# Menopause and Chronic Kidney Disease

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**Summary:** Premature menopause defined as secondary amenorrhea is common in women with kidney disease. Moreover, the aging population has resulted in increasing numbers of postmenopausal women with kidney disease. Though the pathophysiology is poorly understood, kidney transplantation and more frequent hemodialysis can restore menses and fertility, highlighting the challenges of diagnosing and managing the menopausal transition in the female population with kidney disease. Postmenopausal sex hormone levels affect renovascular physiology, but the clinical impact of menopause on kidney function is unclear. There are no guidelines on the use of postmenopausal hormone therapy specific to the population with kidney disease, and studies on the effects of postmenopausal hormone therapy in patients with kidney disease are limited to surrogate measures of cardiovascular and fracture risk. Studies examining the effects of postmenopausal hormone therapy on kidney function and albuminuria report conflicting results, which is likely reflective of differences in formulation, route of administration, accompanying progestin, and timing of initiation of treatment. Large, prospective studies examining the relationship between kidney function and menopause as well as the effects of postmenopausal hormone therapy on important clinical outcomes in women with kidney disease are warranted.

Semin Nephrol 37:404-411 

***Keywords:*** Amenorrhea, chronic kidney disease, end-stage kidney disease, estrogen, menopause, postmenopausal hormone therapy

Menstrual disorders, infertility, and early menopause are common in women with chronic kidney disease (CKD), an issue that may be under-recognized by the nephrology community.[1] With the increasing global prevalence of CKD coupled with an aging population,[2] managing this important transition period in a woman's life to optimize kidney health and other important clinical outcomes remains a challenge for nephrologists and other health care providers.

## AGE OF MENOPAUSE IN CKD

Using the Stages of Reproductive Aging Workshop +10 definition of menopause (absence of menses for 12 months),[3] it would appear that the onset of secondary cessation of menses occurs significantly earlier in the population with CKD or at least end-stage kidney disease (ESKD), as no studies have examined the nondialysis population. The average age of menopause in the general population is between 51 and 52 years of age[4]; in contrast, the mean age of menopause in the ESKD population is almost 5 years earlier.[5,6] Primary ovarian insufficiency (POI), defined as cessation of menses prior to 40 years of age, is more common in women with CKD. In 2 studies of premenopausal women with ESKD, 3.9%[7] and 20%[1] reported POI whereas the prevalence of POI in the general population is estimated at only 1%.[8] Though the use of cyclophosphamide is associated with POI,[9] the increased prevalence of POI appears to be independent of exposure to this therapy, suggesting that the presence of decreased kidney function plays an important role.

## DIAGNOSIS OF MENOPAUSE IN CKD

There are significant challenges associated with the diagnosis of menopause in the female population with CKD. First and foremost, the onset of menopause in the "traditional" sense marks a woman's permanent reproductive and ovarian senescence. However, in the case of the patient with CKD, the absence of menses and loss of fertility can be completely reversible with kidney transplantation[10] or more frequent hemodialysis,[11] highlighting that conventional definitions of menopause do not always apply in the nephrology patient population. The Stages of Reproductive Aging Workshop +10 guidelines[3] from the North American Menopause Society emphasize that menstrual cycle criteria remain the most important criteria in the diagnosis of menopause and that biochemical markers be considered only supportive secondary criteria, particularly in light of the lack of standardization of assays.

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*Financial support: Dr. Ahmed is supported by Alberta Innovates: Health Solutions and a joint initiative between Alberta Health and Wellness and the Universities of Calgary and Alberta.*

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*0270-9295/ - see front matter*

*http://dx.doi.org/10.1016/j.semnephrol.2017.05.013*

However, how these guidelines may apply to the woman with CKD is unclear, as multiple factors appear to influence menses in this population and studies in this area are limited. In one of the earliest studies of menstruation in the hemodialysis population, only 1 of 17 premenopausal-aged women reported regular menses and 10 women were amenorrheic.[12] In a prospective single-center gynecology study of women with ESKD (including a functioning kidney transplant), 7 of 35 menopausal women developed secondary amenorrhea prior to 40 years of age.[1] In a survey of 76 women under 55 years of age (average age 41.7 ± 11 years at the time of the survey) with ESKD treated with either hemodialysis (68%) or peritoneal dialysis (32%), only 63% reported menstruating at dialysis initiation. This proportion decreased to 42% after 4.5 ± 4.2 years on dialysis with the median age of menopause reported as 47 years.[5] Data from 238 women from the HELP (Hemodialysis and Estrogen Levels in Postmenopausal) patients study revealed a median age of menopause of 48 years.[6] More recently and highlighting the difficulty associated with ascertaining menopausal status based on menstrual history, a prospective study of 129 premenopausal-age women with ESKD reported that 43.1% were amenorrheic at dialysis initiation, a number that decreased to 23.1% after kidney transplantation.[7] Similarly, although 41.7% of premenopausal age women reported no menstruation pre–kidney transplant, only 15.5% had no menses post-transplantation.[13]

