Reproductive Health and Contraception in Females with Chronic Kidney Disease

Chang, Danica


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Abstract

**Background:** Chronic kidney disease (CKD) is a global epidemic that affects >13% of the population worldwide. Abnormal uterine bleeding is common in CKD, but most studies are limited to the kidney failure population. Abnormal menstruation is associated with cardiovascular risk, despite CKD already being a risk factor for cardiovascular disease. Pregnancy is known to be risky in CKD, therefore, contraception is paramount to prevent unplanned pregnancies in this reproductive-aged population; however, existing literature, though limited to the dialysis and transplant populations, has found that contraceptive use is low.

**Objectives:** Using two separate yet complementary studies, we had multiple objectives. Project 1 aimed to describe self-assessed menstruation and contraceptive use among females across all stages of CKD using a global online survey. Project 2 aimed to (1) describe menstruation and changes in menstrual patterns with CKD progression, and (2) assess associations between reproductive hormones and menstrual patterns among females with kidney failure.

**Methods:** In Project 1, females aged 18-50 years with a CKD diagnosis were invited to participate in an online survey. The survey was disseminated globally through 112 kidney organizations, patient groups, and social media. Whereas, in Project 2, females aged 18-50 years were recruited from dialysis clinics around Calgary, Alberta and completed a self-administered survey to capture demographic, kidney health, and menstrual health histories. Blood samples were also collected to measure the following reproductive hormone levels: follicle-stimulating hormone, luteinizing hormone, estradiol, progesterone, testosterone, prolactin, sex hormone binding globulin, and anti-Müllerian hormone.

**Results:** Project 1 included 98 participants [n=20 dialysis (age 35±1 years), n=59 non-dialysis (age 32±1 years), n=19 transplant (age 35±2 years)]. One participant each in the dialysis and
non-dialysis groups experienced primary amenorrhea, though more reported secondary amenorrhea (n=5 dialysis, n=9 non-dialysis, n=5 transplant). Of those experiencing current menses (n=14 dialysis, n=49 non-dialysis, n=14 transplant), 86%, 94%, and 100% of the dialysis, non-dialysis, and transplant groups reported heavy menstrual bleeding. Regarding, contraception, 50%, 63%, and 37% of dialysis, non-dialysis, and transplant participants reported no use, though among users, male condoms were notably popular in the dialysis (33%) and non-dialysis (48%) groups. Project 2 comprised of 27 females [n=23 hemodialysis (age 36 (IQR: 31,44) years), n=4 peritoneal dialysis (age 38 (IQR: 30,45) years)]. In the hemodialysis group, 52% reported absent menstrual bleeding during dialysis, though only 17% reported this during CKD and 9% before CKD diagnosis (p=0.01); however, there was no difference in proportions across timepoints in the peritoneal dialysis group. Further, in both groups, the prevalence of heavy menstrual bleeding was high, but did not differ throughout the progression of CKD. All the relevant hormone levels did not differ between those with absent and present menstrual bleeding, nor in those with heavy and normal menstrual bleeding.

**Conclusions:** Together, these projects suggest that among the female CKD population, the prevalence of abnormal menstruation is high and contraception use is low, underscoring an important gap in the sex-specific care of this population. Given the lack of associations between hormone levels and menstrual status, we highlight the uncertainty around how kidney disease affects female reproductive health.
Preface

Chapter 1 of this thesis has been published as D.H. Chang, S.M. Dumanski, and S.B. Ahmed, “Female Reproductive and Gynecologic Considerations in Chronic Kidney Disease: Adolescence and Young Adulthood”. Kidney International Reports, vol. 7, issue 2, https://doi.org/10.1016/j.ekir.2021.11.003. © 2021 International Society of Nephrology. Published by Elsevier Inc. Licensed under the CC BY-NC-ND 4.0 license (http://creativecommons.org/licenses/by-nc-nd/4.0/). https://www.sciencedirect.com/science/article/pii/S2468024921015096. Permission to use this publication is shown in the following page.

The remaining portions of this thesis consist of original, unpublished, independent work by the author, D. Chang. The study conducted in Chapter 2 was covered by Ethics Certificate number REB21-0326, issued by the University of Calgary Conjoint Health Research Ethics Board for the project “International Online Survey of Uterine Bleeding and Contraception in Female Patients with Chronic Kidney Disease” on May 13, 2021. The study reported in Chapter 3 was covered by Ethics Certificate number REB19-0822, issued by the University of Calgary Conjoint Health Research Ethics Board for the project “Sexual Function and Activity in Young Women with End Stage Kidney Disease” on June 26, 2019.
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I respectfully acknowledge that the University of Calgary is located on the traditional territories of the people of the Treaty 7 region in Southern Alberta, which includes the Blackfoot Confederacy (comprising the Siksika, Piikani, and Kainai First Nations), the Tsuut'ina First Nation, and the Stoney Nakoda (including the Chiniki, Bearspaw, and Wesley First Nations). The City of Calgary is also home to Métis Nation of Alberta, Region 3.

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for me since the start and continued to show their unwavering support through the many ups and downs over the past two years.
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<td>&lt;</td>
<td>Less Than</td>
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<td>Greater Than</td>
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<td>≥</td>
<td>Greater Than or Equal To</td>
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<td>Margin of Error</td>
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<td>Percentage</td>
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<td>5D</td>
<td>Stage 5 Dialysis</td>
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<td>AKI</td>
<td>Acute Kidney Injury</td>
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<td>AMH</td>
<td>Anti-Müllerian Hormone</td>
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<td>Congenital Anomalies of the Kidney and Urinary Tract</td>
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<td>CVC</td>
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<td>CVD</td>
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<td>ESA</td>
<td>Erythropoietin Stimulating Agent</td>
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<td>FSGS</td>
<td>Focal Segmental Glomerulosclerosis</td>
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<tr>
<td>FSH</td>
<td>Follicle-Stimulating Hormone</td>
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<td>GnRH</td>
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HD     Hemodialysis
HMB    Heavy Menstrual Bleeding
HPV    Human Papillomavirus
HRT    Hormone Replacement Therapy
HTN    Hypertension
ID     Identity
IgA    Immunoglobulin A
IQR    Interquartile Range
IU     International Unit
IUD    Intrauterine Device
L      Liter
LH     Luteinizing Hormone
µg     Microgram
mL     Milliliter
N/A    Not Applicable
nmol   Nanomole
OCP    Oral Contraceptive Pill
PCOS   Polycystic Ovary Syndrome
PD     Peritoneal Dialysis
PDC    Peritoneal Dialysis Catheter
PKD    Polycystic Kidney Disease
pmol   Picomole
POI    Primary Ovarian Insufficiency
<table>
<thead>
<tr>
<th>Acronym</th>
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<tr>
<td>POP</td>
<td>Progestin-Only Pill</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<td>SEM</td>
<td>Standard Error of the Mean</td>
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<td>SHBG</td>
<td>Sex Hormone Binding Globulin</td>
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<td>SLE</td>
<td>Systemic Lupus Erythematosus</td>
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<td>Sexually Transmitted Infection</td>
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Chapter 1: Manuscript – Female Reproductive and Gynecologic Considerations in Chronic Kidney Disease: Adolescence and Young Adulthood

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1.1 Abstract

Chronic kidney disease (CKD) increasingly affects younger people, including adolescents and young adults. CKD among females is accompanied by unique reproductive and gynecologic health concerns, though to date, this area has not been well studied. Hormonal disruptions attributed to CKD may underlie the high prevalence of abnormal uterine bleeding and influence the age of menarche in adolescents. Period poverty as a socioeconomic barrier further exacerbates the female-specific burdens of CKD. Reduced fertility in CKD is likely multifactorial and may be related to a reduction in ovarian reserve, reproductive hormone disturbances, and gonadotoxic medication use in addition to low sexual function and activity. Fertility, sexual function and activity, and risk of sexually transmitted infections increase with transplantation. Pregnancy is possible at any stage of CKD, although often accompanied by high risks of maternal and fetal complications. Contraception is thus an important consideration in CKD, but use is low and the risks and benefits of different forms in the setting of CKD are not well characterized. Though patients with CKD report reproductive health as an important
element of care, many nephrologists report lack of confidence and training in this area, highlighting the need for targeted research and education. The unique reproductive health care needs of the growing transgender youth population warrant attention in nephrology training with multidisciplinary input. This review will discuss female reproductive health and gynecologic considerations in adolescents and young adults with CKD while proposing clinical and research strategies to improve this understudied yet important aspect of kidney care.

1.2 Introduction

The prevalence of CKD in children is steadily increasing, with a higher incidence of kidney replacement therapy in adolescents compared with other age groups worldwide. Although the most common causes of kidney disease at a global level are hypertension and diabetes, childhood onset of kidney disease is most frequently due to congenital abnormalities and hereditary disorders. The reduced rate of congenital abnormalities of the kidney and urinary tract among females may help to explain the lower incidence of CKD compared with males in the adolescent population. Furthermore, compared with the adult population, glomerulonephritides are a more common cause of CKD in children, particularly in the adolescent population after puberty.

CKD in the female population is often accompanied by abnormal uterine bleeding, sexual dysfunction, reduced fertility, and higher risk pregnancies. Commonly used immunosuppressive medications (e.g., cyclophosphamide, mycophenolate mofetil) for autoimmune glomerular disorders, which disproportionately affect females, have important implications for uterine bleeding, fertility, and the potential for fetal malformations. According
to the North American Pediatric Renal Trials and Collaborative Studies database, adolescents represent the largest group of pediatric kidney transplant recipients.\textsuperscript{12} Although CKD is associated with increased abnormal uterine bleeding,\textsuperscript{13-15} kidney transplantation, at least in the adult population, may restore uterine bleeding.\textsuperscript{15,16} Kidney transplantation guidelines\textsuperscript{17,18} discourage pregnancy in females for the first year post-transplant owing to risk of allograft rejection and pregnancy complications. Finally, pregnancy itself can have a detrimental and permanent impact on kidney function.\textsuperscript{19,20} Taken together, these multiple factors underscore the critical value of providing reproductive care to all females living with CKD, including adolescents who require individualized care during this phase of physiological and social transition. This narrative review will broadly summarize female reproductive and gynecologic considerations in the care of the adolescent and young adult populations with CKD.

\subsection*{1.3 Methods}

For the purpose of providing a summary on female reproductive and gynecologic health among adolescents with CKD, the first author (DHC) searched two electronic sources, MEDLINE and Google Scholar. The terms “reproductive health” or “gynecology” in combination with “chronic kidney disease”, “chronic renal insufficiency”, “end-stage kidney disease”, “chronic renal failure”, “dialysis”, “transplant”, and “nephrology” and other related terms helped identify relevant literature. The terms “contraception”, “menstruation”, “sexual dysfunction”, and “adolescent” in combination with the same Medical Subject Headings were also searched in MEDLINE. These searches were completed by May 2021. Reference lists from relevant articles were hand-searched, and the search was further supplemented by key articles from nephrologists with expertise in women’s health (SBA and SMD). Priority for inclusion in this review was
given to original articles reporting original data (i.e., observational studies as randomized control trials were lacking), clinical practice guidelines, and systematic reviews.

