.

Pre-eclampsia or superimposed pre-eclampsia (pre-eclampsia occurring in women with pre-existing chronic hypertension or proteinuria) is reported to occur in 10–20% (Stratta et al., 2006; Williams and Davison, 2008) of women with CKD stages 1 and 2, and 40–60% of pregnancies in women with CKD stage 3 or 4 (Hou, 1985; Jones and Hayslett, 1996; Bramham et al., 2011a), compared with 5% of the general population (Roberts and Redman, 1993). Women with lupus nephritis (25–35%), renal transplants (20–30%) and reflux nephropathy appear to be at further increased risk of pre-eclampsia (Jungers, 1994; Stratta et al., 2006) with the same level of renal function and are discussed in more detail below.

The presence and severity of secondary hypertension and proteinuria are also risk factors for the development of pre-eclampsia in women with CKD (Bramham and Lightstone, 2012). A recent population study identified a greater than sixfold increase in rates

of pre-eclampsia in women with CKD in those with hypertension compared to those without secondary hypertension (Bateman et al., 2012).

Advances in methods of diagnosing pre-eclampsia are rapidly evolving, and frequently reflect placental dysfunction which underlies subsequent clinical manifestations. These diagnostic tools have not been rigorously tested in women with CKD, although appear promising. Rolfo et al. compared soluble fms-like tyrosine kinase receptor (s-Flt) and placental growth factor (PlGF) concentration ratios between women with CKD and women with pre-eclampsia found them to be significantly higher than in women with pre-eclampsia (Rolfo et al., 2013), suggesting they may be useful at discriminating between pre-existing renal disease and pre-eclampsia. The role of angiogenic factors in the diagnosis of superimposed pre-eclampsia in women with CKD has not yet been explored.

Uterine artery Doppler has not been formally evaluated exclusively in large cohorts of women with CKD; however, one study of women with lupus nephritis suggested that its mid-trimester negative predictive value was only 47% (Bramham et al., 2011b). Despite this, most clinicians would measure uterine artery Doppler indices in women with CKD, and plan subsequent fetal assessment according to estimated risk of fetal complications. More recently, Piccoli et al. compared uterine and fetal Dopplers in 17 women with CKD beyond 26 weeks' gestation and 37 women with pre-eclampsia. They concluded that normal flow velocity waveforms distinguished women with CKD from those with pre-eclampsia, but the role for Doppler for diagnosing superimposed pre-eclampsia is unknown (Piccoli et al., 2013).

Overall management strategy of chronic kidney disease in pregnancy

A management strategy for CKD in pregnancy is described in Fig. 295.1. Specific pregnancy and renal outcomes for women according to stage of CKD are given below, and can be used to inform women of risks at pre-pregnancy counselling and antenatally. Renal biopsy in pregnancy is considered in Chapter 297.

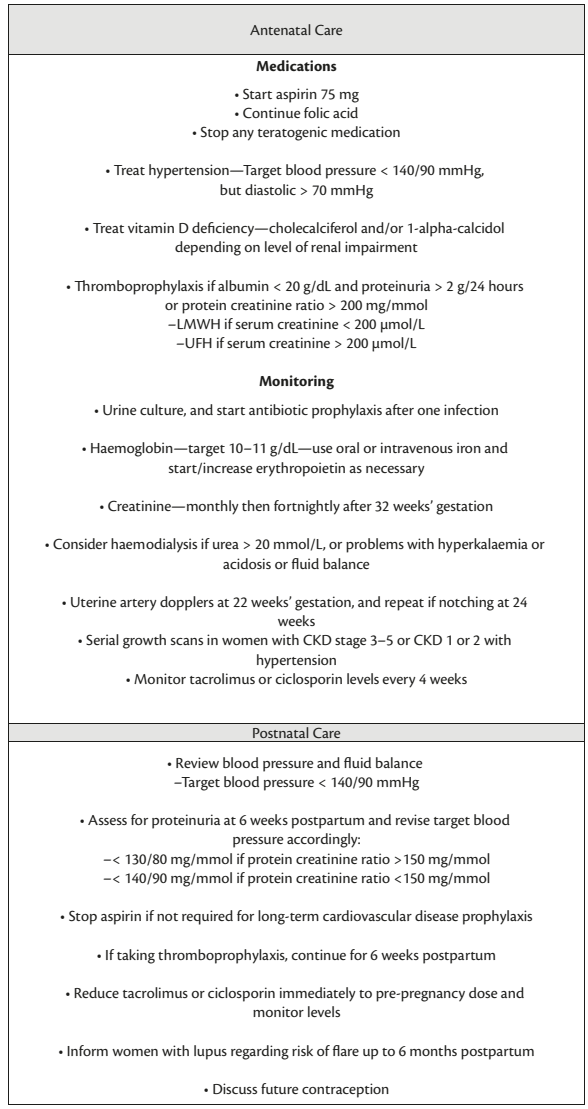

Fig. 295.1 Management strategy for CKD in pregnancy.

Pregnancy outcomes in women with chronic kidney disease stages 1 and 2

Mode of delivery

It is unusual for CKD to be a valid indication for caesarean section; however, operative deliveries are common. In a series of pregnancies in women with CKD, 57% and 40% of infants of mothers with stage 1 and stage 2 respectively were delivered by caesarean section (Piccoli et al., 2010) (Table 295.2).

Neonatal outcomes

The incidence of early fetal loss in women with CKD stages 1 and 2 is unknown. Data on rates of early fetal loss and termination of pregnancy for medical reasons are limited due to under-reporting, but small studies of women with specific renal diseases (Chapman et al., 1994; Jungers, 1994) suggest that it is higher than the general population.

A study of pregnancy outcomes in 61 women with CKD stage 1, and 15 women with stage 2 reported rates of preterm delivery (< 37 weeks) of 33% and 40% of women (Piccoli et al., 2010). Small for gestational age infants were not more frequent than the general population but may reflect increased fetal surveillance. Eighteen and 20% of infants of mothers with CKD stage 1 or 2 respectively required admission to neonatal intensive care. A comparison of women with CKD stage 1 with healthy controls confirmed that rates of pre-term delivery and neonatal admission to intensive care occur more frequently than in the general population (Piccoli et al., 2010).

A series of 908 pregnancies in 676 women studied between 1988 and 2005 stratified according to pre-pregnancy creatinine reported similar rates of preterm delivery (< 37 weeks) (30%) in women with pre-pregnancy creatinine < 125 µmol/L (Williams and Davison, 2008). Fetal growth restriction occurred in a quarter of infants, and perinatal death in 1%.

Renal outcomes

Women with CKD stages 1 and 2 are not expected to have a significant decline in renal function during or after pregnancy (Katz et al., 1981). Only 2% of women with pre-pregnancy serum creatinine had a temporary reduction in renal function (> 25%) during

Table 295.2 Estimated pregnancy outcomes for women with CKD stages 1 and 2

CKD stages 1 and 2	
Approximate pre-pregnancy creatinine μmol/L (non-black)	<100
Approximate pre-pregnancy creatinine μmol/L (black)	<120
Maternal pregnancy outcomes	
Pre-eclampsia/superimposed pre-eclampsia	10–20%
Caesarean section	40–57%
Neonatal outcomes	
Live birth	99–100%
Preterm delivery	30–40%
Small for gestational age	10–25%
Maternal renal outcomes	
Temporary decline in renal function (> 25%)	2%
Permanent decline in renal function (> 25%)	0
Requires replacement therapy	0

Adapted from Williams and Davison (2008) and Piccoli et al. (2010)

pregnancy, and none had a permanent loss of function (Williams and Davison, 2008).

Pregnancy outcomes in women with chronic kidney disease stages 3 and 4

There is a reduction in fertility with increasing severity of renal impairment due to adaptations in hypothalamic and pituitary axis function, associated with amenorrhoea and reduced libido (Hou, 1985).

Mode of delivery

Delivery by caesarean section occurs in the majority of women (59–81%) with CKD stages 3 and 4 (Jones and Hayslett, 1996; Imbasciati et al., 2007; Piccoli et al., 2010; Bramham et al., 2011a), and is likely to be associated with the increased number of iatrogenic preterm deliveries.

Neonatal outcomes

Fetal loss occurs more frequently than in the general population in women with more severe renal disease, including both early and late miscarriages (Hou, 1985; Abe, 1991a; Jungers et al., 1997). A useful early predictor of success of an individual pregnancy is the adaptation to increased GFR (Davison and Noble, 1981). If creatinine does not fall in the late first or early second trimester, complications appear to be more frequent (Jones and Hayslett, 1996). Fig. 295.2 illustrates the changes in creatinine expected in normal pregnancy, and a pregnancy in CKD with impaired adaptation to pregnancy. Perinatal death is likely to have fallen with advances in neonatal care, but occurred in 10% of pregnancies in women with pre-pregnancy creatinine > 180 μmol/L (Williams and Davison, 2008).

Preterm delivery in CKD stages 3 and 4 is also common (39–64%) (Abe, 1991a; Jones and Hayslett, 1996; Imbasciati et al., 2007; Williams and Davison, 2008) and > 90% of women with pre-pregnancy creatinine > 180 μmol/L have deliveries before 37 weeks' gestation (Williams and Davison, 2008). More than half of infants of mothers with CKD stages 3 and 4 require admission to neonatal intensive care (Imbasciati et al., 2007; Piccoli et al., 2010; Bramham et al., 2011a). Women should be counselled about the possibility of physical disability and neurocognitive and sensory impairment in infants born at very early gestations. The majority of preterm deliveries are iatrogenic, predominantly for maternal reasons including progression of hypertension, proteinuria, or decline in renal function (Piccoli et al., 2010).

Fetal growth restriction is also commonly recognized and is estimated to be up to five times more common in women with CKD (Holley et al., 1996), with increasing risk with severity of renal disease (Williams and Davison, 2008; Nevis et al., 2011). Serial growth scans are recommended from 24 weeks' gestation in women with reduced GFR, hypertension, or significant proteinuria (Brown, 2008).

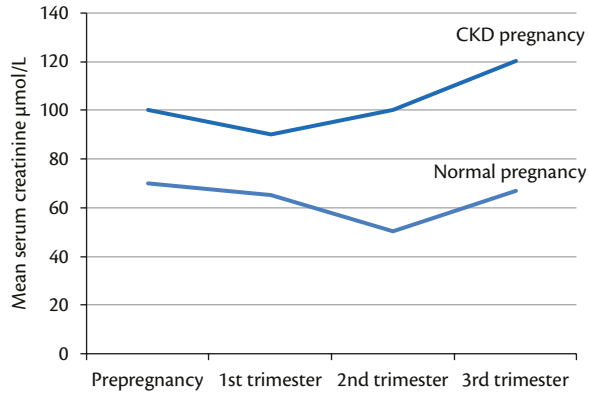

Fig. 295.2 Normal and maladaptive renal response to pregnancy with CKD. LMWH = low molecular weight heparin; UFH = unfractionated heparin.

Renal outcomes

Women with CKD stages 3 and 4 are at risk of pregnancy-associated accelerated decline in renal function. Estimated renal outcomes from a large UK series (1985–2007) describing pregnancies which reached 24 weeks' gestation (Williams and Davison, 2008) are shown in Table 295.3. One in two women with pre-pregnancy eGFR < 30 mL/min/1.73 m^2 have a > 25% loss of renal function postpartum, and one in three require renal replacement therapy within 1 year of pregnancy. An earlier study of 89 pregnancies in 62 women with pre-pregnancy serum creatinine > 125 μmol/L reported a decline in renal function (25% change in 1/serum creatinine) in 20% of women during pregnancy and 23% of women postpartum (Jones and Hayslett, 1996). At 6 months, 31% of women had a persistent reduction in renal function. Imbasciati et al. studied 49 women with CKD stages 3–5 and identified the simultaneous presence of pre-pregnancy GFR of < 40 mL/min/1.73 m^2 and proteinuria > 1 g/24 hours were risk factors of a 50% decline in renal function or requirement of renal replacement therapy (Imbasciati et al., 2007).

The complexities of life as a new mother combined with the practical and psychological issues of commencing dialysis needs to be considered, and discussed in detail with women at risk of a progression of their renal disease.

Table 295.3 Estimated pregnancy outcomes for women with CKD stages 3 and 4

CKD stages 3 and 4		
CKD stage	3	4
Approximate pre-pregnancy creatinine µmol/L (non-black)	100–180	180–300
Approximate pre-pregnancy creatinine µmol/L (black)	120–200	200–400
Maternal pregnancy outcomes		
Pre-eclampsia/superimposed pre-eclampsia	40%	60%
Caesarean section	60–80%	
Neonatal outcomes		
Live birth	95%	90%
Preterm delivery	60%	>90%
Small for gestational age	40%	65%
Maternal renal outcomes		
Temporary decline in renal function (>25%)	40%	70%
Permanent decline in renal function (>25%)	20%	50%
Requires replacement therapy	2%	35%

Adapted from Williams and Davison (2008) and Piccoli et al. (2010).

The mechanism for decline in renal function is unclear. Whilst hyperfiltration injury is possible, there is no evidence from animal studies to support this hypothesis. Furthermore, women who have pregnancy-associated progression of disease, usually do not exhibit an early reduction in serum creatinine reflecting a lack of adaptation of GFR, and absence of hyperfiltration; however, relative changes in glomerular pressure are unknown.

The additional glomerular injury of pre-eclampsia has been proposed to exacerbate pre-existing damage. Renal biopsies are frequently reported to show features of thrombotic microangiopathy in association with pre-eclampsia (Lafayette et al., 1998), but unlike other thrombotic microangiopathies, capillary thrombi are not commonly seen. Focal segmental glomerulosclerosis is seen in up to 50% of cases of pre-eclampsia in post-partum biopsies (Karumanchi et al., 2005), and whilst these lesions could be present prior to pregnancy in some women with undiagnosed renal disease, this may be the common pathway for pregnancy-associated decline in renal function (Epstein, 1996).

Pregnancy outcomes in women with chronic kidney disease stage 5

Pregnancy in women with stage 5 CKD is rare due to reduced fertility (Hou, 1985). Two large surveys of women on dialysis in the United States have estimated that pregnancy occurs in up to 1–1.5% of women of child-bearing age (Hou, 1987b; Okundaye et al., 1998). Early identification of pregnancy may be challenging due to irregularity of menstrual cycles, and a fall in haemoglobin, with no other cause identified, may be the first indicator of pregnancy. Conception can be confirmed by measuring serum beta human chorionic gonadotropin concentrations in oliguric/anuric women.

Table 295.4 Estimated pregnancy outcomes for women with CKD stage 5

CKD stage 5	
Maternal pregnancy outcomes	
Pre-eclampsia/superimposed pre-eclampsia	75%
Caesarean section	90–100%
Neonatal outcomes	
Live birth	50–100%
Preterm delivery	>90%
Small for gestational age	>90%
Maternal renal outcomes	
Temporary decline in renal function (>25%)	90–100% if not on dialysis
Permanent decline in renal function (>25%)	90–100% if not on dialysis
Requires replacement therapy	90–100% if not on dialysis

Adapted from Williams and Davison (2008) and Piccoli et al. (2010).

Mode of delivery

Vaginal delivery is preferred, but the majority of women require caesarean sections at early gestations. Spontaneous preterm labour is also more common, and therefore when the fetus is viable, dialysis should ideally be performed in a centre with obstetric services nearby.

Neonatal outcomes

Expected pregnancy outcomes for women with CKD stage 5 are shown in Table 295.4. Early fetal loss is reported to occur in up to 25% of pregnancies, but is likely to be under-reported (Okundaye et al., 1998). Overall pregnancy outcomes have dramatically improved over recent decades, with the use of erythropoietin and more intensive dialysis regimens. Small series have 100% successful pregnancy outcomes (Haase et al., 2005; Barua et al., 2008), compared with 23% in 1980 (European Dialysis and Transplant Association, 1980).

Despite more live births, pregnancies in women on dialysis continue to be complex. A systematic review of 222 pregnancy outcomes of women on renal replacement therapy found that women delivered at mean gestations of 32 ± 6.7 weeks with mean birth weights of 1810 ± 1193g (Yang et al., 2010). Women who conceive on dialysis compared with women who start dialysis during pregnancy tend to have worse pregnancy outcomes and years of dialysis prior to conception is also a negative confounder (Yang et al., 2010).

Management of pregnancy in CKD stage 5

There is evidence to suggest that women achieving > 20 hours of dialysis per week have better outcomes (Hou, 2002), and term deliveries have been described in women on nocturnal regimens (Barua et al., 2008). Urea is fetotoxic and it is recommended that dialysis should be commenced when maternal urea levels are 15–20 mmol/L (Hladunewich et al., 2011). High maternal urea causes polyhydramnios, but interestingly polyhydramnios is associated with better pregnancy outcomes, possibly reflecting successful placental function (Luders et al., 2010).

Increased dialysis frequency minimizes volume changes, and a target of < 1.5 L ultrafiltration is recommended per session. Fluid status should be assessed monthly, then weekly in the third trimester (Hladunewich et al., 2011), and fetal amniotic fluid volume estimates can be used to guide target weight adjustment. Intensive dialysis results in a reduction in potassium and phosphate concentration and increase in bicarbonate, which often requires an adjustment in dialysate constituents. Water soluble vitamins including 5 mg folic acid should be prescribed and appropriate dietary advice given. New fistulae or grafts should not be created during pregnancy due to possible combined effects of increased cardiac output and circulating relaxin.

Anaemia is common due to increased erythropoietin requirements, and should be treated aggressively, as women with lower haemoglobin concentrations are at greater risk of fetal or neonatal loss and preterm delivery (Asamiya et al., 2009). Whilst there have been no reports of thrombosis associated with recombinant erythropoietin use, this is a possibility due to the hypercoagulable state during pregnancy and it is advisable to reduce or temporarily withhold erythropoietin in women with haemoglobin > 11 g/dL (Brown, 2010). Intravenous iron should be continued in order to achieve non-pregnant targets. In a randomized controlled trial of intravenous iron sucrose compared with oral ferrous ascorbate there were no episodes of anaphylaxis or hypotensive shock in the 100 pregnant women receiving intravenous iron and parenterally administered iron sucrose elevated haemoglobin and restored iron stores better than oral ferrous ascorbate (Shafi et al., 2012). Thrombosis of dialysis circuits may become problematic and require increased anticoagulation. Both low-molecular-weight heparin and unfractionated heparin are safe in pregnancy.