Of note, the increased use of recombinant human erythropoietin has been associated with a decrease in frequency of reported amenorrhea in women with ESKD on dialysis.[5] Furthermore, the dialysis treatment prescription appears to influence menstrual status. A 6 month prospective study examined the effects of switching from conventional home hemodialysis to nocturnal home hemodialysis in 7 women.[14] At baseline 6 women were postmenopausal or amenorrheic and 1 woman had irregular menstrual cycles; at the end of the study, a nonsignificant increase in estradiol levels was observed and 2 of the 3 women less than 40 years of age had resumed normal menstrual patterns.[14] Studies of female kidney transplant recipients have shown improvement in prolactin, testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), and return of regular menstrual cycling by 6 months following transplantation, though hypothalamic–pituitary–gonadal (HPG) axis abnormalities remain.[15] These investigations highlight the challenges of diagnosing menopause using the conventional definition of absence of menses as is commonly used in the general population.

## PATHOPHYSIOLOGY OF MENOPAUSE IN CKD

The pathophysiology of functional menopause in the CKD population is largely derived from the ESKD population, though even study in this group is limited. The general consensus is that as kidney function declines, there is a proportional increase in HPG axis dysfunction, ultimately leading to loss of menses, infertility, and functional menopause. Although women with CKD may have comorbidities and characteristics that may independently affect ovarian function, such as diabetes,[16,17] systemic lupus erythematosus,[18–20] exposure to cyclosphosphamide,[9] and smoking,[21] the presence of kidney disease itself also appears to play a role.

How kidney disease adversely affects HPG axis function is not entirely clear, but there are a number of hormonal alterations (Fig. 1). The cyclic release of gonadotropin-releasing hormone is reduced in CKD, leading to the loss of pulsatility in LH and FSH release and ultimately decreased estradiol secretion and anovulation. Hyperprolactinemia in CKD is common[22] and is the result of both increased pituitary production due to a resistance to the inhibitory effects of dopamine as well as decreased renal excretion.[23] Increased levels of prolactin result in a decrease in normal cyclic gonadotropin-releasing hormone secretion, which ultimately results in the loss of pulsatile release of LH and FSH, thereby leading to a decrease in estrogen release, the clinical implications being irregular menses, infertility, and functional menopause. However, other factors likely play a role. In a study of 3 premenopausal-aged women with ESKD on hemodialysis with hyperprolactinemia, treatment with the dopamine agonist bromocriptine-reduced prolactin levels, but did not have a consistent effect on gonadotropin hormone responses.[12]

## SEX HORMONE LEVELS IN WOMEN WITH CKD

In the premenopausal-age ESKD population, sex hormone levels do not follow the variation of the normal menstrual cycle. One of the earliest investigations examined 17 premenopausal- and 7 postmenopausal-aged

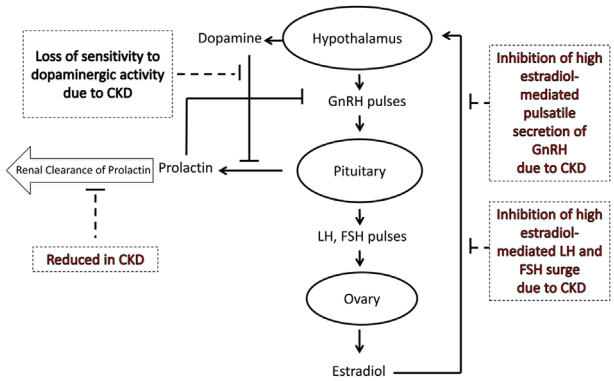


**Figure 1.** The hypothalamic–pituitary–gonadal axis in women with kidney disease. CKD, chronic kidney disease; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.