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Preconceptional counseling for women with chronic kidney disease

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INTRODUCTION

Chronic kidney disease (CKD) reportedly affects 3% of women between the ages of 20 and 39 years[1]. In view of the increasing age at which many women are now contemplating their first pregnancy, as well as the predicted rise in the number of individuals with CKD due to type 2 diabetes[2], it is likely that CKD will become a more common problem in the offices and clinics of those who provide antenatal care. Under these circumstances, it is essential that health care professionals be aware of the potential complications associated with this condition. Preconceptional counseling for women with CKD allows adequate preparation for pregnancy, both physically and psychologically, as many women may be unaware that their condition has any implications for fetal or maternal health.

NEW DEFINITION OF CHRONIC KIDNEY DISEASE

CKD has recently been redefined according to estimated glomerular filtration rate (eGFR). CKD[3] is said to occur when the eGFR is less than 60 ml/min/1.73m^2, or in the combination of eGFR and abnormal renal structure and/or the presence of proteinuria when the eGFR is more than 60 ml/min/1.73m^2. The eGFR compensates to some extent for the inadequacies of serum creatinine as a marker of renal function, namely its variability with age, gender, ethnicity, diet and muscle mass and its inability to detect kidney impairment until as much as 70% of renal function is lost[4]. The stages of CKD are shown in Table 1. According to epidemiological data from the USA, 3% of women age 20–39 have stage 1 or 2 CKD[5]. It is unlikely that this level of renal impairment affects fertility, so theoretically up to 1 in 30 pregnancies may be complicated by CKD as fewer than 39% of women with stage 1 or 2 CKD have detectable hypertension or proteinuria[5], many women with early CKD are undiagnosed. The modified diet in renal disease (MDRD) formula which is used to calculate eGFR significantly underestimates true GFR in pregnancy as measured by 24 hour creatinine clearance and should not be used in pregnancy[6].

WHO SHOULD RECEIVE COUNSELING?

Pre-pregnancy counseling affords the opportunity to adjust medication, optimize hypertension control, stabilize renal function and educate the woman about the possible adverse events which may arise during or as a consequence of her pregnancy. Although every woman with CKD has an increased risk of pregnancy complications, it is impractical for obstetric nephrologists, obstetric physicians or obstetricians to undertake counseling for

Table 1 Stages of chronic kidney disease (CKD) using the modification of diet in renal disease (MDRD) formula to calculate the estimated glomerular filtration rate (eGFR)

CKD stage	*eGFR* (ml/min/1.73 m^2)	*Description*	*Approximate creatinine in non-pregnant women* (μmol/l)
1	>90	Kidney damage* with normal/raised GFR	<70
2	60–90	Kidney damage* with mild/reduced GFR	70–100
3	30–59	Moderately reduced GFR	100–180
4	15–29	Severely reduced GFR	180–350
5	<15	Kidney failure	>350

*Kidney damage with evidence or structural damage or proteinuria; stage 1 or 2 cannot be classified on the basis of GFR alone

every woman with all forms of CKD; therefore, those with mild disease could be managed by their general practitioner (GP) or primary care physician. Table 2 lists certain clinical situations where pre-pregnancy counseling is essential.

Table 2 Women with renal disease who should be referred for pre-pregnancy counseling

- Women with CKD stage 4 or 5
- Women with CKD stage 3 and adverse risk factors, e.g. significant proteinuria, hypertension or previous adverse obstetric history
- Women with kidney transplants
- Women on dialysis who are contemplating pregnancy
- Women with CKD stage 1 or 2 and adverse risk factors, e.g. systemic diseases such as lupus or vasculitis, significant proteinuria, hypertension or previous adverse obstetric history
- Women with a family history of heritable renal disease

CKD, chronic kidney disease

TIMING OF CONCEPTION

One of the essential components of pre-pregnancy counseling is a discussion on the timing of conception, the importance of which varies on an individual basis according to patient age, disease etiology and activity. Evidence from a large series of transplant recipients who subsequently became pregnant identified delaying conception until 12 months post-transplantation was associated with better pregnancy and renal outcomes[7]. A year is now recommended by the European Best Practice Guidelines for care of the renal transplant recipient, to allow for medication adjustments and to reduce the risk of acute graft rejection[8].

Lupus nephritis has also been studied in considerable detail with respect to pregnancy. The risk of disease flare and adverse pregnancy outcomes are increased in women who conceive with active disease[9,10]. Pregnancy and renal complications are significantly reduced in those who have quiescent disease for 6 months prior to conception[11]. It is currently recommended that a period of 6 months after the latest episode of disease flare, including non-renal involvement, pass before attempting to conceive.