1.4 Kidney Disease and the Menstrual Cycle

The menstrual cycle encompasses the time between the first day of uterine bleeding to the next first day of uterine bleeding\textsuperscript{21} and a healthy menstrual cycle lasts 24-38 days with bleeding occurring for \( \leq 8 \) days (on average, 5 days).\textsuperscript{22} Details regarding the healthy menstrual cycle are outlined elsewhere.\textsuperscript{21,23}

In CKD, disruption of the hypothalamic-pituitary-ovarian axis results in an abnormal reproductive hormone profile, where the degree of disruption increases with CKD progression (Figure 1).\textsuperscript{13,14,24} As such, those with kidney failure are believed to have the most severe hormonal disruptions, and most studies have been conducted in this population.\textsuperscript{13,24} In kidney failure, the pulsatile release of gonadotropin-releasing hormone is impaired, resulting in a lack of follicle-stimulating hormone and luteinizing hormone cyclicity.\textsuperscript{13} Consequently, estradiol levels stay relatively low, inhibiting the surge and ovulation of the luteinizing hormone. Elevated prolactin levels owing to reduced clearance and increased production also contribute to anovulation.\textsuperscript{13,24,25} A possible mechanism of hormonal abnormalities in kidney failure is that high prolactin levels negatively feed back into the hypothalamic-pituitary-ovarian axis and inhibit gonadotropin-releasing hormone secretion, thus preventing gonadotropin release and resulting in abnormal uterine bleeding.\textsuperscript{26-28} In a prospective study of 57 female adolescents with stage 4 CKD and kidney failure treated with hemodialysis and peritoneal dialysis, 49% had
hyperprolactinemia.\textsuperscript{29} When comparing participants with and without menstrual disturbances, prolactin levels were higher in those with menstrual disturbances.\textsuperscript{29}

1.5 Kidney Disease and Age of Menarche

Menarche is the first occurrence of uterine bleeding and the beginning of the female reproductive lifespan. Among healthy adolescents, the median age of menarche is approximately 12-13 years.\textsuperscript{30,31} Multiple factors are associated with the onset of menarche in the general population. An inverse association between body mass index,\textsuperscript{32-34} height, and weight\textsuperscript{35} with age of menarche has been found. Earlier menarche is reported amongst those living with anyone other than a family consisting of 2 biological parents,\textsuperscript{33,36-38} though study results vary regarding the impact of low socioeconomic status on early\textsuperscript{36,38,39} and late\textsuperscript{33} onset of menarche. Urban residence and Black race/ethnicity have been associated with earlier menarche, although these differences may or may not be in part attributed to socioeconomic status.\textsuperscript{33,34,38,40} Increasing reports reveal associations between both early and late menarche and adverse health outcomes, including risk of cardiovascular disease, CKD, and overall mortality.\textsuperscript{41-43}

Given the multiple factors associated with onset of menarche, it is challenging to elucidate the association, if any, between CKD and onset of uterine bleeding. In a prospective cohort study of 57 female adolescents with stage 4 CKD and kidney failure treated with hemodialysis and peritoneal dialysis, Serret-Montaya et al\textsuperscript{29} reported a median age of menarche of 12 years after exclusion of participants with primary amenorrhea. The primary causes of CKD were glomerulonephritis (22.8\%) and congenital abnormalities of the kidney and urinary tract (22.8\%), and most participants had a healthy nutritional status. Although the median age of
menarche was similar in those with and without abnormal uterine bleeding, information including estimated glomerular filtration rate, ethnicity, and socioeconomic status was not reported. In a cross-sectional study of 287 girls with CKD onset before menarche, the median age of menarche was 12 years, though 10% had delayed menarche (defined as menarche at ≥15 years) which was associated with African-American race, lower estimated glomerular filtration rate, corticosteroid use, and longer CKD duration, concluding delayed menarche may suggest a risk of short stature.  

From the perspective of nephrologists, being aware of age of menarche is an important consideration as the American Academy of Pediatrics has suggested that the menstrual cycle is a vital sign in female patients. Nevertheless, in a study of 75 nephrologists (95% pediatric, 5% adult) practicing in the United States and Puerto Rico, Vasylyeva et al reported that 17% never/rarely documented the age of menarche of adolescent patients and more than a third never/rarely documented the date of the patient’s last menstrual period. This discrepancy highlights the need for nephrologists to take comprehensive menstrual histories, including age of menarche, to consider this sex-specific factor in the care of adolescents living with kidney disease.

### 1.6 Kidney Disease and Abnormal Uterine Bleeding

Abnormal uterine bleeding is defined as any disruption of a healthy menstrual cycle in terms of the volume of blood loss, duration, frequency, and regularity of menses. Abnormal uterine bleeding, particularly irregular or long (≥40 days) menstrual cycles, has been associated with premature mortality in comparison to regular or short cycles in the general population.
Abnormal uterine bleeding is also associated with absenteeism in school and work.\textsuperscript{47-49} In the general population of reproductive-aged women, the estimated prevalence of abnormal uterine bleeding is at least 10\% to 30\%,\textsuperscript{50} whereas heavy menstrual bleeding affects 30\% of women throughout their reproductive lifespan.\textsuperscript{51} Heavy menstrual bleeding is defined as the loss of $\geq 80$ mL of blood on each menstrual cycle, which is clinically indicated by 1 or more of the following factors: bleeding that lasts $>7$ days, bleeding that soaks through $\geq 1$ menstrual products every hour for several hours, bleeding that requires simultaneous use of multiple menstrual products to manage flow, bleeding that requires a change of menstrual product during the night, or the presence of blood clots at least the size of a quarter.\textsuperscript{52,53} Abnormal duration of menses includes prolonged ($>8$ days) and shortened ($<3$ days) uterine bleeding, whereas abnormal frequency of menses includes infrequent ($>38$ days apart) and frequent ($<24$ days apart) uterine bleeding.\textsuperscript{22} Absent uterine bleeding is defined by an absence of menses for 90 days and irregular uterine bleeding is defined by variation in cycle length by $\geq 10$ days.

Among adolescents in the general population, the prevalence of heavy, infrequent, and absent menstrual bleeding is reported as 34\%, 20\%, and 8\%, respectively.\textsuperscript{54} Nevertheless, information on abnormal uterine bleeding is sparse in the adolescent CKD population. A prospective cohort study found that $>50\%$ of adolescent girls with stage 4 CKD and kidney failure treated with dialysis reported abnormal uterine bleeding.\textsuperscript{29} Moreover, although 54\% reported regular menstrual cycles at baseline, only 47\% reported regular menses a year after. Nevertheless, in premenopausal adult female populations with CKD, the prevalence of abnormal uterine bleeding is high and becomes increasingly common with disease progression.\textsuperscript{13,14,24} In a small study of 17 women aged 18-42 years with kidney failure treated with hemodialysis, only 1 woman reported
regular uterine bleeding, whereas 6 reported irregular uterine bleeding and 10 had absent uterine bleeding. In a cross-sectional study of women <55 years of age with kidney failure treated with hemodialysis and peritoneal dialysis, 58% reported absence of uterine bleeding. Furthermore, most of the menstruating women experienced irregular uterine bleeding, which was most often heavy menstrual bleeding. Abnormal uterine bleeding, especially heavy menstrual bleeding, is an important consideration in the CKD population, as potential implications include worsening anemia, increasing the need for erythropoietin stimulating agents, and blood transfusions. This may be especially relevant for those in need of a kidney transplant, given the risk of sensitization. In a retrospective cohort study of 129 women with kidney failure (aged 41.6 ± 14.2 years with follow-up for 9.5 ± 10.2 years) treated with dialysis or kidney transplantation and followed by a gynecologist, 78.7% had regular uterine bleeding before dialysis, though this decreased to 30.6% after dialysis initiation. The remaining participants reported infrequent (26%) or absent (43%) uterine bleeding after dialysis initiation.

We are unaware of any specific treatment regimens for abnormal uterine bleeding that differentiate between stages of CKD. Nevertheless, possible treatment for abnormal uterine bleeding must be balanced with the risks of worsening patients’ kidney health and evaluation of their comorbidities, contraindications, preferences, and suitability for adolescents and young adults. Hormone therapy using progestin-only or combined estrogen-progestin hormonal contraception can temporarily improve uterine bleeding. For instance, with the progestin-only intrauterine device, injectable, and subdermal implant, some individuals experience a cessation of bleeding after months to a year of use despite initially having irregular and/or heavy bleeding. The combined oral contraceptive pill, transdermal patch, and vaginal ring can
also regulate bleeding and if used continuously without hormone-free weeks (i.e., long/extended-cycle use), they can prevent uterine bleeding and related symptoms.\textsuperscript{57,59} It is important to note, however, that estrogen-containing options increase thrombotic risk.\textsuperscript{59} Tranexamic acid, danazol therapy, gonadotropin-releasing hormone agonists, and nonsteroidal anti-inflammatory medications are additional treatment options, though risks and timelines of use must be assessed carefully in the context of CKD, especially with the latter.\textsuperscript{56}

Though abnormal uterine bleeding is prevalent in the context of kidney disease, a study consisting of largely pediatric nephrologists from the United States and Puerto Rico reported that almost 90\% were not at all confident/somewhat confident in managing abnormal uterine bleeding.\textsuperscript{45} In addition, in a study of adult nephrologists from the United States and Canada, more than 65\% of the respondents reported a lack of confidence in women’s health issues, including menstrual disorders,\textsuperscript{60} whereas only 15\% reported discussing menstrual irregularities with their patients.\textsuperscript{61} These findings highlight a gap in knowledge with regard to the gynecologic care of female patients with CKD and underscore the need for accessible educational resources and training for nephrologists in this important area of patient care.

1.7 Kidney Disease and Period Poverty

Period poverty is defined as a lack of knowledge pertaining to uterine bleeding and an inability to access menstrual products,\textsuperscript{62} serving as a socioeconomic, cultural, and political barrier. CKD is associated with significant socioeconomic disparities,\textsuperscript{63,64} and period poverty only exacerbates the economic toll of CKD. Menarche and menstrual management are fundamental aspects in adolescent female health,\textsuperscript{65} but a lack of education and resources leads to challenges with
menstrual management, leaving female adolescents to deal with stigma, shame, fear, and anxiety; for some, there are direct effects on education, health, and wellbeing.\textsuperscript{66} Period poverty results in some young people to miss up to a fifth of their school year.\textsuperscript{67} Coupled with missing school for medical appointments, adolescents with CKD may be at greater risk of absenteeism, leading to grade retention, academic underachievement, and interruption of studies, all compromising their psychosocial wellbeing and quality of life.\textsuperscript{68,69} Finally, although there are no studies focusing on period poverty among menstruating individuals with CKD, socioeconomic position and country income level may also influence one’s access to safe menstrual products and hygiene management facilities.\textsuperscript{63,64,70-72}

1.8 Kidney Disease and Sexual Activity and Function

Adolescents with CKD tend to experience later onset of puberty\textsuperscript{68} and initiate sexual intercourse at a later age compared with the general age-matched population.\textsuperscript{73} American adolescents with CKD are less likely to report ever having sex compared with age-, gender- and race-matched high-school students, and they became sexually active at a later age than controls (26.7\% versus 41.6\%; mean ± SD 15.1 ± 1.6 versus 14.6 ± 1.6 years, respectively). The percentage of participants having ≥2 partners and/or engaging in unprotected sex or using alcohol or illicit drugs during sex were comparable in the 2 groups.\textsuperscript{73} Nevertheless, whether these results differ by sex and gender is unknown.

