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Pre-pregnancy counseling for women with chronic kidney disease

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Abstract

Pre-pregnancy counseling should be available for all women with chronic kidney disease (CKD) so that conception occurs at the right time in the course of their disease and while they are on the right medications, with the aims of minimizing risks for both mother and fetus. Key areas to consider are the factors which are associated with worse prognosis and the influence of underlying kidney conditions and their treatment, in particular lupus nephritis, advanced renal impairment and transplantation. This experience-based review provides a guide to clinicians managing women with CKD, before and during their pregnancy.

Key words: *CKD, Lupus nephritis, Pre-pregnancy counseling, Transplant*

Introduction

Chronic kidney disease (CKD) affects 3% of women aged 20-39 years (1); CKD stages 3-5 complicate only 1 in 750 pregnancies (2), but theoretically up to 1 in 30 pregnancies may be complicated by CKD as a consequence of many women now contemplating their first pregnancy later in life and a predicted rise in type 2 diabetes associated with nephropathy (3). Frequently CKD may be diagnosed during pregnancy; however, where possible, pre-pregnancy counseling for women with CKD affords the opportunity to adjust medication, optimize hypertension control, stabilize renal function and educate the woman about possible adverse events which may arise during or as a consequence of her pregnancy (4). All women with CKD are at increased risk of pregnancy complications (5), although many women may be unaware that their condition has any implications for fetal or maternal health. A recent systematic review has suggested that women with CKD have at least at twofold higher risk of developing adverse fetal outcomes compared with women without CKD, and that adverse maternal events were more than fivefold higher (6).

It is impractical for obstetric nephrologists, obstetric physicians or obstetricians to undertake counseling for every woman with CKD; therefore, those with CKD stages 1 and 2 without adverse risk factors can be managed by their general practitioner or primary care physician. Table I lists the clinical situations where pre-pregnancy counseling is essential, and these are the focus of this review.

Although estimations of glomerular filtration rate (GFR; by the Modification of Diet in Renal Disease [MDRD] Study (7) or Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] (8) equations) significantly underestimate true GFR in pregnancy as measured by inulin or 24-hour creatinine clearance, a more accurate assessment of renal function can be made pre-pregnancy, and therefore the newer classification of CKD will be used here.

Pregnancy complications: maternal and fetal

CKD stages 1 and 2

CKD stages 1 and 2 are defined by estimated GFR (eGFR) >60 ml/min per 1.73 m^2 plus urine abnormalities or structural kidney abnormalities, with serum creatinine usually <100 µmol/L. Pregnancy with early CKD generally does not precipitate either a worsening or an accelerated wors-

TABLE I
WOMEN WITH RENAL DISEASE WHO SHOULD BE REFERRED FOR PRE-PREGNANCY COUNSELING

- Women with CKD stage 1-2 and adverse risk factors:
  - ➢ Significant proteinuria
  - ➢ Hypertension
  - ➢ Systemic diseases such as lupus or vasculitis
  - ➢ Previous adverse obstetric history
- Women with CKD stage 3 to 5 including women on dialysis
- Women with renal transplants
- Women with a family history of hereditary renal disease

CKD = chronic kidney disease.

ening of maternal kidney function (9-13), although the risk of preeclampsia (10%-20%) remains greater than that for pregnant women without CKD (5%) (4, 14). Recently successful fetal outcomes have been reported to be as high as 98% (15); however, rates of preterm delivery (11%-40%) and low birth weight (5%-26%) continue to be higher than in healthy controls (4, 6, 16-18), even in those with CKD stage 1 (19), including those with isolated microscopic hematuria (19). A systematic review has demonstrated that complications are seen more frequently in women with the following adverse risk factors (20).

Proteinuria

Some authors report that the presence of proteinuria in pregnancy is associated with a worse outcome (21-23). Up to 30% of women with CKD without proteinuria pre-pregnancy develop significant proteinuria [300 mg/24 hours or 30 mg/μmol creatinine (24)] during pregnancy (25) due to increased GFR and alterations in renal handling. Urinary protein loss may become nephrotic, particularly in those with preexisting proteinuria (25).