Diabetes is independently associated with less than optimal pregnancy outcome, even in women with normal renal function. Hyperglycemia adversely affects rates of preterm delivery, cesarean section, still birth,

perinatal mortality and congenital abnormality[12,13]. Hence, women with type 1 as well as type 2 diabetes are advised to optimize their glycemic control before embarking on pregnancy. Similarly, poorly controlled hypertension is a predictor of adverse outcome, and women are advised to delay conception until this is adequately controlled[14], although if renal function is deteriorating rapidly some women may be better advised to conceive sooner rather than later.

The most complicated scenario for advising when to conceive is in an older individual with moderate–severe renal impairment. If the condition is progressive, a younger woman can confidently be advised to wait until she has received a kidney transplant, which will not only improve her fertility, but will increase the chances of a successful, uncomplicated pregnancy. Unfortunately, for women older than 35 years the opportunity for transplantation may not arise until their fertility has declined substantially. For such individuals, the best option, in order to allow her the best possible chance of having a baby at all, is to advise not to delay conception, but to accept that the pregnancy will be high risk.

Contrary to the previously held beliefs of nephrologists and obstetricians a few decades ago 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'[15], there are few situations when conception is not recommended. Such a circumstance requires a complex counseling process, in which the woman needs to be made aware that the chances of a successful pregnancy are very low, and that in commencing pregnancy she will be putting her own health in jeopardy. A powerful argument which may be helpful is a detailed explanation of the life-style adjustments required by renal replacement therapy, together with the anticipated shortened life expectancy, factors which should be important considerations for a potential new mother.

MEDICATION ADJUSTMENTS

Another valuable component of preconceptional counseling for women with CKD is a medication review. Several drugs commonly used by nephrologists and in primary care are teratogenic or have consequences for the fetus later in pregnancy. For the purposes of this discussion, we focus on two major categories: immunosuppressive agents and angiotensin converting enzyme (ACE) inhibitors.

Immunosuppression

Nearly all transplant recipients and many women with glomerulonephritis regularly take immunosuppressive agents. Prednisolone is metabolized by the placenta to relatively inactive 11-ketoforms by 11β-hydroxysteroid dehydrogenase, and only 10% crosses into the fetal circulation at maternal doses of less than 20 mg[16]. Exposure to corticosteroids in the first trimester may slightly increase rates of cleft lip and palate[17,18]; however, this has not been substantiated in all studies[19,20]. Cyclosporine[21,22] and tacrolimus[23] are non-teratogenic; however, there is an increased risk of gestational diabetes in women taking tacrolimus[24], and a glucose tolerance test is recommended at 28 weeks. Azathioprine has also been shown to be safe in pregnancy[25–27].

Mycophenolate mofetil (MMF) is now a first line agent for prevention of allograft rejection and for the treatment of lupus nephritis. Emerging animal data have demonstrated teratogenicity[28], and in 2004 the first case of human teratogenicity was described[29]. Since then 26 cases of early exposure in 18 renal transplant patients have been reported, and a clinical syndrome similar to that found in animal studies has been identified including hypoplastic nails, shortened fifth fingers, diaphragmatic hernia, microtia (ear deformity), micrognathia, cleft lip and palate, and congenital heart defects[30]. These reports, assessed broadly,

resulted in a reclassification of MMF status by the FDA to class C. Women are now advised to switch from MMF at least 3–6 months before conception to an immunosuppressive agent which has a safer profile in pregnancy, e.g. azathioprine, cyclosporine or tacrolimus. There are some clinical situations, however, where alternatives have already been tried without success and MMF is the only treatment able to achieve disease stability. In such a situation the individual needs to be counseled carefully about the relative risks to the fetus if she remains on MMF during her pregnancy. It is currently unknown whether such defects can be detected by antenatal ultrasonography.

Data regarding the use of sirolimus (rapamycin) in pregnancy are limited. Although no evidence of teratogenicity has been identified in animal or clinical studies[30], more information is required before it can be recommended in pregnancy, and women taking sirolimus should be advised to change to an alternative agent at preconceptional counseling.

Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers

Before 2006, exposure to ACE inhibitors in the first trimester was considered acceptable. ACE inhibitors were not advised in the second or third trimester, however, due to an association with fetal complications including growth restriction, oligohydramnios, hypocalvaria, renal dysplasia, anuria, renal failure and often fetal death[31]. However, Cooper *et al*. published a landmark paper in 2005 which suggested that even first trimester only exposure to ACE inhibitors is associated with a 2.7-fold increase in congenital malfomations[32]. Abnormalities include cardiovascular, central nervous system and renal defects.