Sexual dysfunction in females is defined as loss of libido, reduced vaginal lubrication, and inability to orgasm, including vaginismus, dyspareunia, and infertility.\textsuperscript{74} In the United States, almost 30\% of high-school students reported being sexually active,\textsuperscript{75,76} with nearly 50\% of
young females reporting sexual dysfunction. The prevalence of sexual dysfunction in the adolescent CKD population is unknown. In the adult CKD population, a systematic review found that 30% to 80% of women with CKD reported sexual dysfunction and scored lower overall and in each domain of the Female Sexual Function Index questionnaire compared with healthy women. In a cross-sectional study of 106 women under the age of 50 years, rates of female sexual dysfunction were highest in the CKD group (81%) and lowest among kidney transplant recipients (50%). In a prospective cohort study of 39 women (mean age 36 ± 5.9 years) with kidney failure treated with hemodialysis for more than 6 months, 41% reported an active sexual life compared with 88% after kidney transplantation, in conjunction with improved reproductive hormone profiles and Female Sexual Function Index scores. Factors that may affect sexual function in the CKD population include the adverse psychosocial effects of having a chronic illness, depression, anxiety, and negative body image. Physical challenges such as decreased libido and vaginal lubrication, orgasmic impairment, and dyspareunia, are common among women with CKD, whereas comorbidities and sociodemographic factors can exacerbate the risk.

1.9 Kidney Disease and Sexually Transmitted Infections
Youth aged 15 to 24 years account for approximately half of new sexually transmitted infection (STI) cases in the United States, and it is estimated that 1 out of 4 sexually active adolescent females have an STI, most often Chlamydia trachomatis infection and human papillomavirus (HPV) infection. Adolescents in general are particularly at risk for STIs from both behavioral and biological standpoints. Adolescents are more likely to engage in high-risk sexual behaviors such as having concurrent partners or sex without a condom. From a biological perspective,
adolescent females are particularly susceptible to STIs, such as *Chlamydia trachomatis* and HPV because of lower production of cervical mucus and increased cervical ectopy.\textsuperscript{85}

For many adolescents living with kidney disease, the nephrologist functions as the primary care provider and may be the only contact to perform STI screening and reproductive health counseling.\textsuperscript{86} A high index of suspicion for STIs is particularly important in transplant recipients owing to their maintenance immunosuppressant medications. In a single-center American retrospective medical record review study of all pediatric transplant recipients aged 13 and older (n=49) spanning up to 11 years of follow-up, more than half of adolescent female kidney transplant recipients reported being sexually active, 75% of those sexually active reported using hormonal contraception, and 37.5% had had at least 1 STI.\textsuperscript{87} STIs identified in this study included gonococcal and chlamydial urethritis/cervicitis, *Trichomonas* vaginitis, herpes simplex virus 2 genital sores, pelvic inflammatory disease, and human immunodeficiency virus. Owing to the retrospective nature of the study, assessment of condom use was not possible.

Though not specifically studied in the pediatric population, the prevalence of syphilis was found to be significantly higher in the kidney failure population treated with dialysis.\textsuperscript{88,89} The incidence of syphilis in the adult kidney failure population is $>3x$ higher than in the general population and many affected patients had late-stage syphilis.\textsuperscript{90} Potential reasons for increased STI diagnoses include immunosuppression and recognizing that patients with kidney failure have a tremendous burden of symptoms that may prevent STI detection at an early stage. The apparent elevated rate of STIs among patients with CKD may suggest increased sexual activity; however, this has not been well studied in the CKD population.
There are no guidelines for primary prevention of STIs specific to adolescents with CKD; the Centers for Disease Control and Prevention recommends that this important aspect of health be incorporated into all types of health care visits for adolescents and young adults. HPV causes most of the cervical, anal/rectal, and oropharyngeal cancers in women. A US Renal Database System study of older women (mean age 65 years) between 2005 and 2011 revealed that the incidence of HPV-associated cancers in women with kidney failure is rising annually and is overall higher than in women of the general population. The incidence of HPV-associated cancers in younger female populations across the stages of CKD, however, is unknown.

In the United States, HPV vaccination is recommended through the age of 26 years for those not vaccinated previously at the routine age of 11 or 12 years. General recommendations with respect to counseling adolescents on sexual behaviors include discussions surrounding risk-reduction behaviors (e.g., consistent and correct condom use and reduction in the number of sex partners including concurrent partners). Unfortunately, pediatric and adult nephrologists practicing in the United States and Puerto Rico never/rarely reported documenting patient sexual activity (29.5%), number of sexual partners (74.7%), and STI history (38.1%). Increasing the dialogue on sexual activity and STIs among adolescents with CKD is important to providing better care, considering the immunosuppressed states of patients.

1.10 Kidney Disease and Contraception

In a retrospective cohort study of 35,732 women receiving dialysis in the United States (115,713 person-years) aged 15 to 44 years from 2005 to 2014, the rate of contraceptive use was low at
5.3%, with the intrauterine device and oral contraceptive pill being the most common methods of contraception. Younger age, Native American and Black race/ethnicity, kidney failure owing to glomerulonephritis, kidney failure treatment with hemodialysis, and predialysis nephrology care were associated with a higher likelihood of contraceptive use. In a national survey evaluating high-risk behaviors in American adolescents with CKD, 54.8% of sexually active adolescents reported condoms as the most common contraception method, though whether use differed by sex and gender was not reported. Although the oral contraceptive pill is the second most common contraceptive used by adolescents in the general population in high income countries, oral contraceptive use by adolescents with CKD is unknown.

Hormonal composition of contraceptive options is an important consideration in adolescent females with CKD (Figure 2). Estrogen-containing oral contraceptive pills are associated with increased risk of proteinuria, increased blood pressure, venous thromboembolism, arterial thrombosis, and cervical cancer in part due to activation of the renin-angiotensin-aldosterone system, and should be used with caution in people with CKD. Similar concerns on the estrogen-containing transdermal patch and vaginal ring also exist, though this has not been studied specifically in the population with CKD. Of note, bone mass accrual continues up to approximately age 25 years, and although there are conflicting data on the effects of estrogen-containing hormonal contraception on bone mineral density, there is currently no evidence supporting increased risks of osteoporosis or fracture among users. How estrogen-containing hormonal contraception may affect bone health in adolescents with CKD is unknown.
Long-acting reversible contraceptives, and specifically intrauterine contraception, are recommended by multiple international societies as the first line of contraception for adolescents owing to their low typical-use failure rates and high 1-year continuation rates.107-112 Use of long-acting reversible contraceptives in the adolescent CKD population is unknown, but compared with estrogen-containing contraceptives, these progestin-only alternatives confer lower risks of venous thromboembolism in the general population.113 Clinical practice guidelines for contraception in kidney disease recommend that the progestin-only pill, progestin subdermal implant, and progestin intrauterine device are safe and effective for women with CKD.114,115 In addition, the progestin-only injectable may be another contraceptive option as it confers lower thrombotic risks compared to estrogen-containing choices. Of note, there are older case reports of nonhormonal intrauterine devices being associated with peritonitis in women on peritoneal dialysis,116-118 though one study highlights this association with progestin intrauterine device use.119

As with the general adolescent population, contraception counseling in the adolescent population with CKD is of critical importance. Although most contraceptives are intended for use by females, it is imperative to highlight that contraception and the consequences of unprotected sex are important priorities to discuss with patients with CKD of all gender identities. Kidney health care providers play an important role in ensuring that adolescents with CKD have access to high-quality and safe reproductive health care services and contraceptive methods. Nevertheless, in surveys of 200 German and 196 American nephrologists, fewer than half report contraception counseling to adult women on dialysis.120,121 Nephrologists who do provide contraception or preconception counseling report counseling an average of <1 woman per month, citing lack of
training and personal knowledge/confidence. In contrast, nearly two-thirds of nephrologists caring for adolescents with CKD report being very confident or confident providing contraceptive counseling, although most reported being comfortable discussing barrier methods rather than other forms of contraception such as long-acting reversible contraceptives, which are recommended as the first line of contraception among adolescents and are safe in CKD. Although a clinical practice guideline on pregnancy and kidney disease exists, increased attention is urgently required to aid nephrologists provide patient-centered and disease-specific contraceptive care. Especially for those taking teratogenic medications, such as angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, and mycophenolate mofetil for the treatment of kidney disease, it is imperative that these patients use contraception to avoid adverse pregnancy outcomes. Reports of congenital malformations after taking angiotensin-converting-enzyme inhibitors, neonatal and long-term complications for fetuses exposed to angiotensin receptor blockers, and an elevated incidence of structural malformations with mycophenolate mofetil exposure during pregnancy highlight the need for effective contraception when pregnancy is not desired.

1.11 Kidney Disease and Fertility

Reduced fertility has been observed in the female CKD population compared with the general population postulated secondary to multiple factors, including a reduction in ovarian reserve. Individuals with female biology are born with a finite number of ovarian follicles and anti-Müllerian hormone (AMH), produced by preantral and small antral ovarian follicles, is the gold-standard measure of ovarian reserve. As a woman’s ovarian reserve
naturally depletes with age, AMH levels also decline. AMH levels can be used to evaluate female fertility and menopausal status.9,133

We are unaware of any studies evaluating ovarian reserve in the adolescent population with CKD; however, AMH levels in women of reproductive age with CKD and kidney failure, particularly in those treated with kidney transplantation, seem to be lower compared with age-matched healthy individuals, suggesting a reduced ovarian reserve in women with CKD.127-129 Furthermore, in a prospective study of 46 females with kidney failure treated with hemodialysis, those with normal uterine bleeding had higher concentrations of AMH compared with those with abnormal uterine bleeding, and an unexpected decline in AMH level was found after kidney transplantation.128

Fertility can be negatively affected by treatment for CKD, such as cyclophosphamide.11 There is limited evidence that co-treatment with a gonadotropin-releasing hormone agonist may decrease the gonadotoxicity of this alkylating agent.134-136 Therefore, fertility preservation is an important consideration for young patients undergoing gonadotoxic treatment. For females, options include cryopreservation and banking of oocyte, embryo, and ovarian tissue; preservation of fertility in the context of kidney disease has been reviewed in detail elsewhere.9,82 Assisted reproductive technologies, such as in vitro fertilization, seem to be safe in kidney transplant recipients,137-139 although we are unaware of related studies in the non-transplant CKD population.