Women with pre-pregnancy proteinuria should be warned of the possible requirement for thromboprophylaxis, which is currently advised to be commenced with proteinuria (>3 g/24 hours), and with serum albumin <20 g/dL in non-pregnant women or serum albumin of <25 g/dL in pregnant women, because of theoretical urinary losses of antithrombin and associated changes in coagulation factors (4). Dosing of low-molecular-weight heparin should be prescribed according to the level of renal impairment.

Hypertension

The absence of hypertension, almost regardless of renal function, predicts the best outcome; however, hypertension may worsen or arise de novo in pregnancy and is associated with more complications in women with CKD (18, 26). Women may need to take multiple antihypertensive agents to control their blood pressure.

The distinction between progressive hypertension with proteinuria and preeclampsia may be difficult, and women with CKD should be warned about potential clinical uncertainties which may require admission. Serial growth scans are often performed to help guide decisions about delivery.

Lupus nephritis

Cyclophosphamide is traditionally the first-line agent for active lupus nephritis. Its use has previously been associated with ovarian failure (27). However, it has now been demonstrated that total dose of cyclophosphamide and age >32 are the most important predictors of anovulation (28, 29). Gonadotropin-releasing hormone (GnRH) agonists are occasionally used preemptively for preservation of ovarian function in women undergoing chemotherapy with cyclophosphamide (30). However, given the association with premature menopause, women with prior exposure to cyclophosphamide should be referred promptly to infertility specialists if there are delays in conceiving thereafter.

Women with lupus nephritis tend to have worse pregnancy outcomes than women with systemic lupus erythematosus (SLE) without nephritis (31), and also compared with women with the same level of renal impairment with different etiologies of CKD (20, 25). The reason for this finding is unclear, but may be related to the systemic nature of the disease and is probably independent of class of lupus nephritis (32). A systematic review reported successful pregnancy outcomes in 77%, but rates of lupus nephritis flare (16%), extrarenal flare (26%), preeclampsia (8%), preterm delivery (39%) and intrauterine growth restriction (13%) remain high (32). Preeclampsia often occurs earlier in women with lupus nephritis than in those with SLE without nephritis and is responsible for many iatrogenic preterm deliveries, although spontaneous preterm labor is also frequently seen (31).

Predictors of poor pregnancy outcome in women with lupus nephritis include level of renal impairment, hypertension (31), low complement levels (22) and disease activity at conception (33). Women whose lupus nephritis is quiescent for 6 months prior to conception have better pregnancy outcomes compared with those with active disease (34, 35). A period of 3-6 months following changes in medication is

recommended to enable stabilization and dose adjustment with the new drug.

Renal disease activity appears to be more common postpartum (36), whereas extrarenal disease flare occurs predominantly in the second and third trimesters (37, 38). Woman need to be instructed not to stop their medication once conceiving, as flare is also associated with worse pregnancy outcome. Pregnancy-associated decline in renal function does not appear to be greater than in women with other etiologies of CKD (22, 39). and following renal transplantation, pregnancy outcomes in women with lupus nephritis are reported to be similar to those who had undergone renal transplantation for other reasons (40).

Pulmonary hypertension (defined as a resting pulmonary arterial pressure of >25 mm Hg in the nonpregnant state) is an absolute contraindication to pregnancy and will need to be excluded if there are any features in the history or examination to suggest this. Mortality rate in secondary pulmonary hypertension is 25%-30% (41). Women with lupus nephritis should also be assessed for the presence of anti-Ro and anti-La antibodies due to their associations with congenital heart block and neonatal lupus. Women with SLE and concurrent antiphospholipid antibodies (aPLs) have a higher rate of fetal loss (33, 42), and complications such as fetal growth restriction and preterm delivery have also been reported to occur 3 times more often when aPLs are positive (43). Suggested investigations pre-pregnancy for women with lupus nephritis are listed in Table II.

