



## **PREGNANCY PROBLEMS IN CHRONIC KIDNEY DISEASE**

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<b>Article history:</b>	<b>Abstract:</b>
<b>Received:</b> August 20 <sup>th</sup> 2024 <b>Accepted:</b> September 14 <sup>th</sup> 2024	<i>While pregnancy among end-stage kidney disease patients is rare, the number of females becoming pregnant has been increasing worldwide during the last decade. Confirmatory data of this trend are found in the ANZDATA registry (Australian and New-Zealand Dialysis and Transplant registry), which showed an increase in pregnancy rates of women under hemodialysis over the years, from 0.67 per 1000 patients per year between 1986 and 1995 to 3.3 per 1000 between 1996 and 2024. PrThe aim of this review is to summarize the latest guidelines and practice points for ensuring the best outcome for both the fetus and the mother.</i>

**Keywords:** pregnancy, chronic kidney disease, hemodialysis, peritoneal dialysis, transplant, outcome, dialysis

### **INTRODUCTION**

Chronic kidney disease is now widely classified into five stages according to the level of renal function (table 1).w2 Stages 1 and 2 (normal or mild renal impairment with persistent albuminuria) affect up to 3% of women of child bearing age (20-39 years).w3 Stages 3-5 (glomerular filtration rate <60 ml/min) affect around one in 150 women of childbearing age,w3 but because of reduced fertility and an increased rate of early miscarriage, pregnancy in these women is less common. Studies of chronic kidney disease in pregnancy have mostly classified women on the basis of serum creatinine values, but we estimate that around one in 750 pregnancies is complicated by stages 3-5.w4 Some women are found to have chronic kidney disease for the first time during pregnancy. Around 20% of women who develop early pre-eclampsia ( $\leq 30$  weeks' gestation), especially those with heavy proteinuria, have previously unrecognised chronic kidney disease.

Women with chronic kidney disease are less able to make the renal adaptations needed for a healthy pregnancy. Their inability to boost renal hormones often leads to normochromic normocytic anaemia, reduced expansion of plasma volume, and vitamin D deficiency. The gestational rise in glomerular filtration rate is blunted in women with moderate renal impairment and usually absent in those with a serum creatinine higher than 200  $\mu\text{mol/l}$ . If pre-eclampsia develops, maternal renal function often deteriorates further, but the addition of a prerenal insult that will reduce renal blood flow, such as peripartum haemorrhage or regular use of a non-steroidal anti-inflammatory drug, can seriously threaten maternal renal function. In such circumstances,

nephrotoxic drugs must be avoided and maternal circulation restored with careful fluid management, as women with pre-eclampsia are prone to pulmonary oedema. This guidance covers the care of women with CKD (including renal transplant recipients) who are planning a pregnancy, pregnant, or in the post-partum period. It also covers contraception and fertility for women with CKD.

This guideline can be used in the following settings:

- General practice
- Community and hospital antenatal clinics
- Antenatal, labour and postnatal wards
- Renal out-patients
- Renal wards
- Dialysis units

### **LITERATURE REVIEW**

- Medication
- Pre-pregnancy care
  - 3.1. Contraception
  - 3.2. Fertility
  - 3.3. Pre-pregnancy counselling and optimisation for pregnancy
- Pregnancy care
  - 4.1 Assessment of renal function in pregnancy
  - 4.2 Antenatal care
  - 4.3 Pre-eclampsia prophylaxis
  - 4.4 Blood pressure management
  - 4.5 Thromboembolism prophylaxis
  - 4.6 Anaemia
  - 4.7 Bone health
  - 4.8 Renal biopsy
  - 4.9 Peripartum care