Diagnosis of pre-eclampsia/superimposed pre-eclampsia can be challenging in women with CKD stage 5 who predominantly are hypertensive and may be anuric. Regular fetal scanning is required to monitor fetal growth. Two reports suggest that antiangiogenic factors may be beneficial in guiding management of such women (Shan et al., 2008; Cornelis et al., 2013), but further work is needed.

Peritoneal dialysis

Pregnancy is two to three times less common in women on peritoneal dialysis than haemodialysis (Hou, 1987a; Holley and Reddy, 2003). This may be due to the hypertonic dialysis fluid having adverse effects on the ovum, or its transport down the fallopian tubes. Furthermore, previous episodes of peritonitis may result in adhesions and failure of fertilization and implantation (Hou, 1987a). When compared with pregnancy outcomes of women on haemodialysis, women on peritoneal dialysis have higher birth weights and fewer episodes of pre-eclampsia but are more likely to deliver preterm (Chang et al., 2002). Peritonitis during pregnancy is commonly reported (Chang et al., 2002)

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CHAPTER 296

Pre-eclampsia and related disorders

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Introduction

Pre-eclampsia is a multisystem disorder that can affect any maternal organ including the kidney. It is a common direct cause of maternal death in the United Kingdom (Knight et al., 2014) and causes one-third of all serious obstetric morbidity (Waterstone et al., 2001). Effects of pre-eclampsia on the fetus include intrauterine growth restriction, low birth weight, and preterm delivery with potential for neurological and respiratory sequelae. Seven per cent of intrauterine deaths are directly caused by pre-eclampsia (Maternal and Child Health Research Consortium, 2001).

Pre-eclampsia is a pregnancy-specific disorder leading to new-onset hypertension and proteinuria after 20 weeks' gestation. Hypertension is defined as a blood pressure > 140/90 mmHg on at least two occasions, 4–6 hours apart, in women previously known to be normotensive. The proteinuria of pre-eclampsia is defined as a urinary protein excretion of > 300 mg/24 hours. A 24-hour urine collection is considered the gold standard for quantification of proteinuria but is limited by time-consuming and potentially inaccurate collection, compounded in pregnancy by physiological dilatation of ureters and incomplete bladder emptying (Côté et al., 2008). Therefore a spot urinary protein:creatinine ratio may also be used for diagnosis (Fischer, 2007). A protein:creatinine ratio of 30 mg/mmol has been identified as the best pragmatic cut-off point to define significant proteinuria in the hypertensive disorders of pregnancy (NICE, 2011). Random urine protein:creatinine ratios have been found to correlate highly with 24-hour protein collection results in women with pre-eclampsia (Park et al., 2013). Signs of pre-eclamptic disease should remit by 12 weeks post partum (Turner, 2010).

Pre-eclampsia encompasses a spectrum of disease ranging from a mild increase in blood pressure with minimal proteinuria at term, to accelerated hypertension with associated renal, hepatic, cerebral, and coagulopathic manifestations. Pre-eclampsia causes acute kidney injury (AKI) in only 1.5–2% of pregnancies (Gammill and Jeyabalan, 2005), with a requirement for temporary renal replacement in 0.55% of women with severe pre-eclampsia in the United Kingdom (Tuffnell et al., 2005). However, the fact that pre-eclampsia affects approximately 5% of all pregnancies means that pre-eclampsia is the commonest cause of AKI in pregnancy.

In contrast to pre-eclampsia, pregnancy-induced hypertension is the development of hypertension after 20 weeks' gestation without coexisting proteinuria. The threshold for treatment is currently set at > 150/100 mmHg (Visintin et al., 2010) and it is managed with the antihypertensive medication detailed below. Women with gestational hypertension are checked regularly for the remainder of their pregnancy for proteinuria, thrombocytopenia, and transaminitis, which may indicate transformation from gestational hypertension to pre-eclampsia with end-organ pathology. The earlier in pregnancy gestational hypertension develops, the higher the risk of the condition evolving into pre-eclampsia such that for gestational hypertension presenting before 30 weeks, the risk of pre-eclampsia is 42%, at 34–35 weeks it is 20%, and at 37 weeks is only 7% (Saudan et al., 1998).

The diagnosis of pre-eclampsia is based on a new rise in high blood pressure and new-onset proteinuria being detected in pregnancy. This diagnosis becomes more difficult when chronic renal disease, hypertension, and/or proteinuria pre-date the pregnancy. Chronic kidney disease (CKD) and pre-eclampsia occur with a similar prevalence in the pregnant population and both can present with hypertension and proteinuria. In addition, CKD, hypertension, and proteinuria are all independent risk factors for pre-eclampsia (Vidaeff et al., 2008; Piccoli et al., 2013). Preconception data may allow the two conditions to be distinguished but pregnancy may be the first time a young, asymptomatic woman presents for medical review. In the United Kingdom, all pregnant women undergo a 'booking' appointment in the first trimester. The 'booking' blood pressure and urine screen are very valuable to the nephrologist looking to distinguish pre-existing disease from pregnancy-associated disease. However, it must be remembered that normal pregnancy is associated with prominent early vasodilatation and a lowering of blood pressure. Therefore a diastolic blood pressure of > 80 mmHg should be considered abnormal in the first trimester (Nelson-Piercy, 2010). Limited retrospective data suggest that normal flow waveforms seen on uterine and umbilical arterial Doppler are more commonly seen in CKD, whilst an abnormal Doppler of both arteries is found more commonly in pre-eclampsia (Piccoli et al., 2013). However, study numbers are small with a degree of overlap and any conclusion remains dependent upon being able to make the difficult clinical distinction between the inter-related diagnoses of CKD and pre-eclampsia in the research population.

Although oedema is not a criterion for the diagnosis of pre-eclampsia it remains a common presenting symptom. However, the oedema in pre-eclampsia is not due to intravascular hypovolaemia driving the renin axis and causing secondary sodium retention. It is better comparable to the 'overflow' state of the acute nephritic syndromes in which glomerular filtration rate (GFR) decreases

disproportionately to renal plasma flow and a glomerular-tubular imbalance is hypothesized as the reason for salt retention and consequent oedema (Karumanchi et al., 2005). The suppressed renin activity (August et al., 1990) and increased atrial natriuretic factor (Bond et al., 1989) seen in pre-eclampsia are consistent with a clinically overloaded state. Decreased GFR, increased capillary permeability, and hypoalbuminaemia all contribute to the oedema which is seen clinically in pre-eclampsia.

Histopathology of acute kidney injury in pre-eclampsia

The prevalence of pre-eclampsia means that it is the commonest glomerular disease in the world (Stillman and Karumanchi, 2007). The primary locus for kidney injury in pre-eclampsia is the glomerular endothelium. This may explain why diseases of endothelial dysfunction, including diabetes and antiphospholipid syndrome, carry an increased risk for the development of pre-eclampsia.

Endothelial cell swelling leads to capillary occlusion and 'endotheliosis': a swelling of the glomerulus, the degree of which correlates with disease severity (Nochy et al., 1980). Antiangiogenic factors are hypothesized to play a role in the interruption of normal endothelial health causing the endotheliosis that is pathognomonic for pre-eclamptic renal injury. Impaired hydraulic permeability of the glomerular capillary wall leads to reduced plasma flow and a fall in GFR (Dragun and Haase, 2010). The AKI in pre-eclampsia is therefore felt to be structural with haemodynamic elements merely contributory (Moran et al., 2003).

In pre-eclampsia, GFR and renal plasma flow decrease by 24–40% compared with normal pregnancy of the same gestation (Moran et al., 2003; Lafayette, 2005). The difficulty of diagnosing AKI in pregnancy on the basis of creatinine measurement is highlighted by studies of GFR in pregnancy which record a mean GFR value of 149 mL/min/1.73 m^2 in normal pregnancy, reducing to 91 mL/min/1.73 m^2 in pre-eclampsia (Lafayette et al., 1998). Despite AKI being clearly demonstrated by the fall in GFR in pre-eclampsia, the measured GFR value is still much greater than that seen in AKI outside of pregnancy.

Of note, mild glomerular endotheliosis is seen in up to 50% of pregnancies complicated by hypertension without coexisting proteinuria suggesting that pregnancy-induced hypertension is part of the spectrum of pre-eclamptic renal disease (Nochy et al., 1980).

Monitoring in pre-eclampsia

Once a diagnosis of pre-eclampsia is made, the risk of maternal and perinatal morbidity and mortality is increased. Of all the clinical, biochemical, and haematological parameters that can be affected by pre-eclampsia, only systolic and diastolic blood pressure are significantly predictive of maternal complications (Nisell et al., 2000). In the absence of data to inform frequency of blood pressure monitoring in pre-eclampsia, guidelines advocate monitoring four times daily in moderate hypertension (< 159/109 mmHg) (NICE, 2011). Severe hypertension (≥ 160/110 mmHg) increases the risk of maternal cerebral haemorrhage and therefore closer monitoring of blood pressure, including confirmation of a response to antihypertensive treatment, is necessary.

The diagnostic cut-off of 300 mg proteinuria in 24 hours is recognized to be arbitrary with no consensus as to what 'severe' proteinuria might be (Lindheimer and Kanter, 2010). Given that renal protein handling is altered by pregnancy with maximization of tubular reabsorption, small changes in tubular protein can have a disproportionate effect on proteinuria quantification. This includes the use of steroids for fetal lung maturation, which may be given in pre-eclampsia when preterm delivery is anticipated (Turner, 2010). Management decisions cannot therefore be based on the level of proteinuria. There is a weak association between proteinuria of < 5 g/24 hours and adverse perinatal outcome but data are not strong enough to advocate repeat quantification of proteinuria once a diagnosis of pre-eclampsia is made (NICE, 2011).

Urine microscopy can reveal other elements in addition to proteinuria. Non-visible haematuria can occur in normal pregnancy. In addition, a small series has found granular, hyaline, tubular, and red cells casts in the urine of women with pre-eclampsia, none of which correlated with either renal function or clinical outcome (Leduc et al., 1991).

Incomplete, retrospective data show an association between a serum creatinine > 110 μmol/L and maternal outcome, but there is no link with perinatal outcome (Menzies et al., 2007).

Management of pre-eclampsia

Treatment of hypertension

The treatment of pre-eclampsia aims to maintain blood pressure at levels low enough to reduce the risk of cerebral haemorrhage in the mother whilst maintaining adequate uteroplacental perfusion.

Treatment is mandatory for a blood pressure > 160/110 mmHg due to the risk of both maternal cerebral haemorrhage and placental abruption. However, the treatment of less severe hypertension in pregnancy has insufficient robust literature for guidance. Interpretation of the same data has produced variable guidelines with different thresholds for the treatment including systolic pressures from 140 to 159 mmHg and diastolic pressures between 90 and 109 mmHg (Magee et al., 2011). Treatment goals are also poorly defined with systolic targets of 110–140 mmHg and diastolic targets of 80–105 mmHg although some of this variance is explained by comorbidities including diabetes and CKD (Magee et al., 2011). A study of > 200,000 babies in the United Kingdom has examined the relationship between diastolic blood pressure and pregnancy outcome in terms of birth weight and perinatal mortality (Steer et al., 2004). This prospective study generated an optimum diastolic blood pressure of 82 mmHg. For babies born after 34 weeks' gestation, birth weight was maximal when the highest recorded diastolic blood pressure in pregnancy was between 70 and 90 mmHg. Diastolic pressures of < 70 mmHg were associated with lower birthweight and higher perinatal mortality. This study, however, excluded all women with proteinuria and therefore cannot be used to draw conclusions about blood pressure targets in women with pre-eclampsia. In the United Kingdom, it was advised that only patients with a raised cardiovascular risk and/or target-organ damage are treated in pregnancy to a blood pressure below 140/90 mmHg (Palma-Reis et al., 2013). For women with pregnancy-induced or chronic hypertension, the CHIPS (control of hypertension in pregnancy) trial demonstrated that a target diastolic blood pressure of 80–85 mmHg was associated with no increased risk to the fetus/neonate compared to a diastolic blood pressure target of 100–105 mmHg but was associated with a reduced risk of severe hypertension in the mother. This study did not include

women with proteinuric hypertension and pre-eclampsia (Magee et al., 2015).

Common agents used in the treatment of hypertension are outlined in Table 296.1.

Labetalol is recommended as the first-line antihypertensive in pregnancy. It is effective, safe, and licensed for use in pregnancy. Bolus doses of intravenous labetalol can be used to gain more rapid control of severe hypertension. Historically, there was concern that the use of beta blockers in pregnancy was associated with fetal growth restriction. However, this is now considered to be due to their effectiveness at reducing blood pressure rather than a class-specific side effect. A meta-regression of randomized controlled trial evidence, including the use of 15 different antihypertensives in pregnancy, shows that a 10 mmHg fall in mean arterial pressure is associated with a 145 g reduction in birth weight (von Dadelszen et al., 2000). Treatment of blood pressure in pregnancy therefore aims to reduce the maternal risk associated with hypertension in the moderate-severe end of the spectrum, whilst avoiding excessive treatment that may affect fetal growth. There is no evidence that treatment of hypertension to maintain a diastolic pressure 90–99 mmHg has a detrimental effect on fetal growth but treatment to a diastolic pressure < 80 mmHg is avoided (NICE, 2011).

Where a second blood pressure agent is required for control, either methyldopa or nifedipine can be used. There is extensive obstetric experience in the use of methyldopa in pregnancy with no association with fetal malformation. Its mood-related side effects mean that it should not be used post partum due to an increased risk of postnatal depression. Equally, nifedipine has no adverse effects on fetal development and use in the second and third trimester does not affect fetal or neonatal heart rate. It is recognized in the non-pregnant population that patients of Afro-Caribbean origin have a better hypotensive response to treatment with calcium channel blockers, as compared to beta blockers. There are insufficient data available to determine whether this trend is maintained in pregnancy-induced hypertensive disorders. For women who fail to show an adequate response to labetalol, nifedipine should be considered.

Hydralazine is a potent vasodilator available in oral and intravenous form. When compared to labetalol, hydralazine has been shown to be more effective in reducing blood pressure but also to result in more hypotension and side effects (Magee et al., 2003). Intravenous hydralazine can be used to treat severe pre-eclampsia, especially in those either unresponsive, or inadequately responsive, to labetalol. To reduce the risk of sudden, marked hypotension with intravenous hydralazine, pre-loading with 500 mL of intravenous

Table 296.1 Common pharmacological agent used to treat hypertension in pregnancy and the post-partum period

Agent	Dose	Side effects	Comments
Antenatal			
Labetalol	100 mg bd–500 mg tds		Avoid in asthma
Methyldopa	250 mg bd–1 g tds	Lethargy Depression	Documented safety profile 7-year follow-up of off-spring
Nifedipine slow release	10 mg–40 mg bd	Headache Flushing Swollen lower limbs	Tocolytic Synergistic interaction with magnesium sulphate
Hydralazine	25 mg bd–75 mg tds	Headache Flushing Tachycardia	
Amlodipine	5–10 mg od	Swollen lower limbs	
Doxazosin	1 mg od–8 mg bd		
ACEIs and angiotensin receptor blockers	CONTRAINDICATED	Congenital cardiac and CNS anomalies Fetopathy Oligohydramnios Fetal growth restriction Neonatal renal failure	
Postnatal			
Enalapril	5–20 mg bd		Safe in breastfeeding
Nifedipine SR	10–40 mg bd		Safe in breastfeeding
Amlodipine	5–10 mg od		Safe in breastfeeding
Atenolol	25–50 mg od		Safe in breastfeeding

Adapted from NICE (2011) and Palma-Reis et al. (2013).

crystalloid should be considered. However, this is dependent upon the individual patient's fluid state, which can be difficult to assess and manage when oedema is a prominent clinical feature of pre-eclampsia (see 'Fluid balance').

Angiotensin converting enzyme inhibitors (ACEIs) cause a severe fetopathy when exposure occurs in the second and third trimester including fetal hypotension, anuria-oligohydramnios, growth restriction, pulmonary hypoplasia, renal tubular dysplasia, and hypocalvaria (Pryde et al., 1993). Acute neonatal anuric-renal failure can occur with CKD, hypertension, and polycythaemia developing in childhood (Laube et al., 2007). Angiotensin receptor antagonists have similar fetal effects.

Because of these severe side effects in the second trimester and later, ACEIs should be discontinued as soon as pregnancy is confirmed, and they should not be commenced in pregnancy. There is some evidence of an increased rate of fetal malformations in patients becoming pregnant (NICE, 2011) while taking ACEIs, but also more reassuring studies suggesting that any increase is more likely to be a consequence of background diagnoses than of the drugs (e.g. Li et al., 2011; Porta et al., 2011). Possible risks of conceiving while on ACEIs need to be weighed against the risks of prolonged periods not taking the most effective nephroprotective drugs we have, and should be discussed with patients. This is particularly important as conception may be very delayed in women with 'highest risk' CKD and a policy of complete avoidance may expose them to significantly greater risk of renal deterioration.

Magnesium

Severe pre-eclampsia is defined as a blood pressure ≥ 160/110 mmHg or the presence of symptoms, or biochemical, or haematological impairment. It is usually managed in a high-dependency care environment with delivery planned within 24 hours. In this setting, magnesium is used as prophylaxis against eclampsia. Data suggest that 50 women with severe pre-eclampsia require treatment with magnesium to prevent one eclamptic seizure (Duley et al., 2010). In women who develop eclampsia, magnesium is superior to both diazepam and phenytoin in preventing further seizures. The Collaborative Eclampsia Trial regimen for magnesium administration is recommended, using a bolus of 4 g followed by an infusion of 1 g/hour for 24 hours (Eclampsia Trial Collaborative Group, 1995).

The therapeutic mechanism by which magnesium works in not fully understood. Hypotheses include reduced seizure activity and cerebral ischaemia via antagonism of *N*-methyl-D-aspartate (NMDA) and a reduction in transport of pro-inflammatory molecules across the blood–brain barrier via calcium antagonism (Duley et al., 2010). It does not work as an antihypertensive (Abalos et al., 2007).