TABLE II
PRE-PREGNANCY INVESTIGATIONS FOR WOMEN WITH LUPUS NEPHRITIS

Laboratory investigations at baseline (preferably pre-pregnancy)
Full blood count
Urea, creatinine, electrolytes, uric acid
Liver function tests, albumin, coagulation profile
ANA
Anti-dsDNA
Complement 3 and 4
Extractable nuclear antigens (ENA), esp. anti-Ro and Anti-La
Lupus anticoagulant, anticardiolipin and β_2-glycoprotein I antibodies
Urinalysis for casts, protein to creatinine ratio (PCR)
Other essential baseline observations
Blood pressure
Body mass index, nicotine use
Evidence of end-organ damage from SLE (or hypertension)
Other investigations to be considered
Electrocardiogram and/or echocardiogram
Pulmonary function tests

ANA = antinuclear antibodies; SLE = systemic lupus erythematosus.

CKD stages 3 and 4

CKD stages 3 and 4 are defined as eGFR <60 ml/min per 1.73 m^2 and eGFR <30 ml/min per 1.73 m^2, with creatinine usually >100 µmol/L and creatinine >180 µmol/L, respectively. There is a reduction in fertility with increasing severity of renal impairment (44), and fetal loss is greater, with frequent early and late miscarriages (45-49). A useful early guide to the success of an individual pregnancy is the adaptation to increased GFR (50). If creatinine does not fall in the late first / early second trimester it is suggestive of future complications.

Preeclampsia may occur in up to 40%-60% of women with CKD stage 3 or 4 (4, 46, 47), which may be early and severe. Prematurity is common (39%-64%) (4, 45-49), and despite major advances in neonatal care, very preterm infants frequently have sensory impairment and intellectual disability. It is therefore important to highlight in prenatal counseling the association of very preterm delivery with long-term disability. Up to 50% of women have a decline in renal function either during pregnancy or postpartum, and in approximately one third, it is persistent (4, 47) particularly in those with worse baseline renal function. Temporary renal deterioration may require iatrogenic preterm delivery to preserve renal function (51) but with the risk of serious neonatal consequences. Important predictors of permanent deterioration of renal disease in women with CKD stages 3-5 are the combined presence pre-pregnancy of GFR of less than 40 ml/min per 1.73 m^2 and proteinuria exceeding 1 g/24 hours (39).

CKD stage 5

Stage 5 CKD is defined as eGFR <15 ml/min per 1.73 m^2 or being on dialysis. Many women on dialysis are oligomenorrheic or amenorrheic, but up to 1 in 200 women of child-

bearing age on dialysis become pregnant (52). Women with more severe CKD often have complicated and unsuccessful pregnancies, previously reported to have rates of fetal and neonatal loss between 24% and 54% (4, 48, 53, 54); however, more recent series suggest some improvement, including reports of 80%-90% successful pregnancy outcomes in small series of women on dialysis (55-58). Preeclampsia occurs in the majority and is associated with worse outcome (58). Mean gestation at delivery is between 32 and 33 weeks (59-61). Those women not already on dialysis have a high risk of deterioration of renal disease, likely to require renal replacement therapy. The lifestyle implications of dialysis and its associated shortened life expectancy need to be explained in detail, particularly with regards to bringing up small children.

An association between high maternal urea levels and preterm delivery and low birth weight has been described (62); therefore it is recommended that hemodialysis frequency be increased to 5-7 times per week, aiming for more than 20 hours to achieve more normal biochemistry and avoid marked shifts in intravascular volume. This regimen appears to have been successful in several cases (55, 57, 59, 61, 63), with even twin pregnancies being successfully supported (58). 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.

The number of pregnant individuals on peritoneal dialysis (PD) is approximately 2 to 3 times lower than that of those on hemodialysis (64, 65). 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 (44, 66) as well as previous episodes of peritonitis resulting in adhesions and failure of implantation (65). Babies born to mothers on PD have higher birth weights compared with those on hemodialysis, there is less preeclampsia but premature labor and peritonitis are more common (66). The majority of women who conceive while on PD are often changed to hemodialysis due to perceived issues of volume, inadequate clearance and less experience.