#### 4.10 Postnatal care

##### Specific conditions

##### 5.1 Renal transplantation

##### 5.2 Dialysis

##### 5.3 Lupus

##### 5.4 Diabetic nephropathy

##### 5.5 Urinary tract infection (UTI)

##### 5.6 Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT)

Clinical issues that will not be covered are acute kidney injury and renal stone disease. In addition, fertility, contraception, teratogenicity and genetic implications in men with CKD will not be addressed. Women with CKD require specific management during pregnancy. Women on dialysis have both lower fertility rates and a higher rate of unsuccessful or complicated pregnancies due to hypertension, preeclampsia, anemia, miscarriage, polyhydramnios, prematurity and intrauterine growth restriction. Medications such as antihypertensive drugs, aspirin, iron, calcium, and ESA should be prescribed according to the clinical situation. It is important to increase the frequency and duration of HD to a minimum of 20 h per week, ideally higher than 36 h per week, to reduce the risk of preterm birth and small gestational age (SGA). The goal of dialysis intensification is to achieve better clearance of uremic toxins, increase ultrafiltration rate, reduce the risk of high blood pressure and cardiac hypertrophy and improve endothelial function. During pregnancy, kidneys undergo several physiological changes. The glomerular filtration rate increases by 50% in the second trimester, followed by a relative decrease in creatinine clearance in the third trimester. In a meta-analysis, Wiles et al. showed that the upper-normal creatinine levels might be 0.86 mg/dL in the first trimester, 0.81 mg/dL in the second trimester, and 0.87 mg/dL in the third trimester. A serum creatinine level greater than 0.87 may indicate acute kidney injury or undiagnosed chronic kidney disease. In previous years, it was believed that pregnancy might worsen kidney function in patients with underlying CKD. Due to their worsening effects on kidney function, glomerular diseases, especially IgA nephropathy and lupus nephritis, are potential risk factors for negative pregnancy-related outcomes. Considering the link between kidney function and materno-fetal morbidity, in the past women with CKD were usually advised to seek a pregnancy after a renal transplant and having achieved stable kidney function. However, this concept has evolved due to emerging evidence. It has been shown that pregnancy does not have adverse effects on renal function, especially in the early stages of CKD. A meta-analysis found no

significant difference in renal outcomes between pregnant women with stage 1–3 CKD and those without CKD-complicated pregnancy. A retrospective study collected clinical data from 293 pregnant women with CKD stage 3–4 between 2005 and 2016, and found that higher serum creatinine levels and proteinuria were major risk factors for adverse kidney outcomes, but pregnancy itself did not significantly affect renal function decline. Another study analyzed the effects of pregnancy on renal function in 49 patients with stage 3–5 CKD and found that the rate of GFR decline did not significantly change from a baseline taken before pregnancy and a data point after delivery. However, for patients with an eGFR less than 40 mL/min/1.73 m<sup>2</sup> and 24 h proteinuria greater than 1 g, the eGFR was significantly reduced after delivery.

## RESULTS

Infertility in women on dialysis is a common issue with a multifactorial etiopathogenesis. End-stage kidney disease (ESKD) alters the hormonal balance in a woman's body. CKD may cause the lack of estradiol-stimulated luteinizing hormone surge which activates the hypothalamic-pituitary axis, and may also lead to an increase in prolactin levels, causing changes in ovulatory cycles. Low anti-Müllerian hormone concentrations in advanced stages of CKD can be used to predict infertility in CKD women, but more research is needed to establish the link between low anti-Müllerian hormone concentrations and infertility in women with CKD. Additional factors such as decreased libido, body image disturbances, depression, the impact of uremic toxins and pharmacologic side effects from antihypertensive agents or immunosuppressants may play a role in infertility. Ideally, reproductive counseling should begin in the early stages of CKD with frequent re-evaluations during follow-up visits up to the conception period, and continue thereafter. Reproductive counselling should regard the desire of the woman to become or not become pregnant and comprise a discussion on fertility and a possible pregnancy with its related risks, as well as an explanation of contraceptive methods. Factors such as woman's age, medical history and stage of CKD can impact the risks to the mother, the child and the graft. Therefore, individualized counseling and risk assessment are essential for women with CKD who want to conceive.

In a retrospective study conducted in the United States from 2005 to 2013, researchers identified 2352 pregnancies among 47,555 women on dialysis, resulting in a rate of 17.8 events per thousand



person-years—a relatively high rate compared to other studies. Several factors correlated with a higher pregnancy rate, such as younger age. More interestingly, compared to diabetic nephropathy, some specific etiologies of CKD, such as glomerulonephritis, vasculitis, neoplasia, and hypertensive nephropathy, have a higher rate of becoming pregnant.

In a subgroup analysis on women on dialysis, it was seen that women who had a shorter time on HD had a greater chance to get pregnant; time on HD correlated to better residual kidney function, which in turn increases the chances of achieving a successful pregnancy. Giatras et al. showed that only 6 out of 120 women who were under dialysis treatment for 10 years had a successful pregnancy. Additionally, 47% of conceptions occurred in the first years of dialysis, further strengthening this relation. Regarding the dialysis modality, one study revealed that women on peritoneal dialysis (PD) treatment were less likely to get pregnant compared to women on HD. In the largest survey on pregnancy in the ESKD population from the United States, only 1.1% of women with PD got pregnant compared to 2.4% of women with HD. The causes for the lower likelihood of conception in women with PD remain vague, especially since PD treatment has fewer hemodynamic complications and higher preserved residual kidney function rates when compared to HD.