It is also important to note nephrologists’ communication of fertility status with their patients, especially if parenthood is considered a meaningful goal. Studies evaluating Canadian,
American, and Puerto Rican pediatric and adult nephrologists found that most discussed potential teratogenicity of medication and risks of infertility with cyclophosphamide use.\textsuperscript{45,60} One study found that 95\% of respondents in an international survey of pediatric and adult nephrologists agreed that kidney function affects reproductive hormone status.\textsuperscript{61} Nevertheless, only 35\% reported regularly discussing fertility with their patients. Although kidney disease affects the entire spectrum of reproductive health, frequent reproductive assessment and counseling should become a common part of nephrologists’ practices.\textsuperscript{45,60,61}

\subsection*{1.12 Transgender Individuals and Reproductive Care}

The proportion of transgender individuals (i.e., gender identity does not align with sex assigned at birth), has increased over time, where youth account for a large proportion of this group.\textsuperscript{140} Transgender adolescents have unique reproductive health care needs. A transgender boy or nonbinary individual requires gynecologic and reproductive care, including contraception counseling, and most transgender and gender-diverse adolescents with female biology express desire to have children in the future.\textsuperscript{141} Despite this important consideration, information regarding the reproductive care of transgender boys and nonbinary individuals within the CKD context is lacking.

\subsection*{1.13 Conclusion}

Female reproductive and gynecologic health in CKD, and particularly in adolescents, is an important yet understudied area. Kidney disease is associated with abnormal hypothalamic-pituitary-ovarian function. Abnormal uterine bleeding and low fertility are common. Although CKD is associated with high-risk pregnancy, contraceptive use is low in the setting of CKD.
Despite the high prevalence of menstrual and fertility disorders, gynecologic and reproductive health is not often addressed by nephrologists with many reporting a lack of knowledge and confidence in this area. Providers should feel comfortable obtaining detailed sexual histories to properly counsel on and test for STIs, particularly given that CKD is an immunocompromised state. With special considerations to the transition from pediatric to adult nephrology and the growing transgender youth population, focused training in these important areas of female health in addition to multidisciplinary collaborations is urgently required. We propose a “roadmap” to female reproductive kidney research and care (Figure 3). Large, prospective studies in addition to dedicated educational resources are required to equip kidney health care providers with the knowledge needed to provide patient-centered and disease-specific care that includes gynecologic and reproductive health.

1.14 Disclosure
All the authors declare no competing interests.

1.15 Acknowledgments
We gratefully acknowledge Sarah Gil and Alexa Desjarlais for the graphic design. DHC is supported by graduate scholarships from the Canadian Institutes of Health Research, University of Calgary, and the Libin Cardiovascular Institute.
1.16 Figures

**Figure 1.** Hypothalamic-pituitary-ovarian axis in females with kidney disease. From Ahmed SB, Ramesh S. Sex hormones in women with kidney disease. Nephrology Dialysis Transplantation, 2016, volume 31, issue 11, pages 1787–1795 © The Author(s). Published by Oxford University Press on behalf of the ERA-EDTA. All rights reserved. CKD, chronic kidney disease; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.
Figure 2. Contraceptive options and considerations for adolescent females with kidney disease.
(Adapted from Ahmed et al.,82 Attini et al.,115 Sachdeva,101 Watnick,104 Wiles and Lightstone102).
CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; N/A, not available; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.
Figure 3. Roadmap to advancing female reproductive health in kidney research and care.
2.1 Abstract

Chronic kidney disease (CKD) in reproductive-aged females is accompanied by menstrual disorders and low contraceptive use. However, most data are limited to the dialysis and transplant populations. This study aimed to describe self-assessed menstruation and contraceptive use among females across all stages of CKD. People aged 18-50 years, with a uterus, and diagnosed with CKD were invited to participate in an online survey. The survey was disseminated globally through 112 kidney organizations, patient groups, and social media. Of 152 respondents, 98 satisfied the inclusion criteria [n=20 dialysis (age 35±1 years), n=59 non-dialysis (age 32±1 years), n=19 transplant (age 35±2 years)], representing 3 continents and predominantly self-identifying as white cisgender women. The most common causes of CKD were congenital anomalies of the kidney and urinary tract (30%), acute kidney injury and glomerulonephritis (15% each), and IgA nephropathy (21%) among the dialysis, non-dialysis, and transplant groups, respectively. One participant each in the dialysis and non-dialysis groups
experienced primary amenorrhea, though more reported secondary amenorrhea (25% dialysis, 15% non-dialysis, 26% transplant). Of participants with current menses, 86%, 94%, and 100% of the dialysis, non-dialysis, and transplant groups reported heavy menstrual bleeding; however, only 50%, 69%, and 43% were always able to afford period products. Regarding, contraception, 50%, 63%, and 37% of dialysis, non-dialysis, and transplant participants reported no use, though among users, male condoms were notably popular in the dialysis (33%) and non-dialysis (48%) groups. Abnormal menstruation and period poverty are common, and contraception use is low among females with CKD, highlighting an important gap in the sex-specific care of this population.

2.2 Introduction

The theme of World Kidney Day 2022 is “Kidney Health for All” to “Bridge the knowledge gap to better kidney care”. Female reproductive health is increasingly recognized as an important predictor of morbidity, mortality, and quality of life. Females living with kidney disease have among the lowest survival rates and quality of life, highlighting the urgency of identifying female-specific factors that contribute to these poor outcomes. Globally, chronic kidney disease (CKD) affects 1 in 10 individuals; however, awareness and understanding of sex-specific CKD considerations remain low. This knowledge gap is especially pronounced within the female CKD population around issues related to reproductive and gynecologic health, despite the higher prevalence of CKD in females compared to males. In reproductive-aged females, CKD is believed to be commonly associated with disruptions of the hypothalamic-pituitary-ovarian axis, resulting in hormonal disturbances and abnormal uterine bleeding. However, abnormal uterine bleeding, defined as any disruption of a healthy menstrual cycle
(e.g., volume, regularity, frequency, duration of menses),\textsuperscript{22,53} has been described in only a limited number of small studies in the CKD population and has been reported as high as 94% among females with kidney failure.\textsuperscript{14,151,152} Additionally, contraceptive use is low in the CKD population\textsuperscript{94} coupled with infrequent contraceptive counselling by healthcare professionals.\textsuperscript{45,60,61} This has important implications regarding the high risks associated with an unplanned pregnancy in terms of both maternal and fetal outcomes as well as CKD progression.\textsuperscript{10,19} However, when examining the scope of the current literature, most menstruation and contraception data are limited to the dialysis and transplant populations. Recognizing the growing prevalence of kidney disease,\textsuperscript{153,154} greater understanding of gynecologic and reproductive health at all stages of CKD is necessary to bridge the knowledge gap for improved kidney care. Therefore, this cross-sectional study sought to describe self-assessed menstruation and contraceptive use among females across all stages of CKD around the world.

\textbf{2.3 Methods}

This exploratory study is comprised of an online survey that was disseminated to potential participants globally. Ethics approval was obtained from the University of Calgary Conjoint Health Research Ethics Board (ethics ID REB21-0326). Participation in the study was voluntary and informed consent was obtained electronically prior to the survey.

\textbf{2.3.1 Survey Development}

The survey instrument (Supplemental File A) and item generation and reduction were developed by reviewing literature and consulting with people with female sex assigned at birth living with kidney disease (n=6) representing 3 different countries and a team of multidisciplinary experts.
nephrologist (n=2), gynecologist (n=1), general internist (n=1), endocrinologist (n=1), family physician (n=1), in-center hemodialysis nurse (n=1), home hemodialysis nurse (n=1), nocturnal hemodialysis nurse (n=1), peritoneal dialysis nurse (n=1), non-dialysis CKD nurse (n=1), nephrology research nurse manager (n=1)]. Pretesting to assess the face validity, clarity, length, and completeness of the survey was performed through semi-structured interviews or by obtaining written feedback from all 17 collaborators. After updating the survey, it was then pilot tested to ensure the questions and items were coherent and relevant. The Checklist for Reporting Results of Internet E-Surveys (CHERRIES) was applied to guide survey development (Supplemental File B) and the online software, Qualtrics version 03.2021 (Provo, Utah: Qualtrics, 2021), was utilized to create the survey.

2.3.2 Survey Dissemination

Included participants were those born with a uterus, aged 18-50 years, and had a CKD diagnosis ranging from stages G1-G5D. Exclusion criteria included those who were pregnant or breastfeeding, underwent surgical menopause (i.e., oophorectomy, hysterectomy), and the inability to provide informed consent. The anonymous online survey was available in four languages (English, French, Hindi, Spanish) and a chance to win 1 in 10 Amazon gift cards ($50 CAD) was offered upon survey completion. An informative online recruitment banner with a quick response code and link to the survey was created and translated in each language. A snowball sampling method of recruitment was employed where targeted emails were sent to contacts at each patient group and organization asking permission to share the survey on their weekly/monthly emails, newsletters, websites, and social media platforms. Additionally, the survey was broadly disseminated via Twitter and Facebook. In total, 112 kidney patient
organizations and groups were contacted. The survey was published on 4 October 2021 and remained open until 7 January 2022 after launching the survey on Twitter. Follow-up emails to kidney-based groups after initial contact were sent up to two times, each at least 2 weeks apart.

2.3.3 Data Collection and Analysis

Demographic (age, country, ethnicity, sex assigned at birth, current gender identity), medical history (kidney, gynecologic, hematologic), menstruation (menarche, uterine bleeding, menopause, ability to afford period products, menstrual counselling and education), and contraception (pregnancy, current contraceptive use, types used, contraceptive counselling and education) data were collected. Participants were collapsed into three groups (dialysis, non-dialysis CKD, transplant) to compare responses across strata. Data were analyzed with descriptive statistics (mean ± SD, proportions, percentages) given the exploratory nature of this study.

2.4 Results

2.4.1 Demographics

There was a total of 152 respondents, and after eliminating those who did not consent to the survey, answer any questions, satisfy inclusion criteria, or provided incomplete responses, there were 98 participants (Figure 4). Of those, 20 were currently receiving dialysis, 59 were not receiving dialysis, and 19 had a currently functioning transplant. Most participants were from a North American or European country, and most were white. The majority of participants reported being assigned female sex at birth and identified as cisgender women. Table 1 summarizes participant demographic characteristics. Causes of CKD were stratified across all
three groups, with congenital anomalies of the kidney and urinary tract (CAKUT) being the most common among dialysis participants, while acute kidney injury (AKI) and glomerulonephritis (GN) were most common among non-dialysis participants, and IgA nephropathy was most prevalent in the transplant group. In the non-dialysis and transplant groups, stages 3 and 2 CKD, respectively, were most prevalent. Additionally, half the participants on dialysis and nearly two thirds of those not on dialysis were taking an erythropoietin stimulating agent, though few transplant participants did receive it. Most of the dialysis and transplant groups reported receiving a previous blood transfusion, compared to only a quarter of the non-dialysis group. In terms of medical history, people with a transplant more commonly reported immunosuppressive medication use than participants in other groups and a large proportion of non-dialysis participants reported a diagnosis of endometriosis and polycystic ovarian syndrome.