Anemia in women on dialysis has been shown to be associated with fetal or neonatal loss and preterm delivery (58, 62). Women who already require erythropoiesis-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.

Transplantation

With the recovery of renal function following renal transplantation, both fertility and libido are restored (67). There is no conclusive evidence that pregnancy increases the risk of graft rejection or causes a deterioration in graft function (68-72), other than in those with moderate to severe renal impairment (73). Unfortunately, women with excellent graft function and "normal" GFR still have an increased risk of preeclampsia (26, 70, 71, 74), potentially due to previous endothelial injury or undetectable graft fibrosis. A recent meta-analysis has highlighted the increased risk of gestational diabetes in pregnant renal transplant recipients, as well as elevated rates of preterm delivery compared with general US population data (74). Again women must be advised not to stop any immunosuppressive agents without medical advice on conception lest they precipitate acute rejection or sensitization.

Urinary tract infection is common with renal transplants, 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, and for those with recurrent infection, prophylaxis throughout the rest of pregnancy is recommended (75).

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, although cesarean section continues to be the most common delivery mode in these women (74).

Hereditary renal disease

Reflux nephropathy

Reflux nephropathy complicates pregnancy due to the increased frequency of urinary tract infections (UTIs). If there is evidence of vesicoureteric reflux in the mother, this should be screened for in the child as soon as possible after birth (76), though some cases may be detected in utero.

Adult polycystic kidney disease

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. Women with known APKD should be advised of the genetic risk to their offspring, although few contemplate termination.

Pregnancy planning

Timing of conception

One of the essential components of pre-pregnancy counseling is a discussion of the timing of conception, the importance of which varies on an individual basis according to patient age, disease etiology and activity. Details for specific disease conditions are shown in Table III.

Medication review

Another valuable component of pre-pregnancy 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.

Immunosuppression

Despite the relative state of immune tolerance consequent to pregnancy, immunosuppression for women with renal transplant or glomerulonephritis should usually be continued. The safety of commonly used agents is reviewed in Table IV.

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers

First trimester exposure to angiotensin-converting enzyme (ACE) inhibitors is associated with a 2.7-fold increase in congenital malformations (84). Abnormalities include cardiovascular, central nervous system and renal defects. With second or third trimester exposure, very significant fetal complications including growth restriction, oligohydramnios, hypocalvaria, renal dysplasia, anuria, renal failure and often fetal death have been reported, and the use of ACE

TABLE III
RECOMMENDED TIMING OF CONCEPTION FOR WOMEN WITH CHRONIC KIDNEY DISEASE (CKD)

Etiology of CKD	Recommended timing of conception	Explanation
Renal transplant	1 year posttransplant (Recommended by European Best Practice Guidelines (75))	• Delay is associated with better pregnancy and renal outcomes (69) • Allows for medication adjustments and to reduce the risk of acute graft rejection
Lupus nephritis	After 6 months of quiescent disease	• Increased disease flare and adverse pregnancy outcomes in those conceiving with active disease (33, 77) • Pregnancy and renal complications shown to be significantly reduced with at least 6 months quiescent disease prior to conception (34)
Diabetes	Adequately controlled blood glucose and blood pressure	• Hyperglycemia adversely affects rates of preterm delivery, cesarean section, still birth, perinatal mortality and congenital abnormality (78, 79) • Poorly controlled hypertension is a predictor of adverse pregnancy outcomes (18)
Woman aged <35 years CKD stage 4-5 with deteriorating renal function	Delay conception until transplantation	• Transplantation is associated with improved pregnancy outcomes
Woman aged >35 years CKD stage 4-5 with deteriorating renal function	Do not delay conception but highlight that pregnancy will be high risk and may result in permanent renal decline requiring renal replacement therapy	• Opportunity for transplantation may not arise until fertility has declined substantially