#### Hemodialysis for Pregnancy Maintenance

Hemodialysis is the most commonly employed dialysis modality. In the past, low-flux dialyzers were recommended to prevent rapid changes in osmolarity and the volemic status during pregnancy. It is now possible to achieve better depuration of middle molecules without rapid fluid or electrolyte fluctuations by using a combination of low ultrafiltration, more frequent dialysis, and high-flux membranes. Providing a higher dialytic rhythm (5–6 times per week and/or longer than 36 h per week), adjusted for residual kidney function, can reduce the risk of polyhydramnios, hypertension, small for gestational age (SGA), prematurity, and maternal malnutrition, in addition to increasing the possibility of live birth. In a comparison of data from an intensively dialyzed cohort in Canada (22 patients, mean of 43 h weekly) versus a retrospective cohort of patients in the United States (70 patients, mean of 17 h weekly), the live birth rates were 48% for those dialyzed for less than 20 h weekly and 85% for patients dialyzed for more than 36 h weekly (n = 13). Nocturnal HD is an intensive dialysis modality that has been shown to offer more clinical benefits compared to other modalities. According to Marques et al., ultrafiltration rates of 6–8 mL/kg/h

during HD sessions did not have any serious negative effects on fetal middle cerebral, placental, and umbilical artery blood flow. Although evidence for adjusting renal-replacement therapy to target a specific BUN threshold is not strong, some experts suggest aiming for a BUN target of less than 35 mg/dL (12.5 mmol/L). In pregnant women with residual kidney function, the physician should prescribe the dialytic regimen according to urine output (>1 L), time on dialysis (<1 year), and most importantly mid-week pre-dialysis urea (<35 mg/dL). However, to achieve a successful pregnancy, the physician must evaluate not only biochemical parameters but also obstetric parameters such as fetal growth and amniotic fluid volume. Due to the high intensity of electrolyte exchanges in the HD regimen, it is recommended to use dialysate with potassium 3.00 mmol/L, calcium 1.50 mmol/L, and high bicarbonate (28–32 mmol/L). Frequent dialysis sessions may lead to a decrease in magnesium levels, which is associated with hypertensive disorders of pregnancy and uterine contraction. Therefore, oral supplementation of magnesium may be necessary. Heparin is considered safe for use during dialysis sessions in pregnant women as it does not cross the blood–placenta barrier. It may be difficult to distinguish excess fluid gained between dialysis sessions from weight gain due to pregnancy-associated weight gain throughout the pregnancy. Dry weight is expected to increase by approximately 0.5 kg/week during the second and third trimesters. Ultrafiltration goals should be adjusted according to the patient's clinical situation and blood pressure to avoid hypotension and hypertension episodes. While the effects of hypotension on fetal outcomes may not be as severe as previously thought, the primary focus during dialysis should be to minimize hemodynamic instability. The CHAP study showed that the treatment of mild chronic hypertension resulted in a decrease in adverse pregnancy outcomes. During the gestational period, it is recommended to transition to in-hospital hemodialysis for better multidisciplinary medical surveillance. Yes. Men on dialysis or those who have a kidney transplant can father children. If you've been trying to father a child for a year or more without success, talk with your doctor. A man with kidney disease or kidney failure may be helped with a routine fertility checkup. Also, some medications that are used after a transplant can reduce a man's ability to father children. If you have a transplant and would like to father a child, talk with your doctor about your mediations.



What kind of birth control is recommended for kidney patients?

Dialysis and transplant patients who are sexually active and have not undergone menopause should use birth control to prevent pregnancy. Your healthcare provider can recommend the type of birth control that should be used. Many women who have high blood pressure should not use "the pill" (oral contraceptives) since this type of medicine can raise blood pressure and increase the chance of blood clots. The diaphragm, sponge, and condom are usually acceptable means of birth control, especially when used with spermicidal creams, foams or jellies. The newer IUD is also possible.

### **CONCLUSION**

Some changes in your body make it hard to become pregnant. For example, most women on dialysis have anemia (a low red blood cell count) and hormone changes. This may keep them from having regular menstrual periods. Women with kidney failure are usually advised against becoming pregnant. The rate of complications is very high. Risks to both the mother and developing baby are high. If you are thinking of becoming pregnant, talk to your healthcare provider. If you become pregnant, you will need close medical supervision, changes in medicine, and more dialysis to have a healthy baby.

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