Delivery

Hypertension is not the cause of pre-eclampsia and antihypertensive treatment is management of risk not amelioration of the disease process. The definitive treatment of pre-eclampsia/eclampsia is delivery of the fetus thereby removing the placenta which is driving the pathogenesis of the pre-eclamptic disease process. Management of pre-eclampsia therefore constitutes a balance between the maternal risk in continuing the pregnancy, with the consequences of pre-term delivery for the baby.

Severe pre-eclampsia is an indication for delivery depending on gestation. In a pregnancy of < 34 weeks' gestation, delivery is only indicated if pre-eclampsia proves refractory to medical treatment or if there are other fetal or maternal indications for delivery such as falling platelet count, AKI, pulmonary oedema, progressive liver dysfunction, coagulopathy, or severe fetal compromise. Randomized trial data show that where stabilization is possible and delivery can be delayed, there is a reduction in neonatal respiratory distress, necrotizing enterocolitis, and requirement for neonatal intensive care; without a compromise in maternal outcome including abruption, HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, and eclampsia (Sibai et al., 1994; NICE, 2011).

After 34 weeks' gestation, fetal outcomes are significantly improved. Delivery is therefore recommended for severe pre-eclampsia after 34 weeks once the blood pressure is controlled and steroids have been given to aid fetal lung maturation.

After 37 weeks, there is no maternal or fetal disadvantage to delivery (Koopmans et al., 2009). Therefore delivery within 48 hours should be considered for management of even mild or moderate pre-eclampsia after 37 weeks to avoid the potential, yet unpredictable progression to severe disease. There are insufficient data to inform the optimum time for delivery in women who develop mild or moderate pre-eclampsia in the gestational window $34–36^{+6}$ weeks. Randomized control trial data are awaited (Langenveld et al., 2011).

Fluid management

Fluid management is important in pre-eclampsia. There is no evidence of benefit from fluid expansion in pre-eclampsia (Duley et al., 2000) and a fluid challenge with either crystalloid or colloid does not ensure improved uteroplacental perfusion (Sehgal and Hitt, 1980). It is important to be aware that oliguria is common in pre-eclampsia but that this does not imply volume depletion (Lee et al., 1987). In addition, aggressive hydration in women with pre-eclampsia is associated with pulmonary oedema and increased maternal mortality. It is therefore advised that women with pre-eclampsia are 'kept dry' to avoid this risk (von Dadelszen et al., 2007). In addition, a case–control study of 114 women with pre-eclampsia found that those treated with volume expansion had babies who were over five times more likely to need artificial ventilation than those babies whose mothers received no intravenous fluids (Visser et al., 1994).

There is a natural diuresis at 36–48 hours post partum. Judicious fluid management is needed until this occurs. A fluid restriction of 80 mL/hour is suggested (Engelhardt and MacLennan, 1999; von Dadelszen et al., 2007). Before the post-partum diuresis, oliguria is common and does not require further management. It is suggested that a urine output > 40 mL in 4 hours is sufficient in the immediate post-partum period (von Dadelszen et al., 2007) although there is no evidence that treating to a target urine output will prevent the rare development of overt renal failure. Urine output is, however, used to guide magnesium treatment in severe pre-eclampsia and eclampsia. The kidney is the key player in magnesium homeostasis and a fall in GFR increases the potential for developing hypermagnesaemia. When urine output falls to < 20 mL/hour, dose adjustment of magnesium sulphate is required. The usual loading bolus dose of 4 g should be given but the maintenance rate should be halved in the presence of AKI.

The reversible glomerular endothelial pathology in pre-eclampsia that temporarily compromises renal function may be complicated both by hypovolaemia and overzealous fluid restriction.

Permanent renal damage in pre-eclampsia is unusual, suggesting that restriction of fluid in pre-eclampsia is either not clinically significant or that permanent clinical sequelae are rare (Engelhardt and MacLennan, 1999). Renal function is, however, vulnerable in patients with pre-eclampsia and a nephrotoxic hit from post-partum non-steroidal anti-inflammatory drugs, which are often routinely prescribed after caesarean section, should be avoided.

Post partum

The glomerular swelling and renal endothelial changes in pre-eclampsia usually resolve by 8 weeks post partum. This coincides with the regression of hypertension and proteinuria that is seen clinically in the post-partum period (Karumanchi et al., 2005). However, persistent hypertension in the immediate post-partum period is common and the risk is higher for those with more severe antenatal disease. Blood pressure tends to peak at day 3–5 post partum which is when a medical opinion is often sought to help facilitate discharge home. Reassuringly, the risk of maternal cerebral haemorrhage and eclampsia is low after the fourth post-partum day (Tan and De Swiet, 2002). Safety data exist for enalapril and captopril in breastfeeding mothers so ACEIs, which are contraindicated in pregnancy, can be re-established post partum. Methyldopa is avoided in the post-partum period due to the association between its use and clinical depression. It is important to consider the practicalities of compliance in the disrupted post-partum period. There may be no rationale in attempting to maintain stable blood pressure using the same three-times-per-day regimen which was required antenatally over single dosing with, for example, amlodipine or atenolol which can be safely used after delivery. Treatment targets in the post-partum period are the same as those antenatally and the threshold for hospital discharge is a stable blood pressure < 150/100 mmHg. Given that uterine perfusion and fetal compromise are not a concern after delivery it could be hypothesized that post-partum blood pressure targets should be lower. However, pregnancy-induced blood hypertension is likely to regress and treatment requirements are predicted to fall. Patients should be advised to withhold antihypertensive treatment in the event of postural symptoms and attend for medical review of their blood pressure and its required management.

It is advised that patients who continue to demonstrate proteinuria at 6–8 weeks post partum are reviewed again at 3 months post partum and a referral to a nephrologist is considered to exclude underlying renal disease. However, research has demonstrated a longer regression trajectory in those with higher blood pressures and greater quantities of gestational proteinuria. Fourteen per cent of women are found to have persistent proteinuria at 3 months, falling to 2% at 2 years post partum. It is estimated to require 16% more time to remission for every 1 g/day increase in proteinuria during pregnancy (Berks et al., 2009).

Pre-eclampsia is known to increase the risk of vascular disease in later life including chronic hypertension, ischaemic heart disease, cerebrovascular disease, and venous thromboembolism (Bellamy et al., 2007). For this reason, women who have developed pre-eclampsia are advised to undergo annual assessment of their vascular risk, appropriate modification of lifestyle factors and preventative treatment when risk thresholds are reached. In addition, pre-eclampsia is an independent risk factor for both renal biopsy and subsequent end-stage renal disease (ESRD). A woman with pre-eclampsia whose baby weighs < 1.5 kg has a 17-fold increased risk of proceeding to renal biopsy (Vikse et al., 2006). In addition, pre-eclampsia increases the risk of ESRD by 3–15 times depending on the number of pregnancies in which pre-eclampsia develops. These data include correction for pre-existing renal disease, rheumatic disease, essential hypertension, and diabetes mellitus (Vikse et al., 2008). However, the absolute risk of ESRD is low and therefore women who are normotensive with no proteinuria at their post-partum check do not require long-term nephrology follow-up.

Managing pre-eclampsia risk

Some women entering pregnancy are considered to have a high risk of developing pre-eclampsia, including those with pre-existing chronic hypertension, CKD, diabetes, systemic lupus erythematosus, and antiphospholipid syndrome. In addition, a history of previous pre-eclampsia confers a sevenfold increased risk of recurrent disease (Duckitt and Harrington, 2005). This recurrence risk varies depending upon the severity with which the pre-eclampsia presented in the past. The risk of recurrence is 16%, increasing to 25% if the pre-eclampsia was severe including HELLP and eclampsia, rising to 55% if delivery was required before 28 weeks' gestation (NICE, 2011).

Low-dose aspirin (75 mg) confers a reduction in the risk of developing pre-eclampsia without increasing ante-partum or post-partum bleeding (Duley et al., 2007). Greater benefit is seen for women at highest risk. Impaired placentation is considered important in the pathophysiology of pre-eclampsia. Therefore prophylaxis with aspirin is felt to be most beneficial if started before 20 weeks' gestation (NICE, 2011). Guidelines advocate the use of aspirin for pre-eclampsia prophylaxis from 12 weeks' gestation to mirror the evidence base currently available. In practice, aspirin prophylaxis is often started whenever high-risk women present to obstetric services and aspirin need not be discontinued in women who are maintained on it prior to pregnancy.

HELLP syndrome

HELLP syndrome is the constellation of haemolysis, elevated liver enzymes, and low platelets and is an important variant of severe pre-eclampsia. The consumptive coagulopathy and microangiopathy of HELLP occurs in 10–20% of patients with severe pre-eclampsia (Nochy et al., 1980). The incidence of renal impairment and AKI are much higher in HELLP syndrome compared to pre-eclampsia, and the largest study estimates that AKI complicates 3–15% of HELLP (Gul et al., 2004). Abruption, disseminated intravascular coagulation, sepsis, haemorrhage, and intrauterine death all increase the risk of AKI in HELLP. A rise in serum creatinine in association with HELLP worsens prognosis (Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists, 2006).

Although AKI in HELLP can be severe enough to necessitate temporary renal replacement therapy, most patients will recover renal function unless there is underlying CKD (August, 2013). In addition, successful cadaveric renal transplantation from patients with HELLP with renal involvement are described (Flynn et al., 2001).

Renal recovery means that there are limited biopsy data on the nature of the renal insult in HELLP. Isolated case reports describe the endotheliosis of pre-eclampsia with additional thrombotic microangiopathy. It is therefore hypothesized that the endothelial

pathology which triggers kidney injury in pre-eclampsia extends to produce a thrombotic microangiopathy in HELLP. The resulting renal tissue ischaemia is more severe and leads to both tubular and cortical necrosis (Abraham et al., 2003; Ganesan and Maynard, 2011), potentially explaining the higher prevalence of AKI in HELLP compared to pre-eclampsia.

Diagnosis of HELLP may not be a straightforward. Complete HELLP syndrome requires aspartate transaminase > 70 IU/L, platelet count < 100×10^9/L and evidence of haemolysis, such as serum lactate dehydrogenase (LDH) > 600 U/L (Audibert et al., 1996). However, partial HELLP is also described with lower threshold for diagnosis which can include normal markers of haemolysis (Van Bogaert, 1997). In addition, although HELLP is part of the spectrum of pre-eclamptic disease it does not always present with significant hypertension: 31% of cases have a diastolic blood pressure < 110 mmHg and 15% of cases have an admitting diastolic blood pressure < 90 mmHg (Sibai et al., 1986). Although up to 30% of cases of HELLP syndrome develop post partum, most will occur within the first 48 hours (Sibai et al., 1993). This mirrors the recognition that all HELLP parameters may continue to deteriorate for 48 hours post partum (Neiger et al., 1991). However, postpartum recovery of haematological and biochemical abnormalities is expected. LDH should fall by day 4 post partum as haemolysis remits (Dildy, 2007). A study of 158 women with HELLP demonstrated that women with a platelet nadir of $50–100 \times 10^9$/L will show recovery to $>100 \times 10^9$/L by the sixth post-partum day, while those with a nadir $< 50 \times 10^9$/L require 11 days for recovery, and that platelet count recovery is seen in all women (Martin et al., 1991). Where platelet consumption and AKI predominate the clinical picture, and where laboratory abnormalities do not remit after delivery, the differential diagnosis of thrombotic thrombocytopenia purpura (TTP) and/or haemolytic uraemic syndrome (HUS) should be considered. In addition, in 20% of cases of severe HELLP, disseminated intravascular coagulopathy develops (Ganesan and Maynard, 2011) whereas a hallmark of HUS and TTP is that coagulation is normal. Table 296.2 highlights some of the clinical features which may distinguish HELLP from HUS/TTP. (See 'Thrombotic microangiopathy').

The management of HELLP is supportive and mirrors that of pre-eclampsia. A double-blind, randomized controlled trial showed that the use of steroids did not alter hospital stay, recovery of laboratory parameters, or complication rates (Fonseca et al., 2005). Although the renal pathology is that of a thrombotic micoangiopathy, and similar complement abnormalities to those in an atypical HUS have been described in HELLP (Fakhouri et al., 2008) (see 'Thrombotic microangiopathy'), there are no prospective trial data to either support or refute the use of plasmapheresis in HELLP.

Table 296.2 Distinguishing features of HELLP versus HUS/TTP (see 'Thrombotic microangiopathy')

Feature	HELLP	HUS/TTP
Incidence	10–20% of severe pre-eclampsia	Rare
Gestation	Pre partum (70%) Post partum (30%)	TTP: 2nd/3rd trimester and post partum HUS: > 75% post partum
Thrombocytopenia	< 10×10^9/L rare	Profound thrombocytopenia more common
Abnormal liver function	Transaminitis	Normal liver function, pre-hepatic hyperbilirubinaemia
AKI	3–15%	30–80% in pregnancy associated TTP 76% ESRF with complement abnormalities
Coagulopathy	20%	None Elevated antithrombin and fibrinogen may be seen
ADAMTS 13	Reduced level in HELLP without coexistent TTP	Deficiency in TTP
Complement abnormalities	Detected in HELLP	Cause HUS

ESRF = end-stage renal failure; HUS = haemolytic uraemic syndrome; TTP = thrombotic thrombocytopenic purpura.

Thrombotic microangiopathy

Pregnancy-associated thrombotic microangiopathy is rare with an estimated incidence of 1 in 25,000 pregnancies (Matthews et al., 2009). It is caused by the presence of thrombi in the microvasculature leading to a consumptive thrombocytopenia, mechanical haemolysis, and end-organ damage. Thrombotic microangiopathy has traditionally been divided into the different clinical phenotypes of TTP with minor renal involvement and HUS with predominant renal dysfunction. However, on clinical assessment alone, the same patient might in the past have been labelled as HUS by a nephrologist and TTP by a haematologist (Furlan and Lämmle, 2000). Historically, the term TTP/HUS was coined to avoided uncertainty of diagnosis.

However, an improved understanding of the molecular pathophysiology of thrombotic microangiopathy now facilitates a more precise subclassification of disease. Four subtypes of disease can now be considered (Fakhouri et al., 2012):

1. Acquired or constitutional deficiency in a disintegrin and metalloproteinase with a thrombospondin type I motif, member 13 (ADAMTS13) leading to the clinical picture of TTP.
2. Complement alternative pathway dysregulation in HUS.
3. Secondary thrombotic microangiopathy including that precipitated by Shiga-like toxin-producing *Escherichia coli* and drugs.
4. Thrombotic microangiopathy of undetermined mechanism.

ADAMTS13-deficient thrombotic thrombocytopenic purpura in pregnancy

TTP is characterized by thrombocytopenia, microangiopathic haemolytic anaemia, and organ dysfunction including AKI. Pregnancy-associated TTP usually occurs in the second or third trimesters or in the post-partum period (Martin et al., 2008). The average gestational age at diagnosis is 26 weeks. Pregnancy is both a trigger factor for new disease and for disease flare in those with a history of TTP.

Von Willebrand factor (vWF) plays a haemostatic role by inducing the formation of platelet plugs. In TTP, von Willebrand proteins do not undergo their normal rapid breakdown due to either a quantitative or functional deficiency of the vWF cleaving protein, ADAMTS13. This leads to platelet aggregation, red cell fragmentation, and the clinical picture of TTP. The pathogenesis of TTP is characterized by the deposition of platelet-rich thrombi in the microcirculation of multiple organs, including the kidneys.

Pregnancy is a pro-coagulant state with increased levels of factor VIIa, factor VIII, vWF, and fibrinogen as well as increased amounts of fibrin degradation products. This suggests that mild intravascular coagulation is a phenomenon of normal pregnancy (Ganesan and Maynard, 2011). In addition, levels of ADAMTS13 decrease in normal pregnancy during the second and third trimesters.

TTP can be difficult to diagnose in pregnancy as thrombocytopenia, haemolysis, renal dysfunction, and neurological symptoms exist in both TTP and HELLP. Twenty per cent of woman with pregnancy-associated TTP are diagnosed with coexisting pre-eclampsia/HELLP (Ganesan and Maynard, 2011). Clotting abnormalities are, however, more common (20%) in HELLP and so elevated antithrombin and fibrinogen levels may increase the clinical suspicion of TTP (Ganesan and Maynard, 2011). (See 'HELLP' and Table 296.2.) ADAMTS13 levels may not be diagnostically helpful as a reduced level has been described in HELLP without evidence of concurrent TTP (Lattuada et al., 2003), however a severely reduced ADAMTS13 level (< 5%) or the presence of an inhibitor or IgG antibody confirms the diagnosis (Scully et al., 2012).

Renal disease in TTP is due to thrombotic microangiopathy within the kidney and is common in pregnancy-associated TTP. Thirty to 80% of pregnant women with TTP will demonstrate renal dysfunction which is a higher rate than in TTP outside of pregnancy (Ganesan and Maynard, 2011). Treatment is with fresh frozen plasma infusion and/or plasma exchange, which will replace the deficiency of normal anticoagulant factors and/or neutralize circulating antibodies against them. Plasma exchange has improved maternal mortality from > 50% to < 10% (Martin et al., 2008). Fetal outcome, however, remains poor with a perinatal mortality rate of 30–80% attributed to microangiopathy of placental arterioles (Gammill, and Jeyabalan, 2005). Reports of long-term renal outcome are variable. The literature describes renal recovery as 'typical' in some cohorts (Ganesan, and Maynard, 2011).

In patients with a known history of TTP who subsequently become pregnant, serial monitoring of ADAMTS13 levels is advised where a quantitative deficiency is measurable, with prophylactic plasma exchange instituted to prevent disease flare.

Complement dysregulatory haemolytic uraemic syndrome in pregnancy

The complement system forms part of the innate immune system. The alternative component of the complement pathway does not rely on pathogen-binding antibodies but is activated spontaneously. Therefore, it is tightly regulated through the inhibition of alternative C3 convertase by factors including factor H, factor I, membrane cofactor protein (MCP), and delay-accelerating factor (DAF). Lack of control leads to pathological overactivation of alternative C3 convertase and complement-induced endothelial damage. Anti-factor H antibodies and inactivating mutations in factor H, factor I, and MCP are all risk factors for the development HUS. Patients with microangiopathy in association with complement dysregulation have significant renal disease and 76% progress to end-stage renal failure (Fakhouri et al., 2010).