2.4.2 Menstruation

Among dialysis, non-dialysis, and transplant groups, nearly all participants had experienced menarche and had ongoing menstrual cycles, while only one individual reported primary amenorrhea in the dialysis and non-dialysis groups (Table 2). However, there were still participants in all groups who reported secondary amenorrhea or absent menstrual bleeding and menopause, defined as the absence of a menstrual period for >12 months. For those on dialysis, nearly a third of participants noted that their periods had stopped and then returned for a variety of reasons.

For participants with current menses, most reported that their bleeding was “predictable” among the dialysis and non-dialysis groups, though most participants in the transplant group reported
that their periods were “usually unpredictable” (Figure 5). When asked about the length of their periods, the most common response for dialysis participants was 7-8 days, while it was 5-6 days for non-dialysis participants, and 3-4 or 7-8 days for transplant participants (Figure 6). In terms of heavy menstrual bleeding, there were five clinical indicators that participants were able to report (e.g., need to change period product at least once an hour for several hours, need to wear multiple period products at once) and the selection of at least one suggested heavy menstrual bleeding. Figure 7 shows that the overwhelming majority of dialysis, non-dialysis, and transplant participants with current menses experienced heavy menstrual bleeding. The most commonly used period products across all three groups were pads (Supplemental Figure 1). Respondents with current menses reported their ability to afford period products. While most participants in each stratum reported that they were always able to afford menstrual products, there was considerable variation in the responses, as some could afford menstrual products most times, sometimes, rarely, and even never (Figure 8).

2.4.3 Sexual Activity and Fertility

Most dialysis and transplant participants reported not having heterosexual sex, while the majority of non-dialysis participants reported doing so (Table 3). Among those trying to conceive, most participants on dialysis and not on dialysis reported trying for ≥12 months, indicative of infertility, although very few reported receiving fertility treatment.

2.4.4 Contraception

Less than half of participants in each group reported currently using contraception (Table 3). The most common reason for using contraception across all strata was to prevent pregnancy. In the
dialysis and non-dialysis groups, the most common form of contraception was the male condom, however, the progestin-only pill and vasectomy in the male partner were most common within the transplant group (Figure 9). In contrast, reasons for not using contraception varied across groups (Supplemental Figure 2). Among participants on dialysis and with a kidney transplant, the most common reason was that they were trying to get pregnant, while fear was the most common reason reported by those not on dialysis.

2.4.5 Reproductive Health Education

In terms of education about menstruation and CKD, participants tended to gather information from their nephrologist, educational websites, social media, and other people living with CKD (Table 2). When asked about with whom participants actually discussed this with, respondents often reported their family members, friends, gynecologist, and nephrologist but there were still desires to have these conversations with others, such as their nurse and primary healthcare provider (Figure 10, panels A, C, E). Similarly, regarding contraception and CKD, many reported learning about this from their nephrologist, educational websites, social media, and other people living with CKD (Table 2). However, when asked about with whom they actually discussed this with, common responses were their family members, friends, gynecologist, and nephrologist but they also wished to have these conversations with other health professionals including their nurse and primary healthcare provider (Figure 10, panels B, D, F).

2.5 Discussion

This was the first study to describe menstruation and contraceptive use among reproductive-aged females across all stages of CKD around the world. While most participants reported
experiencing menarche and current menstrual cycles, absent menstrual bleeding was prevalent, affecting around a quarter of dialysis and transplant participants, and less in the non-dialysis group. Most participants in the dialysis and non-dialysis groups reported their periods as “very predictable” or “predictable” and the duration of menses were within healthy ranges across all three groups. Of respondents with current menses, the vast majority in each group reported at least one clinical indicator of heavy menstrual bleeding, despite many not being able to always afford period products. Infertility was also common in this study population. In terms of contraception, a large proportion of participants reported not using contraception, primarily due to fear; however, among those who used contraception, the male condom was a common option, especially within the dialysis and non-dialysis groups. Finally, respondents learned about menstruation and CKD from similar sources as they did with contraception and CKD, and they often discussed reproductive health with family members, friends, and healthcare professionals, though they still wished to have these conversations with others.

The hypothalamic-pituitary-ovarian axis involving the key reproductive hormones, gonadotropin-releasing hormone, luteinizing hormone, follicle-stimulating hormone, and estradiol, regulates the menstrual cycle. However, CKD appears to disturb this axis, by inhibiting the pulsatile release of gonadotropin-releasing hormone from the hypothalamus, thus interrupting the typical luteinizing hormone and follicle-stimulating hormone cyclicity. Abnormal uterine bleeding was previously found to be common among females with kidney disease, being reported as high as 94% among the kidney failure population. One study examining females treated with dialysis found that 58% of total participants (n=76) reported absent menstrual bleeding; however, 59% of currently menstruating participants experienced irregular
menstrual bleeding and 64% reported heavy flows with blood clots. Another study examining 95 people with a uterus and CKD treated with dialysis or kidney transplantation found that only 12 females had a normal menstrual cycle while 50 participants experienced menorrhagia or heavy menstrual bleeding, and 33 had an absence of menses. In an older study of 17 premenopausal females with dialysis-dependent kidney failure, findings revealed that only 1 participant experienced regular menses, while 6 had irregular menstrual bleeding, and 10 had an absence of menses. Additionally, a study of 75 reproductive-aged females on hemodialysis determined that 75% had menstrual disorders, where almost half could be accounted by absent menstrual bleeding. Unlike these previous studies that focused on the kidney failure population, our study included people across the spectrum of CKD in addition to those with dialysis-dependent kidney failure. For instance, in both the non-dialysis and transplant groups, there were participants who reported currently having stages 1-4 CKD and a transplant recipient who had stage 5 CKD but was not receiving dialysis. However, our results from the dialysis group also differ from previous literature as the majority reported having current menstrual cycles, where most had “very predictable” or “predictable” cycles with normal duration of menses. A quarter of participants treated with dialysis had an absence of menses or secondary amenorrhea, which is less than what was found in previous research. In addition, the prevalence of heavy menstrual bleeding was still high in our study population, aligning with previous findings. Unlike most of these older studies where participants were recruited from a single center, our study design allowed us to have a greater reach around the world, using an online format. This may have captured a greater diversity of experiences, but it may have also influenced how people participated. For instance, if someone had strongly positive or negative experiences with periods or contraceptive use while they had CKD, they may have been more
inclined to participate, whereas the single center studies could have captured people with differing levels of motivations, hence, reducing bias. Interestingly, in our study, there were many participants who reported ever needing a blood transfusion and were currently taking an erythropoietin stimulating agent, though the reasons for blood loss were not specified. This suggests that attention to abnormal uterine bleeding, particularly heavy menstrual bleeding, in collaboration with gynecology may result in improved kidney outcomes due to less sensitization, leading to a greater chance of kidney transplantation. Further, there will be less of a need for erythropoietin stimulating agent use, which is associated with blood clots.

Studies have previously suggested low contraceptive use\textsuperscript{14,94} and infrequent contraceptive counselling within the female kidney disease population.\textsuperscript{45,60,61,121} One study of 76 reproductive-aged females on dialysis reported half of them being sexually active, but only 36\% used contraception (mostly condoms), and 13\% discussed contraception with their nephrologist.\textsuperscript{14} A retrospective cohort study of 35,732 dialysis-dependent females of reproductive age determined that the rate of contraceptive use was low at 5.3\%.\textsuperscript{94} In this case, the intrauterine device and oral contraceptive pill were most commonly used. Similarly, this research was done in the transplant population (n=13,150).\textsuperscript{159} The rate of contraceptive use was 9.5\%, and once again the oral contraceptive pill and intrauterine device were the most common forms used; however, the authors noted that male condom use was not captured. In our study, recognizing that contraception can be used for a multitude of reasons, contraceptive use was still low across the spectrum of CKD. However, we were able to determine that the male condom was especially popular among the dialysis and non-dialysis groups, while there was more variation in the types of contraception used within the transplant group. It is important to note that in this research,
data are often limited to one population or data registry that can only comment on whether the contraception was prescribed or not, without explaining the reason(s) why people chose to use or not use contraception. In our study, we were able to shed light on this topic and determine that the most common reasons people use contraception were to prevent pregnancy and manage their periods, meanwhile, fear was a driving factor for others to avoid using contraception. Unfortunately, the reasons why people held this attitude was not fully elucidated. Given the concerns about an unplanned pregnancy regardless of CKD stage, and understanding that fear of contraception can be managed with patient education, our results suggest that greater discussion about contraception in routine nephrology practice is highly warranted.

The high prevalence of period poverty in the study population deserves mention. Unfortunately, there are no other studies evaluating this within the kidney disease context, but given that people with CKD tend to be disproportionately from lower socioeconomic groups, it is likely that the management of CKD would not only impact their ability to afford safe and clean period products, but result in school or work hours lost. The higher reported prevalence of endometriosis in this study, particularly among the non-dialysis group, was also of concern. Endometriosis affects females’ education, employment, finances, and home life and the severity and number of symptoms are associated with loss of productivity. Therefore, the results of this survey with previous research suggest that period poverty and gynecologic disorders are important female-specific financial burdens that further exacerbate the challenges of living with CKD.
This study has limitations and strengths. Because this was a survey, data were self-reported, which likely introduced recall bias; however, previous studies found recall of certain menstrual and contraceptive characteristics reliable and valid. Snowball sampling to recruit participants may have yielded a sample that does not accurately represent all females with CKD, and failed to capture people without internet access. Nonetheless, we created partnerships with international patient groups during recruitment that helped capture a diversity of participants to improve representativeness. The number of languages the survey was translated in was a limitation, considering this study aimed to have a global reach. Ideally, this study should have been available in the languages based on the countries with the greatest prevalence of CKD, although, English, Hindi, and Spanish are among the top spoken languages around the world.\textsuperscript{168} Finally, using the term “period” instead of “uterine bleeding” in the study is a limitation due to its gendered connotation. Although there are more medically accurate terms, participants may have had difficulty understanding what they mean, compared to the mainstream term. This study also has its strengths. First, the inclusion of people with lived experience with CKD, as well as healthcare professionals involved with kidney and gynecology care, for the design and interpretation of the study ensured that the results filled a meaningful knowledge gap in nephrology. Next, early stages of CKD are asymptomatic, meaning that many people who have it tend to be unaware.\textsuperscript{169} While this could have resulted in an underrepresentation of participants with early stage CKD, the most common stages that were reported in our results were 2 (transplant) and 3 (non-dialysis). However, it is also important to highlight that this is the first study of its kind to include females with all stages of CKD, rather than focusing on those with kidney failure. Reporting gender diversity is another strength of this study. Finally, while the majority of participants identified as cisgender women, we collaborated with experts to have
many gender identity options supported by definitions, with the aim to increase the overall inclusivity of this study. As a result, our study population may be the most representative sample of people with female sex assigned at birth living with kidney disease.