Three possible approaches are available to women with CKD taking ACE inhibitors/angiotensin II receptor blockers (ARBs) considering pregnancy. Women with minimal proteinuria taking ACE inhibitors/ARBs for blood pressure control can be switched to an alternative antihypertensive known to be safe in pregnancy, e.g. nifedipine, amlodipine, doxazosin, or labetolol. Women with proteinuria controlled by ACE inhibitors/ARBs with mild renal impairment can be advised to stop taking their medication when they start trying to conceive, with close monitoring of blood pressure. However, women with heavy proteinuria, a major adverse indicator of progression of renal disease, risk a marked reduction in GFR if they do not continue to take ACE inhibitors/ARBs whilst they are attempting to conceive. This is particularly difficult for older women, those with more severe renal impairment and those with diabetic nephropathy in whom a prolonged interval without ACE inhibitors/ARBs may be ill advisable. In these cases, it is recommended that ACE inhibitors/ARBs not be stopped preconception but be discontinued as soon as the pregnancy is confirmed, as the period of teratogenicity is considered to be from 6 weeks onwards. Women with an irregular menstrual cycle, in whom pregnancy confirmation may be delayed, need to be assessed and advised on an individual basis.

PREGNANCY AND RENAL OUTCOMES

Women with CKD contemplating pregnancy not only have to be aware of the potential complications of the pregnancy for the fetus, but also of the implications for progression of their renal impairment. Over the past five decades, several mainly retrospective series have attempted to assess these issues. An amalgamation of the data of 908 pregnancies in 676 women is shown in Tables 3 and 4. In view of eGFR being invalid in pregnancy, older classifications according to serum creatinine are used to categorize levels of renal impairment.

Table 3 Pregnancy outcome in 908 pregnancies in 676 women (personal communication, Professor John Davison): risks associated with different levels of renal impairment

Creatinine (μmol/l)	*Problems during pregnancy* (%)	*Successful obstetric outcome* (%)	*Long-term renal problems* (%)
<125	26	96	<3
125–250	47	89	30
>250	86	46	53

Table 4 Pregnancy outcome in 908 pregnancies in 676 women (personal communication, Professor John Davison): type of problem encountered with different levels of renal impairment

Creatinine (μmol/l)	*High blood pressure* (%)	*PET* (%)	*IUGR/Prematurity* (%)
<125	Variable	10–20	Increased
125–250	30–50	40	30–50
>250	Most	80	57–73

IUGR, intrauterine growth retardation

Mild renal impairment (creatinine <125 μmol/l)

Women with mild renal impairment usually have successful pregnancies, although the risk of pre-eclampsia remains greater than background (5%) and should be discussed. Successful fetal outcomes have improved for women with mild renal impairment, and more recently have been reported to be as high as 98%[33]; however, rates of preterm delivery (11–20%) and low birth weight (5–26%) continue to be higher than in healthy controls[14,34,35]. Pregnancy in women with mild renal impairment generally does not precipitate either worsening or an accelerated worsening of maternal kidney function[34,36–39].

Moderate renal impairment (creatinine 125–250 μmol/l)

Fertility is reduced with increasing severity of renal impairment[40]. As many as 1 in 750 pregnancies are complicated by stage 3–5 CKD[41], and the majority of these occur in women with more preserved renal function. The most difficult group of women to give accurate preconceptional counseling are those with moderate renal impairment. Pre-eclampsia may occur in up to 60% of these women[42,43], may occur early and may be severe. An important message to ensure the woman understands is the concept of prematurity, which may occur in 39–64% of women[42–46]. Although major advances in neonatal care have led to marked improvements in survival and outcome, very preterm infants frequently have sensory impairment and intellectual disability. It is therefore important to highlight that there is an increased risk of early complications and hence very preterm delivery which can lead to long-term handicap. Fetal loss is higher in this group of women, with early and late miscarriages not being uncommon[42–46]. A useful early guide to the success of an individual pregnancy is the adaptation to increased GFR[47]. If creatinine does not fall in the late first/early second trimester it is suggestive of future complications.

A very important issue to discuss is the risk of deterioration of renal disease. Renal function may deteriorate in 20% of women

during pregnancy and in an additional 23% between 6 weeks and 6 months postpartum. Some of these women recover their pre-pregnancy renal function values by 6 months, but approximately one-third have a pregnancy-related decline which persists[43]. Even temporary renal deterioration may have serious consequences. In a recent series of 36 women (unpublished data) more than 50% of women with preterm deliveries (<37 weeks' gestation) were delivered iatrogenically due to progressive renal impairment.