In the same way that pregnancy is associated with development and/or relapse of ADAMTS13-deficient TTP, it can also trigger complement dysregulation-associated HUS. In addition, complement dysfunction is also described in HELLP (Fakhouri et al., 2008) which, as discussed, can be difficult to distinguish from isolated microangiopathy (see 'HELLP').

Pregnancy-associated HUS accounts for up 21% of non-diarrhoea-associated HUS in women. Eighty-six per cent of this population have a detectable complement gene mutation (Fakhouri et al., 2010). In contrast to TTP, most cases (> 75%) of pregnancy-associated HUS occur in the post-partum period. It is theorized that placental expression of complement regulatory proteins is protective in pregnancy and when this control is lost at delivery HUS can present (Fakhouri et al., 2010).

As for TTP, treatment of HUS includes plasma infusion and exchange. In addition, eculizumab is now licensed for the treatment of non-diarrhoea-associated HUS. Eculizumab inhibits activation of the alternative complement pathway in HUS via anti-C5 blocking antibody. Small prospective studies show an improvement in GFR including dialysis-requiring patients becoming independent of renal replacement for the duration of eculizumab treatment (European Medicines Agency, 2009). Data on eculizumab are limited in pregnancy but use at a lower dose in paroxysmal nocturnal haemoglobinuria is reported (Kelly et al., 2010; Marasca, 2010). Use in pregnancy of drugs in the same 'biological agent' class has not been associated with malformation. Placental transfer does, however, occur and the long half-life of these drugs means that live vaccine in the neonate should be avoided when administration occurs in the third trimester.

Pre-pregnancy counselling of women with known complement dysregulation is difficult as there is incomplete penetrance at a molecular level and pregnancy may, or may not, be a sufficient trigger for clinical disease. A 20% risk of pregnancy-associated disease is quoted (Fakhouri et al., 2010).

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a mitochondrial hepatopathy characterized by hepatic microvesicular steatosis in late pregnancy. It is a rare obstetric emergency with 5 cases per 100,000 maternities in the United Kingdom (Knight et al., 2008). Fulminant liver failure can result.

The disorder has been linked to fetal homozygosity for disorders of beta-fatty acid oxidation in mitochondria. This leads to an excessive, fatty acid load in the mother, who is an obligate heterozygote for the same mutation. Hepatotoxicity and impaired liver function result (Treem et al., 1994). Increased arachidonic acid and oxidative stress in maternal serum due to placental mitochondrial dysfunction is also implicated as a cause of hepatocyte damage.

Diagnosis of AFLP is made using the Swansea criteria which require a combination of six clinical features of AFLP in the absence of another possible cause (Ch'Ng et al., 2002) (see Table 296.3).

Markers of disease severity relate to impaired intrinsic liver function and include the development of encephalopathy, recalcitrant hypoglycaemia or coagulopathy, lactic acidosis, and hyperbilirubinaemia, rather than the level of transaminases. Liaison with a liver unit is advisable in severe cases.

Table 296.3 Diagnostic criteria for acute fatty liver of pregnancy

The presence of six or more of the following features, in the absence of another possible cause, may indicate acute fatty liver of pregnancy

Clinical	Blood tests	Other
Vomiting	Elevated bilirubin	Ascites/bright liver on ultrasound
Abdominal pain	Hypoglycaemia	Microvesicular steatosis on liver biopsy
Polydipsia and/or polyuria	Elevated urate	
Encephalopathy	Leucocytosis	
	Elevated transaminases	
	Elevated ammonia	
	Renal impairment	
	Coagulopathy	

Adapted from Ch'ng et al. (2002).

The main differential diagnosis of AFLP is HELLP with low platelets, AKI and deranged liver function being part of the clinical picture of both conditions. However, low serum glucose and/or raised serum ammonia are more suggestive of AFLP. Prodromal vomiting is also more likely in AFLP, in contrast to epigastric pain which is common in HELLP. Clotting may not be a useful distinguishing feature as prothrombin time will be prolonged with impaired synthetic liver function in AFLP, and disseminated intravascular coagulation complicates one-fifth of HELLP cases (Sibai et al., 1993). Polyuria and polydipsia are recognized symptoms of AFLP. They occur because hepatic metabolism of placental vasopressinase is impaired, leading to inappropriate clearance of antidiuretic hormone. Both subclinical and overt diabetes insipidus can develop in AFLP (Kennedy et al., 1994).

AKI is a common complication of AFLP occurring in 20–100% of patients (Ganesan and Maynard, 2011). Data from a UK series of 57 patients with AFLP gives a 14% prevalence of renal failure with 3.5% requiring renal replacement (Knight et al., 2008). The underlying renal pathology in AFLP varies and includes acute tubular necrosis and the endotheliosis of coexisting pre-eclampsia. Histological examination of the kidney reveals tubular free fatty acid deposition which links directly with current theories of liver pathogenesis (Slater and Hague, 1984).

Treatment requires early diagnosis, supportive care, and prompt delivery. However, morbidity is significant with 65% of cases of AFLP in the United Kingdom requiring intensive care level support and 7% needing artificial ventilation. The hepatic insult can be severe enough to require liver transplantation. Maternal mortality is 1.8% in the United Kingdom and fetal mortality is 10 times higher than the national rate (Knight et al., 2008). However, in most women there is complete liver and renal recovery after delivery (Machado et al., 2012).

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CHAPTER 297

Acute kidney injury in pregnancy

Kate Wiles and Catherine Nelson-Piercy

Epidemiology of acute kidney injury in pregnancy

The incidence of acute kidney injury (AKI) in pregnancy varies depending upon the socioeconomic status of the population studied. AKI has become rare in developed countries and is estimated to occur in 1 per 15,000–20,000 pregnancies (Stratta et al., 1996). The situation was very different 50 years ago, when pregnancy accounted for 30% or more of AKI, with peaks in early pregnancy related to septic abortion, and late pregnancy related to pre-eclampsia (Turner, 2012). However, in developing nations, obstetric AKI remains a significant problem, with prevalence 10 times greater (Abdulkareem, 2012) and constituting 25% of referrals for renal replacement therapy (Goplani et al., 2008). The liberalization of abortion laws, a reduction in septic abortion, and improved prenatal care are significant factors in reducing the prevalence of AKI in pregnancy.

The maternal mortality from pregnancy-related AKI, although rare in the developed world, is estimated to be up to 20% in developing countries (Prakash et al., 2010). AKI is associated with an increased mortality regardless of the underlying aetiology of the nephrological insult (Murugan and Kellum, 2011). Therefore when AKI develops in pregnancy, it is a serious complication.

Definitions of acute kidney injury: difficulties in pregnancy

Consensus definitions of AKI standardize diagnosis and facilitate a gradation of the severity of AKI. They are based upon changes in plasma creatinine measurement or surrogate estimated glomerular filtration rate, and urine output volumes. Such definitions are not validated for use in the pregnant population. The physiological changes in pregnancy include an increase in renal blood flow, an expansion in plasma volume with consequent haemodilution, and a rise in glomerular filtration rate across the first and second trimesters of pregnancy. The resultant changes to plasma creatinine and urine volume mean that alterations in these parameters cannot be interpreted in pregnancy in the same way as in the non-pregnant state.

It is important to recognize that the normal range for creatinine is lower in the pregnant patient. The physiological changes of pregnancy mean that serum creatinine falls by an average of 0.4 mg/dL (35 μmol/L) in pregnancy (Fischer, 2007), leading to a normal average creatinine value in pregnancy of 0.6 mg/dL (53 μmol/L) (August, 2013). (see Chapter 295). It must therefore be remembered that a 'normal' laboratory value for creatinine may be masking functional renal impairment. A creatinine level of > 90 μmol/L can, however, be interpreted as indicative of kidney injury in pregnancy (Girling, 2000). Urine output parameters are also difficult to interpret in pregnancy. Oliguria is very common in both intra- and post-partum periods, especially in the context of pre-eclampsia (see Chapter 296).

Causes of acute kidney injury in pregnancy

Causes of AKI in pregnancy are the same as those outside of pregnancy (see Chapter 220) with the addition of pregnancy-related disease. AKI is not common in pre-eclampsia but pre-eclampsia itself is prevalent and therefore an understanding of the diagnosis and management of pre-eclampsia is important for a nephrologist. Mostly AKI resolves with conservative management provided other insults such as haemorrhage, obstruction from the gravid uterus, non-steroidal anti-inflammatory drugs (NSAIDs), and infection are avoided, removed, or treated. An understanding of the post-partum disease course, timescale, and rationalization of treatment is particularly important, as that is when referral to medical and nephrology services often occurs.

HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome needs to be distinguished from the thrombotic microangiopathies, thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS). Pregnancy is a trigger for both TTP and HUS and distinction from HELLP is pertinent as the required treatment is very different.

Acute fatty liver of pregnancy (AFLP) is rare but AKI is a frequent complication of this liver disease. The potential severity of AFLP needs to be recognized and supportive care instituted rapidly to facilitate post-partum hepatic and renal recovery.

Urinary tract infection (UTI) is common in pregnancy and managed more aggressively due to its association with worsened pregnancy outcome.

Obstruction to the renal tract in pregnancy can be physiological. An appreciation of the clinical and radiological picture of physiological dilatation of the urinary tract in pregnancy is needed to prevent inappropriate investigation of, and intervention to, the pregnant renal tract.

The aetiology of AKI in the pregnant patient is the same as in the non-pregnant patient with the additional consideration of specific pregnancy-related conditions. In the pregnant patient, it is pertinent to rule out obstructive causes of AKI related to the uterus. The pregnancy related causes of AKI are listed in Table 297.1.

Pre-eclampsia and related disorders

These conditions occur after 20 weeks of gestation. They are discussed in detail in Chapter 296.

Table 297.1 Causes of AKI in pregnancy

Pre renal	Renal	Post renal
Hyperemesis gravidarum	Pre-eclampsia	Gravid uterus
Post-partum haemorrhage	HELLP	Papillary necrosis
Placental abruption	Acute fatty liver of pregnancy	Urinary retention
Sepsis	Microangiopathic haemolytic anaemia (TTP/HUS)	Damaged ureters
Heart failure	Acute tubular necrosis	Pelvic haematoma
	Interstitial nephritis	
	Glomerulonephritis	

HELLP = haemolysis elevated liver enzymes and low platelet count; HUS = haemolytic uraemic syndrome; TTP = thrombotic thrombocytopenic purpura.

Adapted from Nelson-Piercy (2010).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is primarily a disease of young women. It therefore has the potential to present for the first time in pregnancy with AKI. The potentially difficult antenatal diagnosis of a lupus flare, the management of lupus in pregnancy, and the indications for renal biopsy are considered in Chapter 298.

Urinary tract infection

UTI can be divided into asymptomatic bacteriuria and symptomatic infection. Asymptomatic bacteriuria is the presence of a single species of bacteria at a concentration > 100,000 per mL of urine in the absence of signs or symptoms of UTI. Symptomatic infection can be divided into infection of the lower urinary tract and infection of the upper urinary tract: cystitis and pyelonephritis respectively. Physiological changes to the urinary tract in pregnancy increase the risk of bacterial colonization, including increased bladder volume, decreased detrusor muscle tone, progesterone-driven ureteric dilatation, and glycosuria. However, increased frequency of micturition, nocturia, and urgency are commonly described by pregnant women making the diagnosis of UTI difficult on symptomatology alone.

Any infection of the urinary tract in pregnancy is associated with an increased risk of adverse outcome for both mother and child. Pyelonephritis represents the most serious urinary tract infection which if untreated leads to pyonephrosis, abscess formation, septicaemia, and organ failure. Antepartum pyelonephritis is associated with adverse perinatal outcomes and is an independent risk factor for preterm delivery (Farkash et al., 2012).

Bacteriuria is detected in 2–9% of pregnant women in the first trimester and symptomatic infection occurs in 17–20% of pregnancies (National Institute for Health and Care Excellence (NICE), 2014). This may be higher in pregnant women with diabetes or in women who are immunosuppressed. There is a 0.07% incidence of pyelonephritis in pregnancy (Farkash et al., 2012) with a high (23%) risk of recurrence in the same pregnancy (Gilstrap et al., 1981).

Screening and effective treatment of asymptomatic bacteriuria in pregnancy reduces the risk of cystitis and pyelonephritis by 70% (Pedler and Orr, 2000). The number of pregnant women with asymptomatic bacteriuria that are needed to treat to prevent a single case of pyelonephritis in pregnancy is seven. Evidence for an effect on birth weight and prematurity is inconsistent (Smaill and Vazquez, 2009).

Dipstick testing of urine to diagnose infection has a sensitivity as low as 53–60% and wide variation in specificity (49–100%) (Mignini et al., 2009; NICE, 2014). Screening for asymptomatic bacteriuria is therefore performed by urine culture in early pregnancy.

Amoxicillin is the treatment of choice with widely documented safe use in pregnancy and a licence which includes antenatal use. However, amoxicillin resistance is common and susceptibility of the organism must be confirmed. Nitrofurantoin is the preferred alternative with a good safety profile in human pregnancy. Trimethoprim is avoided due to concerns regarding exacerbation of folate deficiency. In the UK, where folate status is not routinely checked, trimethoprim is avoided in the first trimester because of the theoretical concern of increasing the risk of neural tube defects in the fetus. If trimethoprim is used in the first trimester it should be prescribed with high-dose (5 mg) folic acid but remains contraindicated in those with known folate deficiency, women taking folate antagonists, and those treated with trimethoprim within the last year (UKTIS, 2013; NICE, 2014). Cephalexin is safe but should not be used first line due to its broad spectrum effects including the risk of both *C. difficile* and antibiotic resistance. Ciprofloxacin is avoided because it impairs cartilage development in studies of animal pregnancy.

Pyelonephritis in pregnancy is managed as an inpatient due to the risks of maternal deterioration and preterm labour (Ramakrishnan and Scheid, 2005). Clinical assessment at 24 hours is important even if urine culture results are still outstanding. Co-amoxiclav and gentamicin can both be safely used in pregnancy. Nitrofurantoin is not used for upper urinary tract infection, as effective concentrations will not be achieved in the blood.

The optimum duration of treatment for UTI on pregnancy remains unknown. A systematic review of single-dose treatment versus treatment for 4–7 days for asymptomatic infection found that single-dose antibiotic treatment was less likely to produce a cure (Widner et al., 2011). For symptomatic bacteriuria the heterogenous nature of studies means that there is no clear evidence for a specific dosage regimen. Given the increased risk associated with any bacteriuria in pregnancy, 7 days of treatment remains the recommendation for both asymptomatic and symptomatic infection (NICE, 2014). Longer courses may be needed for pyelonephritis. Urine culture should be repeated 7 days after completion of the antibiotic course and at subsequent antenatal reviews during the remainder of the pregnancy.

It is important to exclude renal tract anomaly with persistent, recurrent, or clinically significant infection. Recurrent urinary tract infection in pregnancy carries the same risks as primary infection and low-dose antibiotic prophylaxis may be required throughout pregnancy (Romero et al., 1989).

Women with vesicoureteric reflux have a higher incidence of UTI in pregnancy but this is not associated with excess maternal or fetal morbidity provided there is no renal scarring. It is the existence of renal scarring, rather than the presence or absence of reflux, which increases the risk of hypertension and pre-eclampsia in pregnancy (Hollowell, 2008).

Obstructive nephropathy

AKI secondary to an obstructive nephropathy is rare although patients with a single kidney, multiple pregnancy, or polyhydramnios have an increased risk (Jena and Mitch, 1996). Bladder neuropathy in those with transplant-treated diabetic renal disease needs to be remembered.

Evaluation of renal tract obstruction is made difficult in pregnancy as the pelvicalyceal system and ureter dilate from as early as 6–10 weeks' gestation, particularly on the right. Such anatomical changes to the renal tract can become exaggerated with extensive ureteral and renal pelvis dilation and associated cortical thinning can sometimes be seen. Despite a dramatic radiological appearance, this dilatation may not however be clinically significant. Rarely, the 'overdistension syndrome' results in renal tract rupture causing loin pain and AKI and is a potential precipitant of preterm labour (Khanna and Nguyen, 2001).

Ultrasound is the first-line investigation and certain radiological features may be useful in the distinction between physiological and pathological renal obstruction in pregnancy. Firstly, a dilated ureter distal to the pelvic brim suggests a cause other than pregnancy for the dilatation. Uterine obstruction will only dilate the ureter above the pelvis with normal ureteric calibre at the insertion into the bladder. Secondly, resistive indices are normal in physiological hydronephrosis and an increased index, particularly where there is an inter-renal difference, is suggestive of an alternative pathology. Finally, an absence of ureteric jets can suggest obstruction, but the pregnant patient should be examined both supine and in the contralateral decubitus position in order to negate the effect of the gravid uterus before conclusions can be made (Webb, 2000). If positioning the pregnant woman on all fours for ultrasound examination results in decompression of the renal pelvis to < 1 cm, then physiological dilatation of pregnancy is confirmed (Olsburgh, 2008).

Women with urinary tract obstruction in pregnancy are managed with delivery if near term or percutaneous nephrostomy. Indications for intervention are when the obstruction is accompanied by pain, infection, or AKI. With technical expertise, it may be possible to insert a nephrostomy using ultrasound guidance, rather than with the use of fluoroscopy, thereby reducing fetal radiation exposure. The decision to proceed to stent insertion depends upon both the cause of obstruction and the gestation of pregnancy. If it is possible that the obstruction is related to the pregnant state and a nephrostomy can be managed for the remainder of the pregnancy, then fluoroscopic imaging can be delayed until the postnatal period to confirm post-partum resolution and potentially avoid even temporizing stent placement. Although retrograde stenting can be performed under direct vision and without radiation, this can be technically difficult as a result of anatomical variance and compression by the gravid uterus. In addition, frequent stent replacement may be required depending on gestation and level of obstruction.

Acute kidney injury in pregnancy: principles of management

The management of AKI in the pregnant population includes treatment according to the underlying aetiology, in conjunction with optimization of haemodynamic and biochemical parameters. Specific aetiologies of AKI in pregnancy are considered below.