This international study suggests that among reproductive-aged females across the CKD spectrum, there is a high prevalence of abnormal uterine bleeding, including absent and heavy menstrual bleeding, and a low use of contraception. While the physiological explanations regarding abnormal menses may not be fully understood, irregular menstrual patterns are associated with poor outcomes but can be treated to result in an improved quality of life. Given that most nephrologists are not comfortable with the discussion of female reproductive concerns with their patients, this represents an important unmet need in nephrology education and opportunity for multidisciplinary teamwork. Ultimately, female reproductive health is poorly understood in people living with CKD and represents a critical knowledge gap in nephrology research and care.

2.6 Disclosure

All the authors declare no competing interests.

2.7 Acknowledgments

We gratefully acknowledge RB, ND, KF, AG, LH, JH, GH, KJ, HL, JK, EO, LP, NS, JZ, and all study participants for their contributions. DHC is supported by graduate scholarships from the Canadian Institutes of Health Research, University of Calgary, and Libin Cardiovascular Institute.
2.8 Tables

**Table 1.** Participant demographic characteristics. Values are means ± SEM where relevant.  
<sup>a</sup>65 responses included;  
<sup>b</sup>18 responses included;  
<sup>c</sup>28 responses included;  
<sup>d</sup>20 responses included;  
<sup>e</sup>16 responses included. 5D, stage 5 dialysis; AKI, acute kidney injury; ANCA, anti-neutrophilic cytoplasmic autoantibody; CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; DM, diabetes mellitus; ESA, erythropoietin stimulating agent; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HD, hemodialysis; HTN, hypertension; IgA, immunoglobulin A; N/A, not applicable; PCOS, polycystic ovary syndrome; PD, peritoneal dialysis; PKD, polycystic kidney disease; POI, primary ovarian insufficiency.

<table>
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<th>Transplant (n=19)</th>
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<td>0 (0)</td>
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<td>----------------------</td>
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<td>--------</td>
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<tr>
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**Sex at birth:**

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**Cause of CKD:**

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**Age at CKD diagnosis (years):**

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**Stage of CKD:**
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**Type of dialysis:**

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**Age at dialysis initiation (years):** 26±2

**Proteinuria:**

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**Receiving heparin on dialysis:**

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<td>4 (20)</td>
<td>4 (20)</td>
<td>N/A</td>
<td>N/A</td>
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</tbody>
</table>

**Currently taking ESA:**

<table>
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<tr>
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<th>Yes n (%)</th>
<th>50 (51)</th>
<th>10 (50)</th>
<th>36 (61)</th>
<th>4 (21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No n (%)</td>
<td>41 (42)</td>
<td>7 (35)</td>
<td>20 (34)</td>
<td>14 (74)</td>
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</tr>
<tr>
<td>Unsure n (%)</td>
<td>7 (7)</td>
<td>3 (15)</td>
<td>3 (5)</td>
<td>1 (5)</td>
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<tr>
<td>Skipped question n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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</tbody>
</table>

**Ever needed blood transfusion:**

<table>
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<tr>
<th>Ever needed blood transfusion</th>
<th>Yes n (%)</th>
<th>37 (38)</th>
<th>12 (60)</th>
<th>15 (25)</th>
<th>10 (53)</th>
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</thead>
<tbody>
<tr>
<td>No n (%)</td>
<td>52 (53)</td>
<td>6 (30)</td>
<td>40 (68)</td>
<td>6 (32)</td>
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<tr>
<td>Unsure n (%)</td>
<td>4 (4)</td>
<td>1 (5)</td>
<td>2 (3)</td>
<td>1 (5)</td>
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</tr>
<tr>
<td>Skipped question n (%)</td>
<td>5 (5)</td>
<td>1 (5)</td>
<td>2 (3)</td>
<td>2 (11)</td>
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</table>

**Currently taking blood thinner:**

<table>
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<th>26 (27)</th>
<th>8 (40)</th>
<th>10 (17)</th>
<th>8 (42)</th>
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<tbody>
<tr>
<td>No n (%)</td>
<td>59 (60)</td>
<td>9 (45)</td>
<td>41 (69)</td>
<td>9 (47)</td>
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<tr>
<td>Unsure n (%)</td>
<td>8 (8)</td>
<td>2 (10)</td>
<td>6 (10)</td>
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</tr>
<tr>
<td>Skipped question n (%)</td>
<td>5 (5)</td>
<td>1 (5)</td>
<td>2 (3)</td>
<td>2 (11)</td>
<td></td>
</tr>
</tbody>
</table>

**Medical history:**

<p>| Medical history | Chemotherapy n (%) | 5 (5) | 1 (5) | 4 (7) | 0 (0) |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunosuppressive medications n (%)</strong></td>
<td>37 (38)</td>
<td>8 (40)</td>
<td>14 (24)</td>
<td>15 (79)</td>
</tr>
<tr>
<td><strong>Lupron (leuprolide) n (%)</strong></td>
<td>9 (9)</td>
<td>3 (15)</td>
<td>6 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Radiation to pelvis or abdomen n (%)</strong></td>
<td>28 (29)</td>
<td>2 (10)</td>
<td>24 (41)</td>
<td>2 (11)</td>
</tr>
<tr>
<td><strong>None n (%)</strong></td>
<td>23 (23)</td>
<td>8 (40)</td>
<td>14 (24)</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>Unsure n (%)</strong></td>
<td>5 (5)</td>
<td>0 (0)</td>
<td>5 (8)</td>
<td>0 (0)</td>
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<tr>
<td><strong>Gynecologic diagnosis:</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Cancer of female reproductive organs n (%)</td>
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<td>2 (10)</td>
<td>2 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Endometriosis n (%)</td>
<td>26 (27)</td>
<td>1 (5)</td>
<td>23 (39)</td>
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<tr>
<td>History of infertility n (%)</td>
<td>9 (9)</td>
<td>2 (10)</td>
<td>6 (10)</td>
<td>1 (5)</td>
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<tr>
<td>PCOS n (%)</td>
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<td>1 (5)</td>
<td>14 (24)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>POI n (%)</td>
<td>7 (7)</td>
<td>3 (15)</td>
<td>3 (5)</td>
<td>1 (5)</td>
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<tr>
<td>Uterine fibroids or polyps n (%)</td>
<td>13 (13)</td>
<td>3 (15)</td>
<td>8 (14)</td>
<td>2 (11)</td>
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<tr>
<td>Other n (%)</td>
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<td>2 (10)</td>
<td>0 (0)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>None n (%)</td>
<td>29 (30)</td>
<td>9 (45)</td>
<td>13 (22)</td>
<td>7 (37)</td>
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<tr>
<td>Unsure n (%)</td>
<td>9 (9)</td>
<td>0 (0)</td>
<td>8 (14)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>
Table 2. Menstrual characteristics. Values are means ± SEM where relevant. *88 responses included; †18 responses included; ‡52 responses included; §19 responses included; ¶5 responses included; ‖9 response included; ‡‡6 responses included; ‡§2 responses included; ‡¶1 response included; ‡‖3 responses included; ‡†7 responses included. CKD; chronic kidney disease; HD, hemodialysis; IQR, interquartile range.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pooled (n=98)</th>
<th>Dialysis (n=20)</th>
<th>Non-dialysis (n=59)</th>
<th>Transplant (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menarche:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experienced menarche n (%)</td>
<td>88 (90)</td>
<td>18 (90)</td>
<td>52 (88)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Age of menarche (years)</td>
<td>14±0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15±2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13±0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13±1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Primary amenorrhea n (%)</td>
<td>2 (2)</td>
<td>1 (5)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>8 (8)</td>
<td>1 (5)</td>
<td>6 (10)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Menstruation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current menstrual cycles n (%)</td>
<td>77 (79)</td>
<td>14 (70)</td>
<td>49 (83)</td>
<td>14 (74)</td>
</tr>
<tr>
<td>Secondary amenorrhea n (%)</td>
<td>19 (19)</td>
<td>5 (25)</td>
<td>9 (15)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>2 (2)</td>
<td>1 (5)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Menopause:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>8 (42)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2 (40)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3 (33)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3 (60)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median (IQR: 35, 43)&lt;sup&gt;g&lt;/sup&gt; age of last menstrual period (years)</td>
<td>40 (IQR: 35, 43)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>39 (IQR: 35, 43)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>41 (IQR: 0,0)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>39 (IQR: 15,49)&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
<tr>
<td>No n (%)</td>
<td>10 (53)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2 (40)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>6 (67)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2 (40)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>1 (5)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1 (20)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0 (0)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0 (0)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bleeding stopped and then returned:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>6 (6)</td>
<td>6 (30)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Due to transplant n (%)</td>
<td>1 (14)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>1 (14)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Due to home HD n (%)</td>
<td>0 (0)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>0 (0)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Due to nocturnal HD n (%)</td>
<td>1 (14)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>1 (14)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Other reasons n (%)</td>
<td>3 (43)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>3 (43)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>2 (29)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>2 (29)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>No n (%)</td>
<td>12 (12)</td>
<td>12 (60)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>1 (1)</td>
<td>1 (5)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>79 (81)</td>
<td>1 (5)</td>
<td>59 (100)</td>
<td>19 (100)</td>
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Learned about menstruation and CKD from:

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<th>N (%): Female</th>
<th>N (%): Male</th>
<th>N (%): Gender Unknown</th>
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<tr>
<td>Books, magazines, or newspapers (%)</td>
<td>38 (39)</td>
<td>6 (30)</td>
<td>31 (53)</td>
</tr>
<tr>
<td>Educational websites (%)</td>
<td>58 (59)</td>
<td>10 (50)</td>
<td>36 (61)</td>
</tr>
<tr>
<td>Movies, podcasts, radio, television (%)</td>
<td>11 (11)</td>
<td>0 (0)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Nephrologist (%)</td>
<td>51 (52)</td>
<td>13 (65)</td>
<td>32 (54)</td>
</tr>
<tr>
<td>Other healthcare providers (%)</td>
<td>9 (9)</td>
<td>2 (10)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Other people living with CKD (%)</td>
<td>17 (17)</td>
<td>3 (15)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Social media (%)</td>
<td>47 (48)</td>
<td>7 (35)</td>
<td>35 (59)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nowhere (%)</td>
<td>5 (5)</td>
<td>1 (5)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