TABLE IV
SAFETY OF COMMONLY USED IMMUNOSUPPRESSIVE AGENTS FOR CKD IN PREGNANCY (80)

Drug	Transplacental passage	Human teratogenicity	Fetal/neonatal effects	Safe in pregnancy	Safe in breastfeeding
Prednisolone	Limited as most would be metabolized by the placenta	Possible increase in oral clefts	Rare – except at large doses (cataract, adrenal insufficiency and infection)	✓	✓ Breastfeeding is not encouraged if receiving >60 mg prednisolone daily
Azathioprine	✓	✗	Sporadic congenital abnormalities, transient immune alterations in neonates	✓	✓
Mycophenolate mofetil	✓	Hypoplastic nails, shortened fifth fingers, diaphragmatic hernia, microtia (ear deformity), micrognathia, cleft lip and palate, and congenital heart defects (81)	✓	✗ – Stop 3/12 preconception and switch to safer agent Exceptional circumstance: with no other effective agent, continue treatment but counsel about teratogenicity	✗
Tacrolimus	✓	✗	Hyperkalemia and renal impairment	✓ Increased risk of gestational diabetes (82) May need up to 40% increase in pre-pregnancy dose due to increased clearance	Probably possible (83)
Cyclophosphamide	✓ – Animal data	✓	Chromosomal abnormalities and cytopenia	✓ (only after the first trimester and only if there is life-threatening maternal disease)	✗
Cyclosporine	✓	✗	Transient immune alterations	✓ May need up to 40% pre-pregnancy dose due to increased clearance	Probably possible
Sirolimus	Not known	Not reported	None reported (85)	✗ - Stop preconception and switch to a safer agent (until more data regarding safety in pregnancy available)	Probably possible
Intravenous immunoglobulin	✓	✗	None reported	✓	✓
Rituximab	✓ (from 16 weeks of gestation)	Not reported	Yes. Neonatal B cell depletion reported	Limit to severe disease	Inadequate data. However, as these are proteins and will be broken down by the infant's gastrointestinal tract, theoretically it should be safe in breastfeeding

CKD = chronic kidney disease.

TABLE V
APPROACHES TO STOPPING ANGIOTENSIN-CONVERTING ENZYME INHIBITORS / ANGIOTENSIN II RECEPTOR BLOCKERS PRE-PREGNANCY IN WOMEN WITH CHRONIC KIDNEY DISEASE

Reason for ACEI/ARB	Pre-pregnancy strategy
• Blood pressure control with minimal proteinuria	• Switch to alternative antihypertensive safe in pregnancy e.g., nifedipine, amlodipine, doxazosin or labetalol (or methyl-dopa when pregnant)
• Mild/moderate proteinuria controlled by ACEI/ARB	• Stop while trying to conceive, with close monitoring of blood pressure
• Heavy proteinuria	• Discontinue as soon as pregnancy confirmed
• Conception likely to be delayed e.g., older women or • More severe renal impairment or • Diabetic nephropathy	• If irregular menstrual cycle – assess on individual basis

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

inhibitors or angiotensin II receptor blockers (ARB) is contraindicated beyond the first trimester in all women except those with scleroderma where the protection from a renal crisis outweighs the risk to the fetus from the drug (85). Regarding first-trimester exposure, 3 possible approaches are available to women with CKD taking ACE inhibitors / ARBs considering pregnancy, which are shown in Table V.

Aspirin

Low-dose aspirin is reported to reduce the risk of preeclampsia in high-risk individuals by 17% (86) and has specifically been shown to be associated with favorable pregnancy outcomes in women with lupus nephritis (22). Aspirin use (75 mg once daily) should be discussed with all women with CKD considering pregnancy and started preconception, or as early as possible in pregnancy, unless contraindicated.

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 preeclampsia, 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. Women with significant kidney disease and a high risk of pregnancy or kidney-related problems should be counseled pre-pregnancy and followed during pregnancy in specialist centers where high-risk obstetric and renal care are both offered.

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