General supportive measures in the management of AKI apply to the pregnant population as in the non-pregnant population with intervention targeted at maintaining renal perfusion. Fluid requirements need to be assessed by careful clinical examination of the pregnant patient, remembering the physiological reductions in blood pressure and oncotic pressure that occur with pregnancy. Estimated blood loss at the time of delivery is documented for every parturient patient in the United Kingdom. It needs to be remembered, however, that visual assessments of blood loss can underestimate by up to 50% (Sloan et al., 2010) and that clinical assessment of the patient therefore supersedes visual impression and the apparent volume losses that are documented. Furthermore, women suffering post-partum haemorrhage are able to compensate for hypovolaemia and may only become hypotensive and collapse after massive blood loss. The significance of a tachycardia and track and trigger systems when performing observations in the post-partum woman cannot be over emphasized. Management of hyperkalaemia with intravenous calcium and insulin with glucose can, and should, be given if required in pregnancy.

Doses of antibiotics, anticoagulants, insulin, and opiates will need to be adjusted according to glomerular filtration rate. AKI can adversely affect renal erythropoietin response. With a higher baseline erythropoietin requirement in pregnancy, treatment with synthetic erythropoietin agents may need to be commenced or increased with AKI. Nephrotoxic drugs should be avoided including NSAIDs, which often form part of a standard post-partum analgesic protocol, especially for women who have had a caesarean section.

Fluid overload, acidosis, and hyperkalaemia refractory to medical treatment are indications for renal replacement in pregnancy as in the non-pregnant patient. The acid–base status of pregnancy is a compensated respiratory alkalosis, with a 4 mmol/L reduction in serum bicarbonate levels (Lindheimer, 2007). However, this does not affect the threshold of acidosis at which dialysis is considered. In addition, serum levels of urea require extra consideration in pregnancy due to their correlation with birth weight, gestational age, and pregnancy outcome (Asamiya et al., 2009). A blood urea of < 50 mg/dL (18 mmol/L) is recommended in pregnancy (Reddy and Holley, 2007). Renal replacement therapy for end-stage renal failure in pregnancy is considered in Chapter 295.

Kidney biopsy in pregnancy

Biopsy during pregnancy is rarely performed, and should only be considered if it influences subsequent management. Expert recommendation is that biopsy should be performed in the following circumstances (Lindheimer and Davison, 1987):

- Sudden deterioration in renal function without obvious cause
- Symptomatic nephrotic syndrome.

After 32 weeks' gestation, it may be preferable to deliver, and perform the procedure post partum (Brunskill, 2008). Pre-eclampsia is not an indication for renal biopsy. Early pregnancy biopsies may be performed in the supine position, whereas biopsies beyond 16–20 weeks' gestation may be more challenging and require the patient to be sitting.

Safety of renal biopsy in pregnancy has been controversial, with early reports suggesting that complications were high, for example, macroscopic haematuria in 16% of women (Schewitz et al.,

1965). Subsequently Packham and Fairley published a series of 111 biopsies, and reported only a 0.9% rate of macroscopic haematuria and concluded that biopsy was safe in pregnancy (Packham and Fairley, 1987). However, more conclusive evidence has come from a recent systematic review, which compared complications (major or minor bleeding, haematoma or loin pain) in 11 studies of women biopsied during pregnancy (243 biopsies) and post partum (1236 biopsies), and found that biopsies after delivery had a significantly lower rate of adverse events than biopsies during pregnancy (1% vs 7%) (Piccoli et al., 2013a). In antenatal biopsies, major bleeding occurred at a median of 25 weeks of gestation (range 23–26 weeks).

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CHAPTER 298

Specific renal conditions in pregnancy

Kate Bramham and Catherine Nelson-Piercy

Immunoglobulin A nephropathy

The most data for a glomerular disease is available for immunoglobulin A (IgA) nephropathy (see Chapters 65–69), which is common in women of child-bearing age. It is usually associated with good pregnancy outcomes and there is no strong evidence that its outcomes are different from other renal conditions (Table 298.1). No risk of progression of disease secondary to pregnancy was identified in a multicentre study of women with pre-pregnancy creatinine < 110 μmol/L, compared to non-pregnant controls at 10 years of follow-up (Limardo et al., 2010).

Women with pre-pregnancy creatinine >120 μmol/L, estimated glomerular filtration rate (GFR) < 50 mL/min/1.73 m^2, heavy proteinuria, or severe histological lesions on renal biopsy are most likely to have pregnancies complicated by pre-eclampsia, fetal growth restriction, preterm labour, and a pregnancy-associated decline in renal function (Jungers et al., 1987; Abe, 1991; Jungers et al., 1991). A recent study also confirmed that in women with IgA nephropathy, pre-pregnancy proteinuria was associated with a more rapid deterioration in renal function postpartum. The authors concluded that pre-pregnancy treatment of proteinuria may prevent the impact of pregnancy on renal disease (Oh et al., 2011).

Lupus nephritis

Systemic lupus erythematosus (SLE) (see Chapters 161–163) is an autoimmune disease which affects women of child-bearing age, and 20–49% of women have renal involvement (Dooley, 2010) (Table 298.1). It is estimated that in a population of 1 million, there will be a birth rate of 5–10 pregnancies/year complicated by SLE (Venning and Patel, 2008).

Fertility in SLE

In women with SLE and preserved renal function, fertility is normal (Fraga et al., 1974; Grigor et al., 1977), even in those with active disease (Ramsey-Goldman et al., 1993); however, those with more significant renal impairment are likely to have reduced ovulation and oligo/amenorrhea (Hou, 1999). Premature menopause, however, is a common complication in women with SLE (Bove, 2013). Prediction of early menopause may be anticipated by monitoring of follicle stimulating hormone and luteinizing hormone.

Treatment for SLE may include cyclophosphamide, which has been shown to result in ovarian failure (Warne et al., 1973). However, total dose of cyclophosphamide and age > 32 years are the most important predictors of drug-associated anovulation (Boumpas et al., 1993; Ioannidis et al., 2002; Katsifis and Tzioufas, 2004; Park et al., 2004). Gonadotropin-releasing hormone antagonists are occasionally used pre-emptively for preservation of ovarian function in women undergoing chemotherapy with cyclophosphamide (Clowse et al., 2009).

Pregnancy outcomes in SLE

Women with lupus nephritis have more complex pregnancies than those matched for renal function (Stratta et al., 2006), and even those with treated quiescent disease and normal renal function have worse pregnancy outcomes than women with SLE without renal involvement (Bramham et al., 2011). Specific risk factors for other pregnancy complications are not consistently identified in all studies but include black ethnicity, low complement at conception, pre-existing hypertension, proteinuria, positive antiphospholipid antibodies, and severity of renal impairment (Moroni et al., 2002; Chakravarty et al., 2005; Smyth et al., 2010). Class of lupus nephritis does not appear to be a risk factor for complications (Smyth et al., 2010). Active disease at conception is also associated with worse pregnancy outcomes (Huong et al., 2001; Wagner et al., 2009), and it is therefore recommended that women conceive after their disease has been quiescent for 6 months.

Pre-eclampsia occurs in 25–35% of pregnancies, and is more common in women with active lupus nephritis compared to women with SLE without nephritis (Wagner et al., 2009), but is not more likely in women with inactive renal disease (Wagner et al., 2009; Bramham et al., 2011). Women with lupus nephritis are more likely to develop pre-eclampsia than women with chronic kidney disease (CKD) of another aetiology, matched for level of renal function (Stratta et al., 2006).

Differentiating between active lupus nephritis and pre-eclampsia can be challenging, as there are many similar features between the two conditions. Table 298.2 describes distinguishing features. Concentrations of anti-angiogenic markers (s-Flt) have been shown to be useful in discriminating between disease flare and superimposed pre-eclampsia in women with SLE (Qazi et al., 2008; Rhee et al., 2011).

Preterm delivery is common in SLE pregnancies (30-58%), particularly in women with nephritis (Moroni et al., 2002; Cavallasca et al., 2008; Imbasciati et al., 2009; Bramham et al., 2011), and may be both spontaneous and iatrogenic (Bramham et al., 2011) and is more frequent in women with active disease (Smyth et al., 2010).

Table 298.1 Problems according to CKD aetiology

Renal disease	Potential problems in pregnancy
Reflux nephropathy	Increased risk of pre-eclampsia/fetal growth restriction Increased risk of urinary tract infection Increased risk of progression of renal disease Possible inheritance by offspring-infant screening recommended
IgA nephropathy	Worse outcomes if heavy proteinuria or severe lesions on biopsy
Diabetic nephropathy	Nephrotic range proteinuria. Continue ACEI/ARB until conception if possible
ADPKD	Risk of cyst infection or haemorrhage Risk of liver cyst growth 1:2 chance of offspring affected
Lupus nephritis	Worse pregnancy outcomes for level of renal function Risk of flare during pregnancy Risk of congenital lupus syndromes
Renal transplant	Worse pregnancy outcomes for level of renal function Second transplant worse outcomes than first Calcineurin inhibitor requirements increase

ACEI = angiotensinogen converting enzyme inhibitor; ADPKD = autosomal dominant polycystic kidney disease; ARB = angiotensin II receptor blocker.

The incidence of fetal growth restriction is also elevated in pregnancies affected by lupus nephritis, occurring in 13% of infants (Smyth et al., 2010).

Renal outcomes

In a review of 17 studies of pregnancies affected by SLE, 10% of women with lupus nephritis developed acute renal failure, 3% of women with lupus nephritis had a permanent decline in renal function without requiring dialysis, and 6% progressed to end-stage renal failure or death (Bramham et al., 2011), but a more recent study of 81 pregnant women with lupus nephritis in pregnancy, found only three women (2%) suffered a progressive deterioration in GFR and only one needed renal replacement therapy (Imbasciati et al., 2009). Furthermore, another study comparing progression of renal function after pregnancy in women with, and without nephritis, found no difference in change in GFR at 3 years (Bramham et al., 2011).

Effect of pregnancy on SLE activity

Disease activity may be increased by pregnancy (Ruiz-Irastorza et al., 1996; Cervera et al., 2002; Cortes-Hernandez et al., 2002; Chakravarty et al., 2005; Clowse et al., 2005; Clowse et al., 2008), although there are several conflicting reports describing no effect of pregnancy on SLE activity (Moroni et al., 2002; Tandon et al., 2004; Gladman et al., 2010). A meta-analysis of 2751 pregnancies in women with lupus nephritis (1984–2009), reported a pooled incidence of renal disease activation and extra renal lupus flare in 16% and 26% of pregnancies respectively (Smyth et al., 2010). Lupus nephritis may also present *de novo* in previously unaffected individuals. Normal physiological changes in pregnancy may be difficult to differentiate from feature of active lupus (Table 298.2).

Table 298.2 Expected changes in normal pregnancy and pre-eclampsia compared with systemic lupus erythematosus disease flare

Features	Lupus	Pregnancy
General	Fatigue and malaise	Fatigue
Hair	Loss	Loss or gain
Skin	Malar rash	Melasma/chloasma Facial flushing
Joint pain and swelling	Inflammatory synovitis	Mechanical arthralgia Bland knee effusion Pelvic girdle pain
Anaemia	Haemolytic anaemia Anaemia of chronic disease Erythropoietin-deficiency anaemia	Haemodilution Iron-deficiency anaemia
Low platelets	Immune thrombocytopenia	Gestational thrombocytopenia Pre-eclampsia HELLP syndrome
Abnormal liver function tests	Lupus hepatitis (usually transaminases)	Pre-eclampsia HELLP syndrome Obstetric cholestasis
ESR	Elevated	Elevated
Features	**Lupus nephritis**	**Pre-eclampsia**
Haematuria/red cell casts	Present	Absent
Anti-DNA antibodies	Raised	Normal
Complement C3 and C4	Low	Normal or raised
Liver function tests	Normal	Normal or raised
Hypertension	Present	Present and rising
Proteinuria	Present	Present
Oedema	Present	Present
Low platelets	Present	Present
Rising creatinine	Present	Present

Frequently women that have previously experienced a lupus flare, can reliably determine when their disease is active. Post partum is also a period associated with increased disease activity, particularly renal involvement (Tandon et al., 2004) and women should be offered a review within 6 weeks after delivery.

Biopsy during pregnancy may be required in order to determine management; however, a biopsy should not be performed if the suspected diagnosis is pre-eclampsia. See Chapter 297 for details of biopsies in pregnancy.

Immunosuppressive agents in pregnancy

Cessation of immunosuppressive treatment during pregnancy is associated with disease flare (Clowse et al., 2006). In brief, prednisolone, azathioprine, tacrolimus, and hydroxychloroquine are considered to be relatively safe in pregnancy, whereas

mycophenolate mofetil and cyclophosphamide are teratogenic (Ostensen et al., 2008). There are increasing numbers of reports of the use of rituximab in pregnancy, which has not been associated with congenital abnormalities (Chakravarty et al., 2011), but use in the third trimester suppresses neonatal B-cell development and should be avoided (Klinik et al., 2008).

Congenital lupus syndromes

Neonates of mothers with SLE may be affected by congenital lupus syndromes which are mediated by placental transfer of autoantibody, therefore all women with SLE should be assessed for the presence of anti-Ro or La antibody.

Congenital heart block

Maternal anti-Ro antibody transfer may result in fibrosis of the fetal cardiac conducting system, and congenital heart block. The risk of congenital heart block is 2%, but if a previous child has been affected, the risk increases to 15–20% and up to 50% if two children have been affected (Friedman et al., 2007). Identification is possible with fetal cardiac scans which should be performed between 18 and 25 weeks' gestation.

Hydroxychloroquine may reduce the risk of congenital heart block in offspring of mothers with previously affected infants (Izmirly et al., 2012), whereas high-dose steroids, plasma exchange, and intravenous immunoglobulin are not effective (Friedman et al., 2007; Pisoni et al., 2010). Fetal mortality may be up to 30%, and a neonatologist should be present at the delivery of an affected infant.

Neonatal cutaneous lupus

Neonatal cutaneous lupus is a benign, non-scarring, photosensitive rash, affecting approximately 5% of infants of women with anti-Ro/La antibody (Cimaz et al., 2003) (Fig. 298.1). It spontaneously resolves after 6 months, when maternal antibody levels fall. Residual hypopigmentation or telangiectasia may persist for up to 2 years, but scarring is unusual and parents can be reassured. No specific treatment is required, except topical steroids in severe cases. One small study has suggested that intravenous immunoglobulin with high anti-idiotypic antibody (anti-id) activity may prevent neonatal lupus in women with previously affected offspring (Routsias et al., 2011), but further work is required.

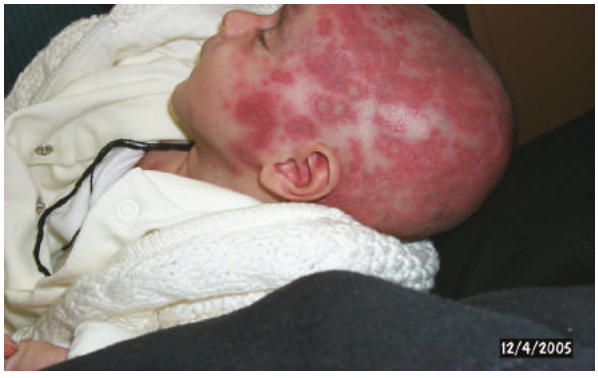

Fig. 298.1 Neonatal cutaneous lupus.

Autosomal dominant polycystic kidney disease

Many women of child-bearing age with autosomal dominant polycystic kidney disease (ADPKD; see Chapters 277–280) have normal renal function, or only mild renal impairment. Their pregnancies tend to be successful, but with a higher risk of pre-eclampsia and early delivery compared to the general population, particularly in women with secondary hypertension, or more severe renal disease (Chapman et al., 1994). The presence of enlarged cystic kidneys does not directly affect fetal growth, but urinary tract and cyst infection are more common in pregnancy, and should be treated promptly and aggressively (Chapman et al., 1994). Renal cyst growth is not enhanced by pregnancy but one report suggests that liver cysts in women with ADPKD with more than one pregnancy may be more likely to progress (Gevers and Drenth, 2013).

There is a 50% chance of ADPKD being inherited by the offspring, and it is usually not identifiable on fetal scanning. Some couples may wish to be referred for genetic counselling, and options of pre-implantation and fetal diagnostic testing discussed.

Diabetic nephropathy

Women with type 1 or type 2 diabetes without renal involvement have complicated pregnancies. Outcomes are much worse than expected for women with diabetic nephropathy (see Chapter 149) compared to women with other causes of CKD with the same level of renal function (Bramham and Rajasingham, 2012).

A systematic review reported rates of pre-eclampsia for women with type 1 diabetes without nephropathy to range from 9% to 17%, but for those with diabetic nephropathy rates were considerably higher (35–66%) (Sibai, 2000). Women with diabetes are also more likely to experience early fetal losses, and have a twofold increase in rates of congenital malformation (4%), with a threefold increase in cardiac and neural tube defects compared with the general population (Confidential Enquiry into Maternal and Child Health, 2007), and therefore should take a higher dose folic acid (5 mg daily) prior to conception.

Risk factors for worse fetal outcome include level of proteinuria, including microalbuminuria, prior to pregnancy (Ekbom et al., 2001), poor glycaemic control and poorly controlled blood pressure (Reece et al., 1998). A small study with intensive use of angiotensinogen converting enzyme inhibitor (ACEIs) for 6 months prior to conception, together with improved glycaemic management in women with diabetic nephropathy showed a reduction in proteinuria, which was maintained during and after pregnancy, compared to women with no treatment (Hod et al., 1995). ACEIs and/or angiotensin II receptor antagonists ideally should be continued until conception in women with significant proteinuria pre-pregnancy (Table 298.1).

Delivery before 34 weeks occurs in 16–45% of pregnancies in women with type 1 diabetes (Gordon et al., 1996; Mackie et al., 1996; Ekbom et al., 2001). Polyhydramnios secondary to hyperglycaemia, which may be exacerbated by maternal high urea concentrations, is associated with spontaneous preterm delivery; however, the majority of preterm deliveries are iatrogenic (Sibai et al., 2000). In view of the increased risk of unexplained intrauterine death, NICE guidelines recommend that women with diabetes should be induced after 38 weeks' gestation (NICE, 2008).

Although women with diabetes frequently have macrosomic infants, the presence of renal impairment appears to outweigh the effects of hyperglycaemia and frequently (31–64%) infants of mothers with diabetic nephropathy are small for gestational age (Biesenbach et al., 1999; Ekbom et al., 2001).