42
Table 3. Participants’ current contraception use.\(^a\) 32 responses included; \(^b\) 3 responses included; \(^c\) 25 responses included; \(^d\) 4 responses included; \(^e\) 40 responses included; \(^f\) 9 responses included; \(^g\) 40 responses included; \(^h\) 10 responses included. CKD, chronic kidney disease; IQR, interquartile range; IUD, intrauterine device; N/A, not applicable; OCP, oral contraceptive pill.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pooled (n=98)</th>
<th>Dialysis (n=20)</th>
<th>Non-dialysis (n=59)</th>
<th>Transplant (n=19)</th>
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<tbody>
<tr>
<td>Having heterosexual sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>45 (46)</td>
<td>5 (25)</td>
<td>35 (59)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>43 (44)</td>
<td>12 (60)</td>
<td>20 (34)</td>
<td>11 (58)</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>6 (6)</td>
<td>2 (10)</td>
<td>3 (5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>4 (4)</td>
<td>1 (5)</td>
<td>1 (2)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Trying to get pregnant:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>30 (31)</td>
<td>3 (15)</td>
<td>24 (41)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>For &lt;12 months n (%)</td>
<td>5 (16)(^a)</td>
<td>1 (33)(^b)</td>
<td>2 (8)(^c)</td>
<td>2 (50)(^d)</td>
</tr>
<tr>
<td>For ≥12 months n (%)</td>
<td>21 (66)(^e)</td>
<td>2 (67)(^b)</td>
<td>18 (72)(^c)</td>
<td>1 (25)(^d)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>6 (19)(^b)</td>
<td>0 (0)(^b)</td>
<td>5 (20)(^c)</td>
<td>1 (25)(^d)</td>
</tr>
<tr>
<td>Receiving fertility treatment n (%)</td>
<td>1 (3)(^a)</td>
<td>0 (0)(^b)</td>
<td>1 (4)(^c)</td>
<td>0 (0)(^d)</td>
</tr>
<tr>
<td>Not receiving fertility treatment n (%)</td>
<td>31 (97)(^e)</td>
<td>3 (100)(^b)</td>
<td>24 (96)(^c)</td>
<td>4 (100)(^d)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>0 (0)(^a)</td>
<td>0 (0)(^b)</td>
<td>0 (0)(^c)</td>
<td>0 (0)(^d)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>62 (63)</td>
<td>16 (80)</td>
<td>33 (56)</td>
<td>13 (68)</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>4 (4)</td>
<td>1 (5)</td>
<td>1 (2)</td>
<td>2 (11)</td>
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<tr>
<td>Using contraception:</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>37 (38)</td>
<td>9 (45)</td>
<td>19 (32)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>54 (55)</td>
<td>10 (50)</td>
<td>37 (63)</td>
<td>7 (37)</td>
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<tr>
<td>Unsure n (%)</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>4 (4)</td>
<td>1 (5)</td>
<td>1 (2)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Reasons for using:</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Prevent pregnancy n (%)</td>
<td>27 (68)(^c)</td>
<td>7 (78)(^f)</td>
<td>15 (71)(^g)</td>
<td>5 (50)(^b)</td>
</tr>
<tr>
<td>Manage periods n (%)</td>
<td>16 (40)(^c)</td>
<td>2 (22)(^f)</td>
<td>10 (48)(^g)</td>
<td>4 (40)(^b)</td>
</tr>
<tr>
<td>Other n (%)</td>
<td>2 (5)(^c)</td>
<td>1 (11)(^f)</td>
<td>1 (5)(^g)</td>
<td>0 (0)(^b)</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>4 (10)(^c)</td>
<td>0 (0)(^f)</td>
<td>2 (10)(^g)</td>
<td>2 (20)(^b)</td>
</tr>
<tr>
<td>Learned about contraception and CKD from:</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Books, magazines, or newspapers n (%)</td>
<td>38 (39)</td>
<td>6 (30)</td>
<td>31 (53)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Category</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>Group 4</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Educational websites n (%)</td>
<td>58 (59)</td>
<td>10 (50)</td>
<td>36 (61)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Movies, podcasts, radio, television n (%)</td>
<td>11 (11)</td>
<td>0 (0)</td>
<td>10 (17)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Nephrologist n (%)</td>
<td>51 (52)</td>
<td>13 (65)</td>
<td>32 (54)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Other healthcare providers n (%)</td>
<td>9 (9)</td>
<td>2 (10)</td>
<td>5 (8)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Other people living with CKD n (%)</td>
<td>17 (17)</td>
<td>3 (15)</td>
<td>6 (10)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Social media n (%)</td>
<td>47 (48)</td>
<td>7 (35)</td>
<td>35 (59)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Other n (%)</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nowhere n (%)</td>
<td>5 (5)</td>
<td>1 (5)</td>
<td>2 (3)</td>
<td>2 (11)</td>
</tr>
</tbody>
</table>
2.9 Figures

Figure 4. Flow diagram of total survey respondents. \(^a\) >50 years (n=7), male (n=5), currently pregnant or breastfeeding (n=3), had a hysterectomy and/or oophorectomy (n=12); \(^b\) answered ≥1 question regarding menstruation or contraception.
Figure 5. Predictability of periods among participants with current menses. “Very predictable” was defined as being able to predict menses within 0-4 days; “predictable” was defined as being able to predict menses within 5-7 days; “unsure” represents skipped, not applicable, and unsure responses.
**Figure 6.** Length of periods (days) among participants with current menses.
Figure 7. Clinical indicators of heavy menstrual bleeding among participants with current menses. Numbers add up to more than 100% as participants were able to submit multiple responses.
Figure 8. Ability to afford period products among participants with current menses.
Figure 9. Contraception use among dialysis, non-dialysis, and transplant participants. Numbers do not add up to 100% (dialysis, n=9; non-dialysis, n=21; transplant, n=10) as participants were able to submit multiple responses or skip this question entirely. IUD, intrauterine device; OCP, oral contraceptive pill; POP, progestin-only pill.
Figure 10. People or groups that participants discussed and wished to discuss menstruation and contraception with among those receiving dialysis, not receiving dialysis, and with a current kidney transplant. (A) People or groups that participants receiving dialysis (n=20) discussed and wished to discuss menstruation with. (B) People or groups that participants receiving dialysis (n=20) discussed and wished to discuss contraception with. (C) People or groups that participants not receiving dialysis (n=59) discussed and wished to discuss menstruation with. (D) People or groups that participants not receiving dialysis (n=59) discussed and wished to discuss
contraception with. (E) People or groups that participants with a current kidney transplant (n=19) discussed and wished to discuss menstruation with. (F) People or groups that participants with a current kidney transplant (n=19) discussed and wished to discuss contraception with. Numbers add up to more than 100% as participants were able to submit multiple responses.
2.10 Supplemental Files

File A: Online survey developed on Qualtrics

Periods, Birth Control, and Kidney Disease Survey

Start of Block: Consent/Basic Demographics

Q1

This survey is intended for anyone born with a uterus who has kidney disease.

Title: International Online Survey of Uterine Bleeding and Contraception in Female Patients with Chronic Kidney Disease

Investigators: Dr. Sofia Ahmed

Affiliations: University of Calgary, Cumming School of Medicine (Calgary, Alberta, Canada)

Funding: Department of Medicine, University of Calgary

Background: Researchers at the University of Calgary in Canada are conducting a study. This consent form is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, please ask. Please take the time to read this carefully and understand any accompanying information.

Why is this study being done? Kidney disease is rising at a rapid rate and 1 in 8 young women are affected. Abnormal hormones and periods are under-recognized in women with kidney disease and birth control use in this population is unknown. We wish to describe periods and birth control use among women with kidney disease worldwide. This may lead to further research and treatment to improve reproductive health in this population.

How many people will participate in this study? We do not have a clear sense of how many people will participate in this study at this time but are expecting about 1,000 participants worldwide.

What will happen if I take part in this study? We are inviting people with kidney disease who were born with a uterus to complete a voluntary survey about their kidneys, periods, birth control, gynecology history, and medical history. If you volunteer to participate in this study, you will be asked to complete an online, anonymous survey. The survey takes approximately 5-15 minutes to complete. No personal or identifying information is being collected (unless participants are interested in entering the prize draw or being contacted for a future interview) and all data will be analyzed in aggregate. Participants will have the option to choose to undergo
an additional telephone interview, in which case you will be asked to provide contact information (email, telephone number).

**What are the potential risks or discomforts?** Some questions may cause personal or psychological discomfort as we ask about your periods and birth control use. Please note you do not have to answer any questions you do not wish to.

**What are the potential benefits?** There are no direct benefits to study participants. However, we expect that the knowledge gained from this research will ultimately be helpful to women with kidney disease.

**Do I have to participate?** Participation in this research study is entirely voluntary. All participants have the option to not answer questions throughout the survey and still continue. You can stop the survey at any time and you may request to have your data removed so that your responses will not be recorded. To withdraw your data, please email the study team immediately with the time you started or stopped the survey. Please note that since we aren’t collecting personal identifiers (unless interested in entering the prize draw or being contacted for a future interview) there is no guarantee that we can identify which response is yours should you wish to remove it.

**Will I receive any compensation or reimbursement?** You will not receive reimbursement for participating. However, after completing the survey, you will have the option of entering a draw for a chance to win 1 in 10 Amazon gift cards ($50 CAD).

**Will information about me and my participation be kept confidential?** All data will be kept confidential and stored securely. We are using a secure online survey platform called Qualtrics. All data are encrypted and stored directly on its secure servers. Researcher access to the survey data is password-protected and the transmission is encrypted. Survey responses cannot be linked to your computer. Only members of the research team will have access to the data, and all data will be analyzed in aggregate.

Some of the information collected in this study may be used in other studies that our research team is involved in. Any personal identifying information will not be shared. A unique identifier code will be used to record your identity. Identifying data (email and/or telephone number if entered the prize draw or requested to be contacted for a future interview) will be stripped from all results derived from this study. Any future use of this research data is required to undergo review by a Research Ethics Board. Some or all the information obtained from this study may be presented at scientific meetings of the medical community and may be submitted for publication in a medical journal. Your identity will not be revealed in any presentation or publication.

**How long will my information be kept?** In accordance with the University of Calgary’s Data Retention Policy, we will keep data for five years after the completion of the study.

**Who can I contact if I have questions about this study?** Please feel free to contact a member of our research team with any questions or comments about this study.
This study has been approved by the University of Calgary Conjoint Health Research Ethics Board (REB21-0326). If you have any questions concerning your rights as a possible participant in this research, please contact a member of the research team (contact information below) or the Conjoint Health Research Ethics Board, University of Calgary at +1 403-220-7990.

Thank you for considering participating in this timely research study.

Dr. Sofia Ahmed – Principal Investigator
University of Calgary, Department of Medicine

Consent from Participants
Please note, the decision to select this option and participate in the survey will be interpreted as an indication of your agreement to participate. In no way does this waive your legal rights nor release the investigators or involved institutions from their legal and professional responsibilities.