Imbasciati *et al*. recently published a comprehensive prospective series of 49 women with mean serum creatinine at conception of 186 ± 88 μmol/l and reported that the most important predictors of permanent deterioration of renal disease were the combined presence pre-pregnancy of GFR of less than 40 ml/min/m^2 and proteinuria exceeding 1 g/24 hours[42]. The authors concluded that both factors need to be present for a statistically significant increase in risk of long-term renal damage[48].

Severe renal impairment (creatinine >250 μmol/l)

Women with stage 4/5 renal disease often have very stormy and unsuccessful pregnancies, with reported rates of fetal and neonatal loss between 24 and 47%[42,46,49], although one more recent series suggests some improvement in these numbers[48]. Pre-eclampsia occurs in the majority of instances, and in recent published case series of women requiring renal replacement therapy, the mean duration of gestation at delivery was 32–33 weeks[50–53]. As previously mentioned, such women have a high risk of deterioration of renal disease, which is likely to result in a need for renal replacement. The life-style implications of dialysis also need to be explained in detail, together with a discussion of shortened life-expectancy. These issues are important for any individual faced with this life changing event, but particularly so for women contemplating bringing up small children.

It is often assumed that women on dialysis never become pregnant due to the negative effects of significant renal impairment on fertility and libido. Many are oligomenorrheic or amenorrheic, but recent data show that 1 in 200 women of childbearing age on dialysis become pregnant[54]. These women are at greatest risk of pregnancy complications and, as such, are one of the most important groups to need thorough and detailed preconceptional counseling. Pregnancy outcomes for those already established on dialysis are worse than for those who require dialysis as a consequence of pregnancy. It is recommended that hemodialysis frequency be increased to 5–7 times per week, aiming for more than 20 hours in order to achieve more normal biochemistry and avoid marked shifts in intravascular volume. This regimen appears to have been successful in several cases[50,51,55]. One of the adverse effects of hemodialysis is the theoretical removal of progesterone from the dialysate, which may be associated with spontaneous preterm labor. An important consideration for these and many other CKD patients is that the obstetric services and nephrology/dialysis facilities need be on the same site. In an ideal world, there would be close communication between the senior care providers of both services and, if there were large numbers of patients being seen by both services, a bi-weekly joint care conference or regular joint care clinics could facilitate this communication.

The number of pregnant individuals on peritoneal dialysis (PD) is approximately two to three times lower than that of those on hemodialysis[56,57]. This is postulated to be due to the hypertonic peritoneal milieu and volume of fluid in the abdominal cavity having adverse effects on the ovum or its transport down the fallopian tubes[40,58] as well as previous episodes of peritonitis resulting in adhesions and failure of implantation[57]. No robust direct

comparison exists between dialysis modalities in pregnancy; however, babies born to mothers on PD have higher birth weights, and there is less pre-eclampsia, whereas premature labor and peritonitis are more common[58]. However, the majority of women who conceive whilst on PD are often changed to hemodialysis due to perceived issues of volume, inadequate clearance and less experience worldwide upon which to draw.

Women who already require erythrocyte stimulating agents are likely to need larger doses throughout gestation, and some women may develop erythropoietin deficiency during pregnancy due to failure of endogenous synthesis to meet the increased demands.

PROTEINURIA

Proteinuria increases in normal pregnancy due to increased GFR and alteration in renal handling. The upper limit of normal proteinuria is doubled in pregnancy to 300 mg/24 hours or 30 mg/μmol creatinine[59]. Up to 30% of women with CKD without proteinuria pre-pregnancy develop proteinuria during pregnancy[60], and those with pre-existing proteinuria may have a dramatic increase in urinary protein loss reaching nephrotic levels in some cases[14]. Some authors report that the presence of proteinuria in pregnancy is associated with a worse outcome, although this is not a consensus view.

If proteinuria reaches nephrotic range (>3 g/24 hours), with serum albumin <30 g/dl, it is advised by consensus expert opinion that women should be commenced on thromboprophylaxis, due to the theoretical loss of antithrombin in the urine and associated changes in coagulation factors[61]. Dosing of low molecular weight heparin should be prescribed according to the level of renal impairment. Women with pre-pregnancy proteinuria should be warned of this possibility, as the concept of daily injections can sometimes be alarming to unprepared individuals.