Renal outcomes

Proteinuria frequently increases dramatically during pregnancy in women with diabetic nephropathy, and may result in hypoalbuminaemia and severe oedema which may require cautious use of diuretics for symptomatic relief. In a review of nine studies of pregnancies in women with diabetic nephropathy, proteinuria increased from 1 to 3 g/24 hours at baseline to 4–8 g/24 hours in the third trimester (Star and Carpenter, 1998). However, proteinuria usually returns to baseline levels post delivery, even in women with nephrotic range excretion (Gordon et al., 1996).

A systematic review of several small single-centre studies of pregnancies in women with diabetic nephropathy suggest that many women experience a temporary decline in renal function during pregnancy, but the rate of progression of renal disease to end stage is unaffected by gestation (Reece et al., 1998). Prospective intervention studies of glycaemic control also have observed no influence on the development of nephropathy, or progression of pre-existing disease associated with pregnancy (Diabetes Control and Complications Trial Research Group 1993; Verier-Mine et al., 2005), nor has the number of pregnancies been shown to affect risk of developing or progression of nephropathy in individuals with diabetes (Miodovnik et al., 1996).

Comorbidities in women with diabetes are common. Rossing et al. reported that 28 out of 91 women (35%) with type 1 diabetes and nephropathy had died during the 16-year post-partum follow-up period (Rossing et al., 2002), and in another study 8 out of 14 women (57%) had significant atherosclerotic disease (Bagg et al., 2003).

Reflux nephropathy

Reflux nephropathy (see Chapter 326) is a common cause of renal disease in women of child-bearing age, and may frequently be identified for the first time in pregnancy (Jungers, 1994). It is associated with worse pregnancy outcomes, than for women with other causes of CKD with similar severity of renal impairment (Imbasciati and Ponticelli, 1991; Jungers and Chauveau, 1997) (Table 298.1). In a series from Australia including 137 women and 345 pregnancies, overall rates of fetal loss were high (18% if pre-pregnancy serum creatinine (Cr) > 110 μmol/L, and 8% if Cr < 110 μmol/L) (el-Khatib et al., 1994). Similarly a French series (1996) of 375 pregnancies in 158 women reported rates of fetal loss of 8% and 37% in women with Cr < and > 110 μmol/L respectively (Jungers et al., 1996). Pre-existing hypertension was identified to be a risk factor for fetal loss. More recent pregnancy outcomes in women with reflux nephropathy have not been reported but are likely to be improved due to advances in neonatal care.

Superimposed pre-eclampsia was reported to occur in 75% of women with reflux nephropathy (Jungers et al., 1996), and is more common in women with bilateral scarring (el-Khatib et al., 1994). Surgical correction of ureteric reflux has not been shown to be associated with better pregnancy outcomes, but both severity of renal impairment and the presence of hypertension are prognostic of adverse events (el-Khatib et al., 1994; Jungers et al., 1996).

Recurrent urinary tract infections in women with reflux nephropathy have been described in three studies to occur in 26%, 28%, and 65% of women (el-Khatib et al., 1994; Mansfield et al., 1995; Jungers et al., 1996), and in one study 6% of women developed pyelonephritis (el-Khatib et al., 1994). Women with uncorrected vesicoureteric reflux were twice as likely to develop infections as those with ureteric reimplantation (Jungers, 1994), and therefore some health professionals suggest that corrective surgery may be beneficial. At least 4–6-weekly screening for asymptomatic bacteriuria is recommended for all women with reflux nephropathy (Jungers et al., 1996). Following one infection in pregnancy, low-dose prophylactic antibiotics are recommended to reduce further infection. In one study, 4 out of 21 women (13%) had an irreversible decline in renal function (Jungers et al., 1996). It is unknown if this was related to recurrent infection.

Hereditary reflux nephropathy is common, and multiple candidate genes have been identified (Feather et al., 2000; Murawski and Gupta, 2006). Fetal abnormalities may be seen on antenatal ultrasound (Blumenthal, 2006) and the offspring should be referred to a paediatric urologist for screening after delivery.

Single kidneys, including live kidney donors

There are few reports of pregnancy in women with congenital absence of a kidney; however, it appears that despite pre-existing hypertrophy, pregnancy-associated changes still occur including increased renal blood flow and glomerular filtration (Davison, 1978). Due to the rise in live kidney donation, increasing numbers of pregnancies are occurring in women after kidney donation. One survey of live kidney donors described an increase in all pregnancy complications post donation (compared with pre-donation pregnancies), with a lower likelihood of delivery at term (73.7% vs 84.6%; $P = 0.0004$) and a higher likelihood of fetal loss (19.2% vs 11.3%; $P < 0.0001$). Post-donation pregnancies were also associated with a higher risk of gestational diabetes (2.7% vs 0.7%; $P = 0.0001$), gestational hypertension (5.7% vs 0.6%; $P < 0.0001$), proteinuria (4.3% vs 1.1%; $P < 0.0001$), and pre-eclampsia (5.5% vs 0.8%; $P < 0.0001$). At least some of these findings may be explained by increased surveillance/screening of pregnancies in women who have donated a kidney. Women were more likely to be older post donation (Ibrahim et al., 2009). However, a Norwegian population study, after adjustment for maternal age, found only an increased incidence of pre-eclampsia (2.6% vs 5.7%; $P = 0.021$) (Reisaeter et al., 2009). A retrospective cohort study of 131 pregnancies in 85 living kidney donors matched with 510 healthy non-donors from the general population found a significantly higher rate of both gestational hypertension and pre-eclampsia (11% versus 5%) in women who had donated a kidney (Garg et al., 2015).

Previous urological reconstruction

Despite correction of congenital urological problems, women with previous urinary tract surgery are at risk of obstructive complications during pregnancy (Mansfield et al., 1995). Explanations include the effects of progesterone on smooth muscle, and the combination of uterine pressure on subclinical narrowing of the

ureter (Olsburgh, 2008). Some experts suggest imaging prior to pregnancy, for example, mercaptoacetyltriglycine (MAG3) or cystoscopy and retrograde imaging, in order to identify any lesion which may benefit from intervention, although evidence is limited. A 12-week ultrasound may be a useful baseline investigation in order to track changes, but gestation-associated dilation should be anticipated.

Women with bowel segments as part of bladder reconstruction may have false positive urinary beta human chorionic gonadotropin (β-HCG) levels, and therefore a serum level should be checked to confirm pregnancy (Greenwell et al., 2003).

Urinary tract stasis is common in pregnancy, and this, in combination with abnormal urinary flow due to previous surgery, is likely to increase the risk of infection. In one series of 29 pregnancies in 20 women, over half developed urinary tract infections (Greenwell et al., 2003). A low threshold for antibiotic prophylaxis should be considered, particularly for women with bowel segment reconstruction. It is unusual for a vaginal delivery not to be recommended for physical reasons in women with previous urinary tract surgery, although in practice, the majority of women have caesarean sections (Greenwell et al., 2003).

Microscopic haematuria

Microscopic haematuria is a frequent finding in pregnancy. In one series of 902 women, it was reported to be present in 20% of women twice or more during pregnancy, but persisted in only half who attended follow-up post partum, and was not associated with an increase in risk of pre-eclampsia, gestational hypertension, or preterm delivery in multiparous women, but nulliparous women had an increased risk of pre-eclampsia (Brown et al., 2005). Urinary tract infections should be excluded and significant underlying renal disease explored by checking serum creatinine, proteinuria, and blood pressure. Particularly if any of these are abnormal, or the haematuria persists post partum, serum IgA levels should be measured as microscopic haematuria is a common feature of IgA nephropathy, and the woman should be referred for appropriate further investigation post partum.

Benign renal angiomyolipoma

Occasionally angiomyolipomas in the kidney may grow rapidly during pregnancy causing frank haematuria and severe loin pain, and are at risk of rupture. Treatment includes selective renal embolization or nephrectomy (Morales et al., 2005). It is recommended that lesions are embolized if identified before pregnancy if > 4 cm (Olsburgh, 2008). Tuberous sclerosis (see Chapter 330) is associated with multiple renal angiomyolipomata.

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CHAPTER 299

Pregnancy after renal transplantation

Kate Bramham and Catherine Nelson-Piercy

Introduction

The first pregnancy in a women with a renal transplant occurred in 1958 (Murray et al., 1963), and several thousand pregnancies have now been reported worldwide. Infertility is rapidly reversed with renal transplantation secondary to restoration of renal function (Davison and Bailey, 2003). Younger women with poor renal function are often recommended to delay conception until they have received a renal transplant, because both maternal and fetal outcomes are likely to be better than pregnancy with severe CKD. Approximately 2% of women of child-bearing age with transplants will become pregnant (McKay and Josephson, 2006) but a recent study of renal transplant recipients in the United Kingdom suggested that a third of pregnancies may be unplanned (Bramham et al., 2013).

Timing of conception

A meta-analysis of 50 studies exploring pregnancy outcomes in women with renal transplants did not identify an association between time from transplantation and conception and pregnancy outcomes (Deshpande et al., 2011). However, European Best Practice Guidelines for Renal Transplantation (2002) recommend that women wait for 12–24 months prior to conceiving in order to minimize the risk of graft rejection during pregnancy. More recently, the American Society of Transplantation guidelines recommended that pregnancy may be considered after 1 year in women who are at low risk of complications (McKay et al., 2005) on the basis of favourable outcomes 12 months after transplant (Fischer et al., 2005; Kim et al., 2008) Appropriate contraception is discussed in Chapter 293.

Medication

Tacrolimus, azathioprine, and prednisolone are most commonly used during pregnancy. Experience of rapamycin in pregnancy is limited, and therefore should be restricted to use in individuals who have unstable graft function on alternative treatment. It is recommended that women switch from teratogenic immunosuppression (usually mycophenolate mofetil to azathioprine) for 3 months in order to ensure washout of drug effects and graft stability before attempting to conceive.

Pregnancy outcomes

Several single centre studies have reported pregnancy outcomes in women with renal transplants, and a meta-analysis has provided pooled incidence for common adverse events in 50 studies (Deshpande et al., 2011). More recently a prospective study of 109 pregnancies in renal transplant recipients compared with healthy controls in the United Kingdom has provided more contemporaneous data (Bramham et al., 2013), and the two reports are summarized in Table 299.1.

Despite advances in nephrological, obstetric, and neonatal care, pregnancies in women with renal transplants are associated with more complications than the general population, possibly reflecting pre-existing endothelial damage of previous end stage renal disease, which is recognized to predispose to adverse pregnancy events. Both women and neonates frequently require high dependency care (20% and 38% respectively) (Bramham et al., 2013).

Women with second or more renal transplants have significantly worse pregnancy outcomes than women with first grafts (45% risk of unsuccessful pregnancy or preterm delivery before 32 weeks), and this should be considered in pre-pregnancy counselling for these women (Bramham et al., 2013).

Renal outcomes

Physiological adaptations to pregnancy seen in native kidneys also occur in renal transplants (Davison, 1985) and an increase in glomerular filtration rate is expected in women with normal and mild renal impairment. Up to 40% of women with renal transplants with no proteinuria prior to pregnancy develop it antenatally (Stratta et al., 2006), and up to 38% of women have a > 20% increase in creatinine from baseline at some point during their pregnancy (Bramham et al., 2013).

Causes for a decline in renal function during pregnancy in women with renal transplants are listed in Table 299.2. Hydronephrosis during pregnancy is common and therefore obstruction secondary to the gravid uterus may be difficult to identify. If it is suspected, it is recommended that women attempt to lie on the side opposite to their graft, and the kidney is rescanned after a few hours. Hydronephrosis secondary to uterine position should resolve but a nephrostomy may be required (Olsburgh, 2008).

Pregnancy effects on long-term graft outcome

There are no reports of increased rates of acute rejection postpartum, with the restoration of cellular immunity. Several single-centre studies have examined the impact of pregnancy on long-term renal function and most report no significant effects of pregnancy on

Table 299.1 Pregnancy outcomes in women with renal transplants: a meta-analysis and recent prospective cohort study (Deshpande et al., 2011; Bramham et al., 2012)

	Deshpande et al., (2011)[a]	Bramham et al., (2012)
Number of pregnancies	4002	101
Year of study (ies)	1963–2010	2007–9
Median time to conception post transplant (years)	3.2 (3.1–3.2)	5 (2–10, IQR)
Median maternal age (years)	29.0 (28.9–29.1)	32 (18–44, range)
Maternal pregnancy outcomes		
Pre-eclampsia/ superimposed pre-eclampsia	27.0% (25.2–28.9)	24%
Caesarean section	56.9% (54.9–58.9)	64%
Gestational diabetes	8.0% (6.7–9.4)	3%
Neonatal outcomes		
Live birth	73.5% (72.1–74.9)	91%
Median gestation at delivery (weeks)	35.6 (35.5–35.7)	36 (27–43, IQR)
Preterm delivery (< 37 weeks)	45.6% (43.7–47.5)	52%
Median birth weight (g)	2420 (2395–2445)	2510 (2005–3070 IQR)
Birth weight < 2500g	–	48%
Maternal renal outcomes		
Decline in renal function during pregnancy (> 20%)	–	38%
Acute rejection during pregnancy	4.2%	2%
Postpartum graft loss at 1 year	6%	–
Postpartum graft loss at 5 years	7%	–
Postpartum graft loss at 10 years	19%	–

IQR = interquartile range.

[a]Pooled incidence and 95% confidence intervals where available.

Reproduced from Bramham, K., Nelson-Piercy, C., Gao, H., *et al.* (2013). Pregnancy in renal transplant recipients: a UK national cohort study. *Clin J Am Soc Nephrol*, 8, 290–8.

graft function. (Crowe et al., 1999; Stratta et al., 2003; Keitel et al., 2004; Gutierrez et al., 2005); however, Thompson et al. found that 10 out of 48 women with renal transplants had a permanent and significant decline in renal function at 6 months post partum (Thompson et al., 2003).

Fischer et al., studied 81 women with renal transplants who became pregnant and non-pregnant controls, matched for risk factors for deterioration in transplant function, and found no difference in graft function between cases and controls after 91 months of follow-up (Fischer et al., 2005). Pregnancy-associated accelerated decline in graft function is more common in women with worse renal function prior to pregnancy (Armenti et al., 1994; Sibanda et al., 2007).

Table 299.2 Causes of acute kidney injury in pregnant transplant recipients

Cause	Features
Pre-eclampsia	Rapidly progressing pre-existing or new-onset hypertension, worsening pre-existing or new-onset proteinuria, possibly abnormal liver function tests or low platelets
Urinary tract infection	Bacteriuria, or positive urinalysis Clinical features may be absent due to denervated kidney
Obstruction	Improved renal function after bed-rest lying away from transplant. Hydronephrosis on ultrasound with no other cause found. Exclude urinary retention.
Calcineurin inhibitor (tacrolimus/ciclosporin) toxicity	High trough drug levels
Hypovolaemia	Hyperemesis, antepartum haemorrhage, sepsis
Viral infections	Polyoma virus, cytomegalovirus
Acute rejection	Confirmed on renal biopsy. Consider pulsed steroids, or intravenous immunoglobulin Avoid monoclonal antibodies or antithymocyte globulin (McKay et al., 2005)

Simultaneous pancreas–kidney transplants

Increasing numbers of women of child-bearing age are receiving simultaneous pancreas–kidney (SPK) transplants worldwide with concurrent improvements in patient and graft survival. Menstrual irregularities are more frequent in women with SPK transplants than women with renal transplants alone, possibly due to persistent abnormalities in gonadotropic hormones (Mack-Shipman et al., 2000); however, several successful pregnancies have now been reported (Bramham et al., 2010), including in a woman with *in vitro* fertilization (Fichez et al., 2008).

Pregnancies appear to be more complicated than in women with single-organ transplants, possibly due to the intraperitoneal position of the graft resulting in frequent renal obstruction (Bramham et al., 2010) (Fig. 299.1). In the latest series of pregnancies in women with SPK published by the National Transplant Pregnancy Register in the United States, complication rates were high including fetal loss (29%), hypertension (66%), infection (48%), pre-eclampsia (34%), preterm delivery (77%), and low birthweight (62%) (Gilbert-Hayn et al., 2007).

Unfortunately graft loss post partum is high, and one series of 43 women identified that 19% of woman had loss of one or both organs (Gilbert-Hayn et al., 2007). Pre-pregnancy creatinine was not a predictor of graft loss (Wilson et al., 2001).

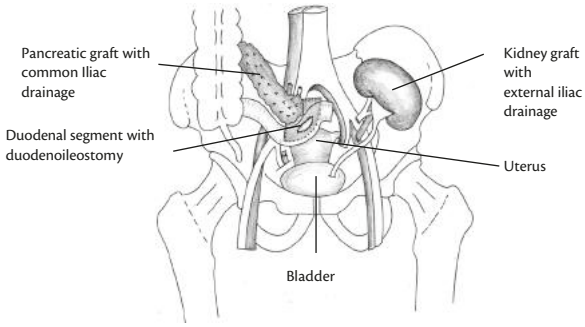

Fig. 299.1 Intraperitoneal position of simultaneous pancreas–kidney transplant.

Pre-existing complications of diabetes of women with SPK transplants need to be considered, including the risk of deterioration in diabetic retinopathy associated with pregnancy, autonomic neuropathy, gastroparesis leading to severe hyperemesis, and chronic urinary retention due to bladder neuropathy (Bramham et al., 2010).

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CHAPTER 300

The kidney in ageing: biology, anatomy, physiology, and clinical relevance

Richard J. Glassock and Andrew D. Rule

Introduction

Ageing is a progressive and inevitably fatal process. From birth to the last breath of old age both cellular function and the fitness of the organism decline, a process we politely call senescence. This universal biological phenomenon is the product of genetic predilection, genetic damage and faulty repair, environmental influences and the element of chance (Finch and Kirkwood, 2000). The rates of decay of function and fitness in are initially imperceptible but as late maturity is achieved they accelerate and tend to be accompanied by ageing-related organ dysfunction and diseases, such as dementia, diabetes, atherosclerosis, osteoporosis, neurodegeneration, or cancer. Organ-based senescence leads to common manifestations of ageing, such as loss of skin elasticity, hair pigmentation, bone density loss, delayed nerve conduction, hearing loss, reduced visual acuity, and diminished lung function. The kidneys are not spared from organ-based senescence and ageing-related diseases (Faubert and Porush, 1998; Nunez et al., 2008). Disentangling the outward effects of the two distinct but related phenomena can be difficult as they can share common functional consequences. Superimposition of ageing-related diseases (such as diabetes, hypertension, and atherosclerosis) on the fundamental and inevitable consequences of a decay in cellular biomechanics with ageing, can alter the apparent rate of functional decline. Thus, the general ageing process manifests itself with the development of abnormalities of organ function that vary in both extent and rate between individuals; the kidneys are no exception. This chapter will deal exclusively with kidney alterations in the ageing process. Several excellent and comprehensive reviews of this general topic have been published (Kaysen and Myers, 1985; Epstein, 1996; Nunez et al., 2008; Xin et al., 2008; Esposito and Dal Canton, 2010; Rodriquez-Castro and Cordova, 2011; Glassock and Rule, 2012; Lim et al., 2012).

