Fertility, Contraception, and Novel Reproductive Technologies in Chronic Kidney Disease

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Summary: Chronic kidney disease (CKD) affects hypothalamic-pituitary-gonadal axis function, leading to menstrual abnormalities, sexual dysfunction, functional menopause, and loss of fertility. Pregnancy in a patient with CKD is associated with a higher risk of complications to both the mother and the fetus, highlighting the importance of contraceptive counseling at all stages of CKD. There has been limited research on the safety and efficacy of different contraceptive methods in the CKD population, and it is important to tailor the choice of contraception to the patient's lifestyle and comorbidity status. Cyclophosphamide is a commonly used immunosuppressive agent that impairs fertility in a dose-dependent fashion, with greater impact in older women of child-bearing age. Strategies to reduce the impact of cyclophosphamide on ovarian reserve as well as fertility preservation technologies are options to consider when treating immune-mediated CKD. A multidisciplinary approach in counseling the woman with CKD who wishes to contemplate or avoid pregnancy is necessary to optimize outcomes. Further research in this important area is required.
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Multiple factors contribute to infertility in women with chronic kidney disease (CKD) and end-stage kidney disease (ESKD), including sexual dysfunction, hormonal alterations, and treatments such as immunosuppression and dialysis.[1] Much of our understanding of these complex issues relies on studies from the 1980s and early 1990s, which are reviewed here with the hope that future investigations will better illuminate these CKD-associated abnormalities.

SEXUAL AND MENSTRUAL DYSFUNCTION

Premenopausal women with CKD commonly experience sexual and menstrual dysfunction and anovulation. Sexual dysfunction is manifested by increased incidences of sexual inactivity and interest, orgasmic impairment, failure of vaginal lubrication, vaginismus or dyspareunia, and infertility. As measured by self-report, 30% to 89% of women on dialysis experience sexual dysfunction.[2–5] The female sexual function index, a self-reported, validated, 19-item scale measures sexual function during the previous 4 weeks and can be used to assess sexual dysfunction in women on dialysis. The presence of comorbid conditions (diabetes mellitus, hypertension), lower educational status, age and menopausal status, and diuretic therapy increase the risk of sexual dysfunction.[3] Despite the frequency of sexual dysfunction in women with CKD, only 19% report dissatisfaction with their sexual lives.[5] Thus, although sexual dysfunction in women with CKD is common, it must be put into context of a life lived with CKD and its effects on quality of life and functioning; the importance of sexual dysfunction to women on dialysis likely is outweighed by other effects of ESKD and dialysis on the quality of their lives.[6]

Menstrual disorders also are more common in women with CKD and ESKD and may have more effects on their lives than sexual dysfunction. Dysfunctional uterine bleeding, including menorrhagia and amenorrhea, occurs in most women on dialysis,[7,8] and is associated with abnormal endometrial morphology.[9] Anemic and iron-deficient premenopausal women on dialysis should be questioned about menorrhagia. Functional menopause occurs earlier in women on dialysis.[8,10] Although increased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels occur, the levels are not as high as in healthy menopausal women, leading most to consider early menopause in women on dialysis a state of functional and not true menopause.[11,12] Figure 1 shows the usual hormone levels in women with CKD. Because of the hormonal alterations occurring in women on dialysis, infertility is common and pregnancy is unlikely in women on standard hemodialysis and peritoneal dialysis.