HYPERTENSION

Pregnancy is a state of systemic vasodilatation in healthy individuals, but in those with chronic hypertension and/or pre-existing CKD this may worsen, or arise *de novo* requiring multiple antihypertensive agents. Hypertension itself is associated with a worse pregnancy outcome in women with CKD[14,62]. It is noteworthy that the absence of hypertension, almost regardless of renal function, predicts the best outcome. The distinction between progressive hypertension and proteinuria and the development of pre-eclampsia can often be difficult in the presence of CKD, and may require admission for observation. Serial growth scans are often performed in women with moderate/severe renal impairment, which helps guide the obstetrician to make decisions about delivery; however, women need to be forewarned that a degree of uncertainty may occur with this complex clinical problem.

URINARY TRACT INFECTION

During pregnancy urinary tract infections (UTIs) are more common, due to the dilatation of the urinary tract and subsequent urinary stasis. Women with CKD are at particular risk of developing UTIs and appropriate advice regarding symptom detection and screening should be given in preconceptional counseling.

CONSIDERATIONS FOR INDIVIDUAL ETIOLOGIES OF CHRONIC KIDNEY DISEASE

Lupus nephritis

Some women with lupus nephritis may have received cyclophosphamide which can lead to ovarian failure. This may be of concern to those women now wanting to conceive, but the majority can usually be reassured, as the

adverse effects of the drug on fertility are determined by the age of the woman at the time of treatment and the amount of cyclophosphamide received[63,64]. However, exposure to cyclophosphamide can be associated with premature menopause. Hence, whilst as previously mentioned it is important for lupus nephritis to be quiescent for 6 months prior to conception[11], women with prior exposure to cyclophosphamide should be referred promptly to infertility specialists if there are delays in conceiving thereafter. A flare of lupus nephritis may often be difficult to differentiate from the development of pre-eclampsia, but certain clinical and laboratory features, e.g. rising dsDNA, may help to distinguish between the two conditions. At earlier gestations where fetal viability is paramount, a renal biopsy may be needed to inform further treatment decisions. Although biopsy is no less safe than in the non-pregnant state, in the majority, and certainly beyond 24 weeks it can usually be avoided. Women with lupus nephritis tend to have worse pregnancy outcomes than women with the same level of renal impairment with different etiologies[60]. The reason for this finding is unclear, but may be related to the systemic nature of the disease.

Transplantation

Renal transplant recipients form a large proportion of women with CKD who contemplate pregnancy due to the restoration of both fertility and libido with renal function[65]. A period of 1 year after transplantation is recommended, and MMF and sirolimus should be avoided as discussed previously. Women should be reassured that there is no conclusive evidence that pregnancy increases the risk of graft rejection, or causes a deterioration in graft function[7,66–69], other than in those with moderate–severe renal impairment[70]. This group of women may already have experienced renal replacement therapy and are often more reluctant than those at the same stage of renal impairment without renal transplants to pursue pregnancy if they consider their graft to be at risk. Unfortunately, women with excellent graft function and 'normal' GFR still have an increased risk of pre-eclampsia[62,67,68], potentially due to previous endothelial injury or undetectable graft fibrosis. Handling of calcineurin inhibitors alters during pregnancy, and levels need to be monitored closely as women may need an increase of up to 40% of pre-pregnancy doses.

Urinary tract infection is common in the presence of a renal transplant, and women should be advised to seek medical advice at the first suspicion of symptoms. Monthly screening for asymptomatic bacteruria is advised by European Best Practice Guidelines (EPBG) and, for those with recurrent infection, prophylaxis throughout the rest of pregnancy is recommended[8]. Women with renal transplants should be reassured that they can have normal vaginal deliveries and that the allograft will not be damaged by pregnancy or delivery due to its anatomical position.

Reflux nephropathy

Reflux nephropathy is a common cause of renal impairment in women of childbearing age. It complicates pregnancy due to the increased frequency of UTIs, but is not associated with any additional risk of complications with regards to the level of renal impairment. If there is evidence of vesicoureteric reflux in the mother, this should be screened for in the child as soon as possible after birth[71], though some cases may be detected *in utero*.

Adult polycystic kidney disease

In common with women with reflux nephropathy, women with adult polycystic kidney disease (APKD) may also experience more UTIs, as well as bleeding into cysts. It is very

unlikely that the size of the kidneys will preclude pregnancy, and women can often be reassured in this regard. Women with known APKD should be advised of the genetic risk to their offspring (1 in 2). However, few if any women contemplate termination. The situation is more challenging when women present for the first time with APKD during the first trimester of their pregnancy.

CONCLUSION

Women with CKD are a diverse group of individuals with a spectrum of pregnancy outcomes, from those with a minimal increase in risk of pre-eclampsia, to those very unlikely to have a normal pregnancy course. One of the most useful guides to pregnancy outcome is obstetric history, as future pregnancies often mirror previous pregnancies.

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