Biology

Normal ageing is accompanied by a wide array of molecular and genetic changes, including mitochondrial dysfunction, oxidative stress, shortening of the telomeres (ends of chromosomes) signalling the onset of replicative senescence, DNA damage and insufficient repair, and the tissue accumulation of advanced glycation products and cross-linking of proteins (such as collagen) (for reviews, see Guarente, 2011; John et al., 2011; Armanios, 2013; Hall et al., 2013; Johnson et al., 2013; Newgard and Sharpless, 2013). Central among cellular pathways regulating ageing (and the ageing-associated disease states) are the mammalian target of rapamycin (mTOR) and the silent mating-type information regulator (sirtuin) family of proteins (SIRT1–7 in mammals) (Guarente, 2011; Hall et al., 2013; Johnson et al., 2013). The mTOR pathway is a 'nutrient response' element extensively conserved in evolution (Johnson et al., 2013). Inhibition of this pathway confers an extended lifespan among model organisms, including mammals, reduplicating the effect of calorie (energy) deprivation on lifespan extension. The sirtuin family of proteins comprise a defensive army against a variety of stress-inducing agents (both endogenous and exogenous) (Guarente, 2011). Activation of one or more of the sirtuin isoforms can have significant effect on the biology of organ senescence and the predilection to ageing-related diseases, across a wide spectrum of species, including yeast, nematodes, fruit flies, mice, and man. The principal action of sirtuins appears to be as a nicotinamide adenine dinucleotide (NAD)-dependent protein de-acetylase enzyme directed at transcriptional proteins (Guarente, 2011) This sirtuin-dependent activation has very diverse effects on metabolism including adjustment of cellular physiology to conditions of energy limitation. Sirtuins are closely coupled to AMP-kinase, thus provide a bridge to the mTOR pathway (Guarente, 2011; Johnson et al., 2013). Together the mTOR and sirtuin pathways influence the development of a number of diseases of ageing, including diabetes, neurodegeneration, cancer, cardiovascular disease, and inflammation (Newgard and Sharpless, 2013). The last mentioned probably plays an important role in the development of the functional manifestation expressed by the ageing kidney, but this is not well understood presently. Klotho deficiency has also been implicated in ageing (John et al., 2011; Kuro-o, 2012). Klotho is a type-1 membrane protein related to beta-glucuronidase with diverse functions, including its action as a co-receptor for fibroblast growth factor 23 (FGF23) protein in the kidneys and elsewhere (except for the myocardium). Recently, evidence has accumulated implicating the angiotensin II/angiotensin receptor type 1 (Ang II/AT1R) system in the pathophysiology of ageing in animals (Benigni et al., 2009; Perico et al., 2011). It is noteworthy, that certain alleles of the *AT1R* gene are associated with extreme human longevity (Benigni et al.,

2013). There are also gender-specific (oestrogen or testosterone) dependent factors that impact ageing and its renal consequences (Gava et al., 2011).

A central hypothesis for the biology of ageing involves augmentation of oxidative stress on the organism at the tissue level, including DNA damage and faulty repair. Severe calorie restriction, which prolongs lifespan, (at least in some species, not yet confirmed in humans) may be effective via limiting energy for such oxidative processes. The pro-oxidative function of Ang II may also be involved.

Decay of cellular function and viability with ageing can certainly affect a number of processes integral to preservation of kidney structure and function, such as glomerular filtration rate (GFR), permselectivity of the glomerular capillary wall, podocyte vulnerability to injury, apoptosis, autophagy, and subsequent repair, tubular resorptive and secretory capacities (sodium, water, H^+, phosphate, calcium, albumin, etc.), countercurrent multiplication and urinary concentration, and synthesis and release of renal-derived hormones and biologically active compounds (calcitriol, erythropoietin, etc.) (Abrass, 2000; Wiggins et al., 2005; Xin et al., 2008; Esposito and Dal Canton, 2010; Hartleben et al., 2010; Huber et al., 2012; Lim et al., 2012; Sataranatarajan et al., 2012; Wiggins, 2012). Glomerular podocytes, crucial for the maintenance of normal glomerular structure and permselectivity, undoubtedly undergo senescent changes with normal ageing. Loss of podocytes (via apoptosis, autophagy, or detachment) coupled with low regenerative capacity and inadequate replacement and repair (possibly from trans-differentiation and migration of adjacent parietal cells of Bowman's capsule) lead to a progressive reduction in podocyte number and alterations in the slit pore membrane affecting albumin permeability and GFR (Huber et al., 2012; Wiggins, 2005, 2012; Zhang et al., 2012). Thus, the molecular biology and disturbed cellular physiology that characterizes the ageing process and its tight connections with specific ageing-associated diseases provides a basis for understanding of the observed changes in renal anatomy and function in older persons and may in the future permit development of drugs that specifically mitigate the ageing processes with attendant benefits for life prolongation and life quality.

The fact that ageing is associated with a number of anatomical changes in the kidney, including the vasculature, the glomeruli, and the tubulointerstitium has long been recognized. Early studies were on material obtained postmortem, then later renal biopsies in living subjects with overt kidney disorders and most recently in healthy subjects (living related donors for kidney transplantation). The classic postmortem studies of Darmady, Offer, and Woodhouse, carried out in 1973 in 'apparently healthy' ageing subjects, showed a reduction in the number of non-sclerosed glomeruli, vascular changes, tubular loss and shortening, and increased frequency of tubular diverticuli (Darmady et al., 1973). Simple cysts (perhaps arising from these diverticuli) progressively increase in prevalence with ageing (Rule et al., 2012).The glomerulosclerosis that accompanies ageing is typically of the focal and global type rather than the focal and segmental type and has many feature to suggest that it has an 'ischaemic' origin—with tuft collapse, intracapsular fibrosis, and wrinkling of the glomerular basement membrane (GBM) (Wiggins et al., 2005; Zhou et al., 2008). The overall thickness of the GBM progressively increases with normal ageing. Tubular atrophy and interstitial fibrosis also increases with ageing (Kappel and Olsen, 1980; Mancilla, 2008; Rule et al., 2010). The sclerotic glomeruli are smaller and the non-sclerotic glomeruli may undergo compensatory hypertrophy (Abdi et al., 1998; Hoy et al., 2003). Thus, the average glomerular size (sclerotic + non-sclerotic) may remain constant with ageing. Glomerular density (number of glomeruli per area of cortex) inversely correlates with glomerular size (Tsuboi et al., 2010, 2011; Rule et al., 2011b). Glomerular density *decreases* in ageing in regions where < 10% of the glomeruli are affected by sclerosis but glomerular density *increases* in regions where > 10% of glomeruli are sclerosed (Rule et al., 2011b). Overall, the proportion of small sclerotic glomeruli increase with age, accompanied by tubular atrophy in the cortex. With ageing, even among individual non-sclerosed glomeruli, the filtration surface density shows a tendency to decline and filtration slit frequency falls. Correspondingly the single nephron K_f (permeability coefficient (k) × filtration surface area (SA)) decreases with ageing (see below) (Tan et al., 2009, 2010). Collectively these studies showed that normal ageing (not overtly complicated by ageing-associated disease, including hypertension) is commonly (perhaps universally) accompanied by a progressive form of 'nephrosclerosis' (defined as global glomerulosclerosis, arteriosclerosis, tubular atrophy, and interstitial fibrosis) occurs throughout adulthood (Rule et al., 2010). Total kidney volume remains relatively constant, except at very advanced age, but the cortical and medullary volumes may show differing patterns of change with ageing, with cortical volumes decreasing and medullary volumes increasing (Wang et al., 2014). A form of compensatory hypertrophy of lesser affected nephrons appears to preserve overall kidney volume, especially cortical volume, despite nephron loss. Although overall glomerular numbers decrease with ageing, this phenomenon does not necessarily directly and entirely explain the decrease in GFR observed with ageing, as individual non-sclerosed glomeruli show anatomical changes that contribute to a lower single nephron GFR (see below) (Table 300.1). It is possible that some of the more severely sclerosed glomeruli undergo complete resorption or are too small to be easily identified with standard histological analyses of renal biopsy sections (Nyengaard and Bendtsen, 1992).The extent to which these anatomic changes with ageing are connected to nephron endowment at birth is not understood, but it is logical to speculate that a low nephron endowment at birth might accelerate the anatomic (and functional) changes that characterize renal ageing (Reyes and Manalich, 2005).

Physiology

Glomerular

It is well established that both renal plasma flow (RPF) and measured GFR (mGFR; equivalent to renal inulin clearance) decline with ageing. The RPF tends to decline in parallel with mGFR until about the seventh decade when RPF declines more rapidly than mGFR; thus, the filtration fraction (FF) initially remains constant (at about 20%) and then increases modestly. On the other hand mGFR decreases, beginning in about the fourth or fifth decade or earlier, depending on the subjects selected for study (Wesson, 1969; Slack and Wilson, 1976; Back et al., 1989; Rule et al., 2004). In renal transplant donors (the healthiest of the healthy), mGFR may be found to decrease at an earlier age, and there are some suggestions that the rate of decline in GFR may accelerate at the extreme of age (see Fig. 300.1) (Poggio et al., 2009). In cross-sectional studies the average decline in mGFR is about 0.75–0.85 mL/min/year, usually beginning after the fourth decade. The finding of a progressive

Table 300.1 Chronic histological abnormalities on a sectioned core needle biopsy by age group among kidney donors. (Rule et al., 2010)

Chronic histologic abnormality	18–29 years (N = 148)	30–39 years (N = 303)	40–49 years (N = 392)	50–59 years (N = 257)	60–69 years (N = 92)	70–77 years (N = 11)
Global glomerulosclerosis	19%	38%	47%	65%	76%	82%
Tubular atrophy	11%	15%	19%	32%	40%	45%
Interstitial fibrosis	1.4%	2.0%	2.0%	9.3%	17%	27%
Vascular luminal narrowing	10%	19%	37%	44%	51%	82%

decline in whole-kidney mGFR beginning after maturity has been quite uniform and consistent in numerous cross-sectional studies involving supposedly 'normal' subjects (including the 'healthiest of the healthy'—living donors for kidney transplantation) and the observed decline in GFR has shown no consistent relationship to hypertension, cardiac function, or 'nephrosclerosis' on renal biopsy (Poggio et al., 2009; Rule et al., 2010). Longitudinal studies in which mGFR is followed for many years (decades or more) in individual subjects is preferred, but such analyses are difficult and the literature is very sparse. The best of longitudinal studies of renal function accompanying ageing is that conducted by the Baltimore Longitudinal Study of Aging and reported by Lindeman, Tobin, and Shock in 1985 (Lindeman et al., 1985). This study relied on endogenous urinary creatinine clearance (Ccr) as an estimate of GFR in 254 'normal' men of varying age, some of whom had diabetes mellitus (presumably type 2) unaccompanied by overt proteinuria. The slope of Ccr versus time (in mL/min/year) became negative after age 39 years and then slowly accelerated to reach values of −3.25 mL/min/year after age 80 years. The average decline was −0.75 mL/min/year. Multiple values for Ccr were obtained in the same subjects—five or more Ccr from over 12 months to about 24 years. Statistically significant (non-zero) slopes for Ccr were found in 31 of the 254 subjects, two were positive (at +1 to +3 mL/min/year) and 29 were negative (−1 to −7 mL/min/year). With multiple hypotheses testing, these two positive slopes may be consistent with chance alone. Overall about 36% of the subjects had 'no change' in Ccr over the periods studied, but it is not clear how many of these had an adequate number of values determined to have a high confidence that the slopes were indeed close to zero over time. The distribution of the slopes of Ccr over time was Gaussian, suggesting a physiological rather than a disease-induced change affecting only a fraction of the subjects. This seminal study has been interpreted by some to indicate that the decline in GFR with ageing is 'not inevitable' (Fliser, 2005; Lindeman, 1998) but the inclusion of diabetics (with possible 'hyperfiltration') and limitations of 'slopes' when inadequate numbers of observations were available for analysis makes this interpretation tenuous. Interestingly, the decline in GFR with ageing is also seen in indigenous/aboriginal societies (e.g. Kuna Amerinds) where hypertension does not occur with ageing, unlike many 'Westernized' cultures (Hollenberg et al., 1997, 1999). It is difficult to attribute the falling GFR in ageing to the development of hypertension-associated vascular disease, although very clearly systolic blood pressure does increase with normal ageing, mostly due to a reduction in compliance in the major vessels (often accompanied by increased cross-linking of collagen in these vessels). Nevertheless, it is entirely possible that some of the decline in GFR seen with ageing is a consequence of superimposition of specific disease states (such as diabetes or atherosclerosis) on the basic process of glomerular senescence (Król et al., 2010). Nephron endowment at birth might be a determinant of the rate of decline in GFR with ageing, but no data is currently available on this point (Luyckx et al., 2013). It also needs to be emphasized that concurrent metabolic factors common in ageing subjects (obesity, insulin resistance, hyperglycaemia) can modify the GFR response to senescence. The ability of the GFR or RPF to increase in response to protein feeding or infusion with certain amino acids can be impaired with ageing in mammals (Musso et al., 2011). Fliser et al. showed that this ageing-related phenomenon (often called 'renal reserve') in humans was primarily due to an impaired renal vasodilator response in the elderly in that the rise in GFR following infusion of an amino acid was the same in young and old individuals, but the RPF response was clearly blunted in the elderly (Fliser et al., 1993). In the oldest old (>75 years of age) the GFR increases to a lower extent than in younger persons in response to an oral protein load (Musso et al., 2011).

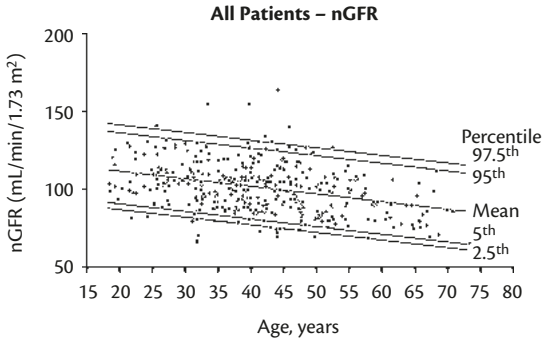

Fig. 300.1 Decline in normalized (mL/min/1.73 m^2) glomerular filtration rate (nGFR) with ageing among 365 healthy potential kidney donors.
Reproduced from Rule, A. D., Gussak, H. M., Pond, G. R., *et al.* (2004). Measured and estimated GFR in healthy potential kidney donors. *Am J Kidney Dis*, 43(1), 112–19.

The mechanisms underlying the changes in mGFR, RPF, and FF with ageing have been discussed above but bear further elaboration. The fall in RPF can be explained by the development of arterio- and arteriolar sclerosis, and this can be complicated by specific atherosclerosis-related disease (such as renal artery stenosis and congestive heart failure). The decline in whole-kidney GFR is a consequence of a decline in functioning glomeruli affected by global glomerulosclerosis (offset to some extent by hypertrophy and an increase in filtration in less affected nephrons) but also by changes in the GFR of individual nephrons, including a reduction in K_f (Hoang et al., 2003). The magnitude of 'nephrosclerosis' in renal biopsies does not clearly account for the decline of GFR in

ageing (Rule et al., 2010). This may be due to an artefact introduced by imprecise detection of nephrosclerosis on standard needle core renal biopsies.

The rate of albumin excretion also increases with ageing, to some extent depending on the gender and the methods used for its assessment (Abdelhafiz et al., 2011; Carter et al., 2012; Tanaka et al., 2013). Urinary albumin to creatinine *ratios* (UACRs) can increase in ageing without much increase in absolute albumin excretion, in part due to the systematic decline in creatinine excretion observed in the elderly, largely due to progressive sarcopenia and reduced creatinine generation (the denominator of the UACR equation) (Kestenbaum and de Boer et al., 2010; Lambers Heerspink et al., 2010). Notably, urinary albumin excretion does not increase with ageing in the healthiest of the healthy living donors for renal transplantation, after taking into account co-morbidity features, such as diabetes or vascular disease, already known to influence albumin excretion rates. Since albuminuria can be influenced by many factors (e.g. obesity, smoking, diet, drugs, remote inflammation, hyperglycaemia, atherosclerotic burden, genetics (cubulin deficiency), diffuse endothelial injury, and hypertension), it is difficult to sort out the specific cause (or causes) which increase albumin excretion in older adults (Glassock, 2010; Król et al., 2010). Podoctye loss and dysfunction due to cellular senescence and inadequate regeneration can underlie a part of the albuminuria associated with ageing. Because both enhanced glomerular permeability and reduced tubular reabsorption (and degradation) can contribute to an increased urinary albumin excretion it is inappropriate to label all abnormal albuminuric states as indicating the presence of specific glomerular diseases.

Tubular function

Disturbances in the physiology of tubular function are common in ageing. Changes in the renal handling of sodium, potassium, ammonium, and water have all been described (Kaysen and Myers, 1985; Epstein, 1996; Nunez et al., 2008; Xin et al., 2008; Esposito and Dal Canton, 2010; Rodriquez-Castro and Cordova, 2011). Elderly patients, free of cardiovascular disease, demonstrate impaired (delayed) renal conservation of sodium when exposed to an acute reduction in sodium intake. This might be due to a sluggish response of the renin–angiotensin–aldosterone system with ageing (see below) or perhaps a 'solute diuresis' among the less affected nephrons in a generally reduced nephron population in the ageing kidney. Similarly, the ability of the ageing kidney to excrete a large amount of acutely administered sodium rapidly can be modestly impaired (Kaysen and Myers, 1985; Epstein, 1996; Nunez et al., 2008; Xin et al., 2008; Esposito and Dal Canton, 2010; Rodriquez-Castro and Cordova, 2011). This might be due to a defect in the 'pressure natriuresis' relationship in the aged kidney.