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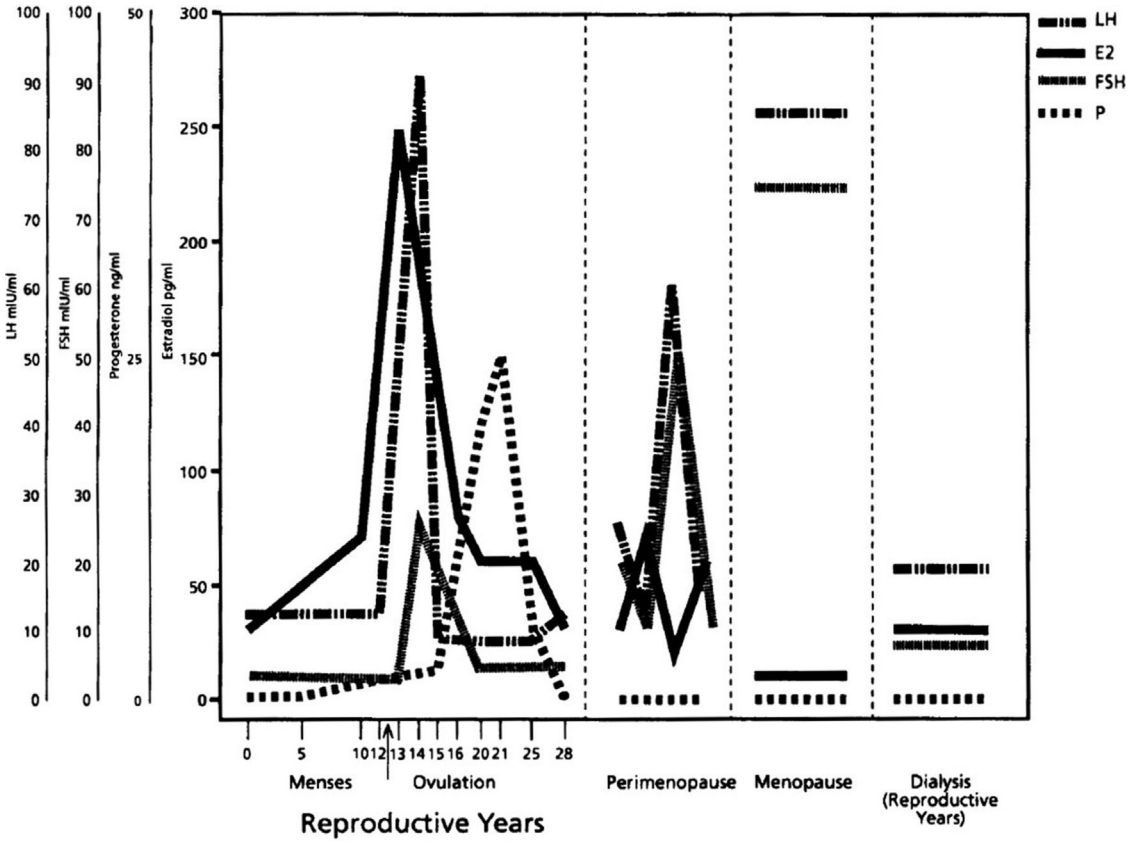

Figure 1. The gonadotropin, estradiol, and progesterone levels throughout life and on dialysis in premenopausal women.[11] E2, estradiol; P, progesterone. Reprinted with permission from Ginsberg and Owen.[11]

HORMONAL ALTERATIONS

Figure 2 shows the hormonal alterations occurring in women on dialysis. Deficient estradiol leads to a lack of LH surge that is required for normal ovulation.[12,13] In addition, loss of the normal cyclic or pulsatile release of gonadotropin releasing hormones (GnRH) from the hypothalamus results in a loss of normal pulsatile gonadotropin (LH and FSH) release by the pituitary gland, leading to impaired ovulation. The absence of pulsatile LH and FSH causes low estradiol and an ensuing lack of progestational changes in the endometrium. This results in irregular menses, anovulation, amenorrhea, and infertility. The contribution of hyperprolactinemia (caused by reduced clearance with CKD and also increased production) to abnormal hypothalamic function and subsequent anovulation is incompletely understood.[14] Table 1 summarizes the effects of CKD on menstrual and reproductive function.

EFFECTS OF RENAL REPLACEMENT THERAPY

Similarly, the direct effects of dialysis modality on fertility in women with ESKD are not well understood. For unclear reasons, women on hemodialysis are two to three times more likely to conceive than women on peritoneal dialysis.[15] Although rare, women on standard hemodialysis three times per week can conceive with a reported pregnancy incidence of 1% to 7%.[15] Interestingly, pregnancy in women on nocturnal hemodialysis is significantly more common, occurring in 15.6% of 45 premenopausal women.[16] The reason for the increased likelihood of conception in these

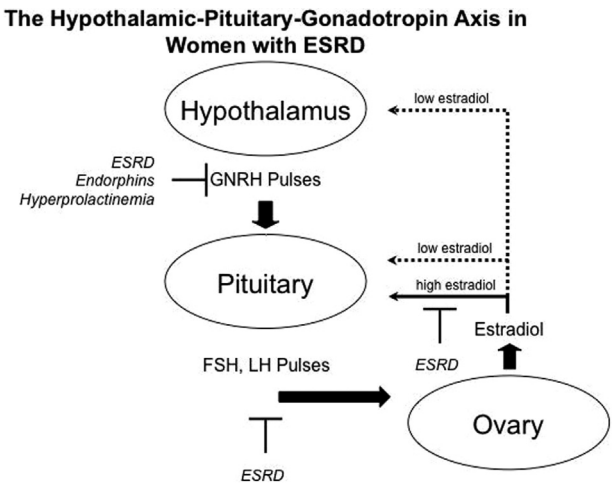

Figure 2. The hypothalamic-pituitary-gonadotropin axis in women with end-stage renal disease. Dotted lines represent inhibition, solid lines represent stimulation. Bars show negative effect. ESRD, end-stage renal disease. Adapted with permission from Holley.[13]