Potassium homeostasis is usually well preserved in aged persons, but an impaired ability to handle acute potassium loads has been described, and might be the consequence of an attenuated renin–angiotensin–aldosterone system (see below) (Kaysen and Myers, 1985; Epstein, 1996; Nunez et al., 2008; Xin et al., 2008). The main abnormality in acid–base homeostasis seen in the elderly is a defect in ammonium exertion and impaired net acid secretion in response to a protein load.

Major disturbances in water handling by the kidney are seen in ageing, both impaired concentrating and diluting capacity. The maximum urinary concentrating ability (Uosm max) is impaired in the elderly (Uosm max in young = about 1200 mOsm/kg H_2O); in elderly = about 800 mOsm/kg H_2O) and maximal minimal urinary diluting capacity (Uosm min) is also impaired in the elderly (Uosm min in young = about 50 mOsm/kg H_2O); in elderly = about 95 mOsm/kgH_2O) (Kaysen and Myers, 1985; Epstein, 1996; Nunez et al., 2008; Xin et al., 2008; Esposito and Dal Canton, 2010; Rodriquez-Castro and Cordova, 2011). Such abnormalities may make the elderly more prone to hypernatremia (i.e. a form of partial nephrogenic diabetes insipidus) especially when thirst mechanisms are impaired simultaneously. Thiazide-type diuretics may further impair the already abnormal diluting capacity and thereby promote hyponatraemia, especially in the presence of low solute intake (Hix et al., 2011). It is not surprising that hyponatraemia is more common than hypernatremia in the elderly (Rodenburg et al., 2013). Sodium and protein deprivation with continue intake of hypotonic fluids (e.g. tea and toast diets), are very common causes of hyponatraemia in the elderly (see also Chapter 28 and below). The origins of the disturbed physiology of water homeostasis and hyponatraemia are many, and are also conditioned by other drugs (e.g. anti-anxiety or antidepressant drugs) and diseases (e.g. cancer-associated syndromes of inappropriate antidiuretic hormone release (SIADH)) which become more common as one ages. The sensitivity for release of arginine vasopressin (antidiuretic hormone (AHD)) by the hypothalamic–posterior pituitary axis in response to hyperosmolality is heightened rather than blunted in the elderly and resting plasma ADH levels tend to rise slowly with ageing (Rondeau et al., 1982). Diuretics and low urea generation, the latter consequent upon the lower-protein diets frequently consumed by the elderly, can have profound effects upon the countercurrent system and the formation of a concentrated or dilute urine. In addition, the expression of urea transporters (UTs), specifically UT-A1 and UT-A2, are reduced in ageing rats (Sands, 2012). The expression of aquaporin isoforms (AQPs), specifically AQP2 and AQP3 and their phosphorylation, are also reduced in the medulla in ageing rats (Combet et al., 2008; Sands, 2012). A decrease in the abundance of the sodium chloride transporter (NKCC2) or the epithelial sodium channel (ENaC) can also occur with ageing (Tian et al., 2006; Sands, 2012).

Taken together, these changes in renal tubular physiology imply that the function of the countercurrent system and the maintenance of medullary hyperosmolality are impaired with ageing. Defects in diluting capacity also develop with ageing, but usually appear later and are less severe than the defects in concentrating (i.e. partial nephrogenic diabetes insipidus). They can largely be attributed to a decrease in GFR and perhaps to changes in 'distal' sodium chloride reabsorption, beyond the proximal tubule, and perhaps to specific abnormalities of transporters (NKCC2), water permeability factors, or channels (ENaC).

Vascular function

RPF declines with ageing with reduced renal perfusion most marked in the cortex according to ^{133}Xe washout studies (Hollenberg et al., 1974). These changes can be correlated with increased tortuosity of pre-glomerular vessels and some tapering of afferent arterioles. The renin–angiotensin–aldosterone system is also perturbed in ageing. Plasma renin levels decline with age, by as much as 40–60% compared to those in young

persons (Weinstein and Anderson, 2010; Seals et al., 2011). These changes are due to decreased synthesis and impaired release of renin by the juxta-glomerular apparatus (JGA). Inhibition of Ang II produces renal vasodilatation in old but not in young animals, suggesting an important role for circulating Ang II in regulation of renal haemodynamics in older individuals. The sensitivity of the renal vasculature to Ang II does not appear to be altered in ageing. The vasculature of the aged person seems to be more sensitive to the effects of nitric oxide synthetase (NOS) inhibitors, leading to enhanced deficiency of nitric oxide (NO) and reduced endothelium-dependent vaso-dilatory capacity (Seals et al., 2011; Baylis, 2012). This may increase the susceptibility of older persons to the effect of inhibition of Ang II action is so far as maintenance of GFR and RPF are concerned. Accumulation of naturally occurring endogenous NOS inhibitors (such as asymmetric dimethyl arginine) might contribute to the well-recognized decline in renal blood flow with ageing.

Hormonal function

Aldosterone production can be impaired in ageing, and insulin secretion can be diminished in older individuals, particularly after long periods of hyperglycaemia induced by peripheral insulin resistance (Beta cell 'exhaustion') (Bauer, 1993; Xin et al., 2008). This section will be limited to comments on hormonal substances synthesized and released by the kidney; specifically erythropoietin (EPO) and 1,25 dihydroxyvitamin D (calcitriol). There is an increasing prevalence of anaemia with declining renal function, including that associated with ageing. Not surprisingly plasma EPO levels tend to increase with age, but the EPO response index (haemoglobin levels at any plasma level of EPO) decline with age, suggesting a state of peripheral EPO résistance in ageing (Ferrucci and Balducci, 2008; Xin et al., 2008). Older subjects (particularly women with post-menopausal osteoporosis) have lower plasma calcitriol levels and normal plasma 25 hydroxyvitamin D (calcidiol) levels, suggesting a defect in 1-hydoxylase enzyme activity (Gallagher et al., 2007; Xin et al., 2008). Klotho deficiency, which is a feature of ageing, and which acts as a co-receptor with fibroblast growth factor (FGF)-23 (derived from bone osteocytes/osteoblasts) in reducing tubular phosphate reabsorption and reducing renal synthesis of calcitriol is likely to explain the lowering of plasma calcitriol levels with ageing (Xin et al., 2008; Kuro-o, 2010).

Clinical relevance

There is no doubt that the biological, anatomical, and physiological alterations that occur in the kidney with ageing have major clinical relevance. This has spawned the new subdiscipline of geriatric nephrology.

Diagnosis and prognosis of chronic kidney disease

The adoption of absolute thresholds for defining 'chronic kidney disease' (CKD), both from the standpoint of GFR and albuminuria, by expert-guided clinical practice guidelines has evoked a substantial controversy (Winearls and Glassock, 2009; Glassock and Oreopoulos, 2011; Moynihan et al., 2013). Essentially, the argument revolves around the notion that a decline in mGFR (and eGFR estimated by any of a number of equations using serum creatinine (creat) or cystatin C (cys) levels; eGFR-creat or eGFR-cys or eGFR creat + cys) that 'normally' occurs with ageing precludes setting arbitrary and absolute thresholds of mGFR or eGFR to define CKD. A substantial number of the 'healthy' elderly (> 65 years of age) will have experienced a decrease in GFR or eGFR to values < 60 mL/min/1.73 m^2 (more females than males), the common threshold for defining CKD adopted by the clinical practice guideline groups (Wetzels et al., 2007; Glassock and Winearls, 2009; Barri et al., 2010; KDIGO, 2013). This theoretically has led to the 'overdiagnosis' of CKD in otherwise normal but older adults, especially in those with so-called stage G3A CKD (GFR of 45–59 mL/min/1.73 m^2) (Moynihan et al., 2013). The counter-argument for the appropriateness of the single non-age calibrated threshold of GFR is that values of GFR < 60 mL/min/1.73 m^2 are associated with an increased risk (hazard ratio (HR)) for renal specific adverse events, such as end-stage renal disease, and acute kidney compared to more normal levels of eGFR regardless of age and even after adjustment for co-morbidities known to influence such risk (Tonelli et al., 2011; Hallan et al., 2012). However, the HRs for mortality events do differ by age according to the underlying level of eGFR (Tonelli et al., 2011). Further, the risk of mortality by level of eGFR differs substantially by age group; and is complicated by a 'U'-shaped association between eGFR and mortality in the elderly (Fig. 300.2). High eGFR-creat appears to be associated with increased mortality in the elderly, and this is likely due to sarcopenia as well as true hyperfiltration (elevated mGFR; > 120 mL/min/1.73 m^2) (Tonelli et al., 2011). Confounding this widely debated controversy (Hallan et al., 2012) is the fact that the various formulas for eGFR all give differing results in the elderly and the values derived are all significantly influenced by non-GFR determinants (such as sarcopenia with eGFR-creat and inflammation with eGFR-cys) which can each independently influence the development of these adverse events (Grams et al., 2013). At present the Berlin Initiative Study Equations 1 or 2 (BIS1 (creatinine only) or BIS2 (creatinine + cystatin C) have the best performance

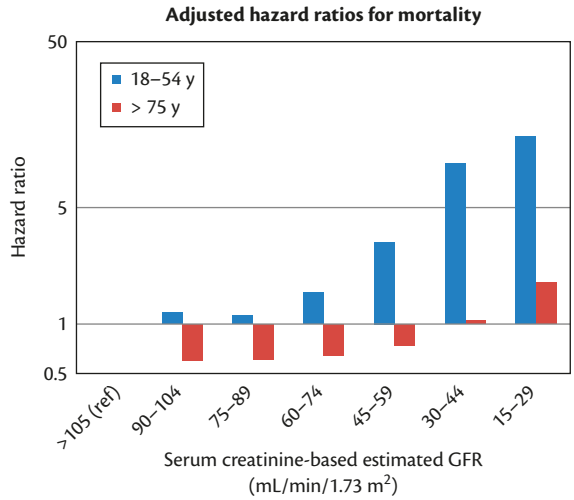

Fig. 300.2 Adjusted hazard ratio for mortality in patients from 33 cohorts with urine albumin:creatinine ratios < 10 mg/g. Using a serum creatinine-based estimated GFR > 105 as the reference group, the risk of mortality is increased at an estimated GFR < 105 in young adults compared to < 45 in elderly adults. This is likely due to a normal GFR (estimated GFR > 105) reflecting hyperfiltration and sarcopenia in elderly patients.

Reproduced from Hallan, S. I., Matsushita, K., Sang, Y., *et al.* (2012). Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*, 308, 2349–60.

characteristics, i.e. low bias, good accuracy) for estimating the true or measured GFR (mGFR) in the elderly (Schaeffner et al., 2012). The addition of abnormal albuminuria (UACR > 30mg/g) to these GFR criteria has helped to clarify and focus the debate, as an increase in albuminuria with an overtly reduced GFR (eGFR or mGFR), is consistently associated with increased risk for adverse events across all ages (Hallan et al., 2012). Nevertheless, doubts remain as to the meaning of a UACR between 30 and 300 mg/g in older subjects with eGFR > 60 mL/min/1.73 m^2, especially in the absence of diabetes, cardiovascular disease, hypertension or known kidney disease (also known as 'isolated' microalbuminuria) (Scheven et al., 2013). Very clearly subjects of advanced age who have an eGFR < 45 mL/min/1.73 m^2 (with or without abnormal albuminuria) or those with severe albuminuria (UACR> 300 mg/g) have clear-cut poor prognosis at all ages and can be easily labelled as having CKD if these values persist for 3 months or more.

Drug dosing in the elderly

Renal function is an important consideration in determining the dosage and frequency of administration of therapeutic agents (including those with nephrotoxic effects) when the compounds are cleared by GFR or by tubular secretion (or both), especially in the elderly where other factors such as non-renal elimination or detoxification of drugs can be impaired or altered. Medications cleared by GFR are almost always water soluble and non-protein bound (Seyffart et al., 2011). Serum creatinine (SCr) levels alone may not be adequate for determining optimum dosage and frequency in older subjects, as creatinine generation (due to sarcopenia) declines as GFR falls with ageing (Rule et al., 2009), thus tending to maintain the serum creatinine level at fairly constant values despite advancing age in healthy adults (Rule et al., 2004). However, there is an increased prevalence of elevated serum creatinine with older age in the general population when not selecting on health (Juraschek et al., 2013). The SCr level rises only from 88 μmol/L (1.00 mg/dL) at ages 20–29 to about 97–106 μmol/L (1.10–1.20 mg/dL) above age 70 years in men (a 10–20% increase) and from about 79 μmol/L (0.90 mg/dL) to about 92 μmol/L (1.05 mg/dL) in women (a 16% increase) over comparable ages. Urine creatinine excretion (24-hour) is about 24 mg/kg in men (212 μM/kg) and 20 mg/kg (177 μM/kg) in women ages 20–29 and steadily declines to about 10–15 mg/kg (88–133 μM/kg) in men and to 8.5–12 mg/kg (75–106 μM/kg) in women over age 70 years of age. Cystatin C values (unaffected by muscle loss, but increased with concomitant inflammation) might be superior to SCr concentration for detecting low mGFR values in this respect. Legitimate debate exists over which of the many eGFR equations is best for application for drug dosing in the elderly (Hudson, 2015). The value of estimating creatinine clearance by the Cockcroft–Gault equation is poor and when doubt exists as to the veracity of the eGFR results (such as those with extreme malnutrition or marked obesity) it is best to actually assess the endogenous 24-hour creatinine clearance or measure the true GFR (mGFR) directly. When utilizing eGFR (in mL/min/1.73 m^2)for calculation of drug doses one should first correct to mL/min units by multiplying by body surface area divided by 1.73 m^2.

Fluid and electrolyte disorders

These disorders are covered in detail elsewhere (see Section 2). Here only brief comments are made on the more common disturbances that arise in the elderly consequent, in part, to age-related disturbances of glomerular and/or tubular function. By far the commonest electrolyte disturbance in the elderly is hyponatraemia, mostly arising from defects in diluting capacity and free water generation, perhaps abetted by reduced solute excretion due to low-protein diets (low urea generation) and/or low salt intake. As indicated above, thiazide-type diuretics can further impair free water generation and promote the development of hyponatraemia (Hix et al., 2011; Rodenburg et al., 2013). If the minimum Uosm is about 100 mOsm/kg and overall solute excretion is 300 mOsm per day (about 1/3 normal) then maximum electrolyte free water intake compatible with retention of normal plasma sodium concentration is about 3 L per day and much less if a drug or a disease state impairs maximum diluting capacity further. This is a common pathophysiology in the 'tea and toast' hyponatraemia of elderly and frail nursing home residents.

On the other hand, hypernatremia can ensue if there is defective thirst or increased solute load (e.g. endogenous urea generation) since concentrating ability is defective in the elderly. If maximum Uosm is about 900 mOsm/kg and the solute excretion is increased to 1800 mOsm/day (twice normal) then any electrolyte-free water intake < 2 L per day will be accompanied by progressive hypernatremia.

Hyperkalaemia is relatively uncommon in the elderly except when agents are administered that further impair K^+ excretion (e.g. aldosterone antagonists, Ang II inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs)) or when high K^+ loads are acutely administered. Because of low calcitriol levels, older subjects can be at risk for hypocalcaemia-induced events if they are also taking bisphosphonates. Erythropoiesis-stimulating agent doses for treatment of anaemia in bone marrow disorders may be higher in older subjects.

The risk of acute kidney injury (AKI) is definitely increased in the elderly, especially following radiocontrast agents and NSAID administration, in part due to lower GFR but also due to physiological changes in the renal circulation that accompany ageing (see Chapter 220).

Specific renal diseases

Older adult subjects are more prone to develop certain renal diseases, especially glomerular disorders (see Table 300.2) (Faubert and Porush, 1998; Glassock, 1998; Nunez et al., 2008). Among the glomerular disorders seen more commonly in older and elderly adults are diabetic nephropathy (due to the rising incidence of type 2 diabetes mellitus with age), primary (AL) amyloidosis, non-amyloid monoclonal deposition diseases, myeloma cast nephropathy, primary and secondary membranous nephropathy (the latter associated with solid malignant tumours, chronic viral infections, or drugs), essential mixed immunoglobulin (Ig)-G/IgM cryoglobulinaemia (especially in women) and crescentic glomerulonephritis due to ANCA-associated small vessel vasculitis. Lupus nephritis, IgA nephropathy, and focal segmental glomerulosclerosis are less commonly observed in the elderly. The details of the specific glomerular diseases are discussed elsewhere. Other renal and genitourinary conditions encountered more commonly in the elderly include renal arterial stenosis (atherosclerotic type), ischaemic nephropathy, cholesterol embolization, drug-induced AKI, renal cell carcinoma, and obstructive uropathy (prostatic disease in men and cervical cancer in women).

Table 300.2 Renal diseases commonly observed in older or elderly adults

Glomerular	Diabetic nephropathy
	ANCA-associated small vessel vasculitis
	Primary (AL) amyloidosis
	Non-amyloid monoclonal immunoglobulin deposition diseases (e.g. light chain deposition disease)
	Membranous nephropathy (primary and secondary)
	Fibrillary glomerulonephritis/immunotactoid glomerulopathy
	Essential mixed (IgG/IgM) cryoglobulinaemia
	Idiopathic nodular glomerulosclerosis
Tubular	Myeloma cast nephropathy
	Acute kidney injury (contrast media; nephrotoxic drugs, NSAID)
	Obstructive uropathy (prostatic disease, carcinoma of the cervix)
	Drug-induced acute hypersensitivity (allergic) nephritis
	IgG4-related kidney disease
	Renal cell carcinoma
Vascular	Renal arterial stenosis (atherosclerotic)
	Cholesterol embolization syndrome
	Chronic ischaemic nephropathy
	Arterial embolization (atrial fibrillation)
	Polyarteritis nodosa
	ANCA-associated small vessel vasculitis (see 'Glomerular')
Genitourinary	Benign prostatic hypertrophy and prostatic cancer
	Carcinoma of the cervix
	Transitional cell carcinoma of the bladder (especially in males)
	Obstructive uropathy (see 'Tubular')

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