Should you wish to not participate in this study, please exit the survey now.

- I understand the above information and consent to my voluntary participation in this research study (1)
- Exit survey (2)

Skip To: End of Survey If This survey is intended for anyone born with a uterus who has kidney disease. Title: International... = Exit survey

End of Block: Consent/Basic Demographics
Q4

Part 1 of 6: Tell us about your kidneys
What is the cause of your kidney disease?

- Acute kidney injury (AKI) (17)
- ANCA vasculitis (1)
- Congenital anomalies of kidney and urinary tract (CAKUT, kidney disease at-birth) (2)
- Diabetes (3)
- Focal segmental glomerulosclerosis (FSGS) (16)
- Glomerulonephritis (GN) (4)
- Hereditary (13)
- Hypertension (5)
- IgA nephropathy (6)
- I donated a kidney (14)
- Kidney stones disease (7)
- Lupus (8)
- Minimal change disease (15)
- Polycystic kidney disease (9)
- Reflux nephropathy (10)
- Something else (please specify) (11) ________________________________
- I don't know (12)
Q5 When were you diagnosed with kidney disease?

- 1921 or before (424) ...
- I don't know (525)

Q6 Are you currently on dialysis?

- Yes (1)
- No (2)
- I don't know (3)

End of Block: Part 1 of 6: Tell us about your kidneys

Start of Block: Yes Dialysis

Q7 Did you ever have a kidney transplant?

- Yes (1)
- No (2)
- I don't know (3)

Display This Question:

If Did you ever have a kidney transplant? = Yes
Q8 What type of transplant (click all that apply)?

☐ Deceased donor (1)
☐ Living related donor (2)
☐ Living unrelated donor (3)
☐ I don't know (4)

Q9 When did you first start dialysis?

▼ 1981 or before (2) ... I don't know (145)

Q10 What type of dialysis are you currently on?

☐ Home hemodialysis (1)
☐ In-center hemodialysis (2)
☐ Nocturnal hemodialysis (3)
☐ Peritoneal dialysis (4)

Q91 When did you start your current type of dialysis (year) nearby

▼ 1981 or earlier (1) ... I don't know (42)
Display This Question:

If What type of dialysis are you currently on? = Home hemodialysis
Or What type of dialysis are you currently on? = In-center hemodialysis
Or What type of dialysis are you currently on? = Nocturnal hemodialysis

Q11 Do you have heparin on dialysis?

- Yes (1)
- No (2)
- I don't know (3)

End of Block: Yes Dialysis

Start of Block: No, IDK Dialysis

Q83 Tell us about your current kidney function based on one of these criteria

- % Kidney function (4)
- Creatinine (1)
- Glomerular filtration rate (GFR) (2)
- Stage (3)

Display This Question:

If Tell us about your current kidney function based on one of these criteria = Creatinine

Q84 Tell us about your creatinine currently (if you don't know, please indicate "I don't know")

______________________________________________________________

______________________________________________________________

______________________________________________________________

______________________________________________________________
Display This Question:

If Tell us about your current kidney function based on one of these criteria = Glomerular filtration rate (GFR)

Q12 What is your current glomerular filtration rate (GFR)?

- <15 (1)
- 15-29 (8)
- 30-44 (9)
- 45-59 (10)
- 60-89 (11)
- >90 (12)
- I don't know (13)

Display This Question:

If Tell us about your current kidney function based on one of these criteria = % Kidney function
Q86 What is your current % kidney function?

- (1)
- 15-29% (2)
- 30-44% (3)
- 45-59% (4)
- 60-89% (5)
- >90% (6)
- I don't know (7)

Display This Question:
If Tell us about your current kidney function based on one of these criteria = Stage

Q87 What is your current stage of kidney disease?

- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- I don't know (6)

End of Block: No, IDK Dialysis

Start of Block: Part 1 of 6: Tell us about your kidneys
Q14 Do you currently have a functioning kidney transplant?

- Yes (1)
- No (2)
- I don't know (3)

Display This Question:
If Do you currently have a functioning kidney transplant? = Yes
Or Do you currently have a functioning kidney transplant? = I don't know

Q15 When did you get your transplant?

▼ 1981 or before (2) ... I don't know (144)

Q16 Do you currently have protein in your urine?

- Yes (1)
- No (2)
- I don't know (3)

Q17 Are you currently taking erythropoietin stimulating agent or ESA (e.g., Aranesp, Darbepoetin, Eprex, Erythropoietin (EPO))?

- Yes (1)
- No (2)
- I don't know (3)
Q18 Is there anything else you would like to tell us?

____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________

Page Break

End of Block: Part 1 of 6: Tell us about your kidneys

Start of Block: Part 2 of 6: Tell us about your periods

Q19

Part 2 of 6: Tell us about your CURRENT experience with periods
How old were you when you first had your period (i.e., bleeding from your uterus that typically happens each month)?

○ Age  (1) __________________________________________________________

○ I never had my period  (2)

○ I don't know  (3)

Skip To: Q20 If Part 2 of 6: Tell us about your CURRENT experience with periods How old were you when you first h... = I never had my period
Q23 Within the last **3 months**, did you get a period?

- Yes (1)
- No (2)
- I don't know (3)

Display This Question:

If Within the last 3 months, did you get a period? = No
Or Within the last 3 months, did you get a period? = I don't know

Q24 Within the last **12 months**, did you get a period?

- Yes (1)
- No (2)
- I don't know (3)

Display This Question:

If Within the last 12 months, did you get a period? = No
Or Within the last 12 months, did you get a period? = I don't know

Q25 How old were you when you last experienced a period?

- Age (1) ____________________________________________
- I don't know (2)

Display This Question:

If Are you currently on dialysis? = Yes
Q26 Did your periods ever stop and then come back?

- Yes (1)
- No (2)
- I don't know (3)

Display This Question:

If Did your periods ever stop and then come back? = Yes
Or Did your periods ever stop and then come back? = I don't know

Q27 What was happening when your periods came back (click all that apply)?

- Received kidney transplant (1)
- Started home hemodialysis (2)
- Started nocturnal hemodialysis (3)
- Something else (please specify) (4) ________________________________
- I don't know (5)

Q28 Do you think your period has stopped permanently?

- Yes (1)
- No (2)
- I don't know (3)
Q20 Who do you talk to about never having a period (click all that apply)?

☐ Family members (1)

☐ Friends (2)

☐ Gynecologist (3)

☐ Kidney doctor (4)

☐ Nurse (5)

☐ Online support groups (6)

☐ Partner (10)

☐ Primary healthcare provider (e.g., family physician, nurse practitioner, primary care physician) (7)

☐ Someone else (please specify) (8) ______________________________________

☐ Nobody (9)
Q21 Who do you wish you could talk to about never having a period (click all that apply)?

- Family members (1)
- Friends (2)
- Gynecologist (3)
- Kidney doctor (4)
- Nurse (5)
- Online support groups (6)
- Partner (10)
- Primary healthcare provider (e.g., family physician, nurse practitioner, primary care physician) (7)
- Someone else (please specify) (8) ________________________________
- Nobody (9)

Display This Question:
If Part 2 of 6: Tell us about your CURRENT experience with periods How old were you when you first h... = I never had my period
Q22 Where do you learn about periods and kidney disease (click all that apply)?

- Books/magazines/newspapers (2)
- Educational websites (e.g., gynecology foundation websites, kidney foundation websites) (1)
- Kidney doctor (11)
- Movies/podcasts/radio/television (4)
- Other healthcare providers (12)
- Other people living with kidney disease (13)
- Social media (e.g., Facebook, Instagram, TikTok, Twitter, YouTube) (6)
- Somewhere else (please specify) (8) ________________________________
- Nowhere (9)

End of Block: Part 2 of 6: Tell us about your periods

Start of Block: Yes Period Stopped
Q29 Individuals whose periods have stopped may experience or have experienced new symptoms. Have you experienced any of these new symptoms (click all that apply)?

☐ Chills (1)
☐ Hot flashes (2)
☐ Irregular periods (3)
☐ Loss of breast fullness (4)
☐ Mood changes (5)
☐ Night sweats (6)
☐ Sleep problems (7)
☐ Thinning hair and/or dry skin (8)
☐ Vaginal dryness (9)
☐ Weight gain and slowed metabolism (10)
☐ None of these apply to me (11)

Q30 Have you ever been on menopausal hormone therapy?

☐ Yes (1)
☐ No (2)
☐ I don't know (3)
Q31 Have you ever been **offered** menopausal hormone therapy?

- Yes (1)
- No (2)
- I don't know (3)

Q32 Periods can be very predictable (i.e., you know exactly when the next one will occur), highly unpredictable (i.e., you don’t know when the next one will occur) or some pattern in between. How predictable was the start of your period?

- Very predictable (I could predict it within 0-4 days) (1)
- Predictable (I could predict it within 5-7 days) (2)
- Usually unpredictable (3)
- Always unpredictable (4)
- I don't know (5)

Q33 How many non-bleeding days did you usually have between your periods?

- Number of days (1) ________________________________________________
- I don't know (2)

Q34 How many days did you usually bleed?

- Number of days (1) ________________________________________________
- I don't know (2)
Q35 Which period products did you use (click all that apply)?

☐ Pad (1)

☐ Pantyliner (2)

☐ Period cup (3)

☐ Period underwear (4)

☐ Reusable cloth pad (5)

☐ Tampon (6)

☐ Something else (please specify) (7) ____________________________________

☐ None (8)

Q36 Did you ever use at least 2 period products together at the same time (e.g., tampon and pad together)?

☐ Yes (1)

☐ No (2)

☐ I don't know (3)
Q37 I was able to afford period products when I needed them:

- Always (1)
- Most times (2)
- Sometimes (3)
- Rarely (4)
- Never (5)

Q38 Tell us about your bleeding (click all that apply):

- During my period, I had to change my period product (e.g., pad, tampon, etc.) at least once an hour for several hours in a row (1)
- Sometimes, I had to wear multiple period products (e.g., multiple pads, pad and tampon, etc.) at the same time to control flow (2)
- Sometimes, I had to wake up in the middle of the night to change my period product (e.g., pad, tampon, etc.) (3)
- I passed blood clots at least the size of a quarter during my period (4)
- My period bleeding interfered with daily activities (5)
- None of these applied to me (6)
Q39 Who did you talk to about your periods (click all that apply)?

☐ Family members (1)
☐ Friends (2)
☐ Gynecologist (3)
☐ Kidney doctor (4)
☐ Nurse (5)
☐ Online support groups (6)
☐ Partner (10)
☐ Primary healthcare provider (e.g., family physician, nurse practitioner, primary care physician) (7)
☐ Someone else (please specify) (8) ________________________________
☐ Nobody (9)
Q40 Who did you wish you could talk to about your periods (click all that apply)?

☐ Family members (1)

☐ Friends (2)

☐ Gynecologist (3)

☐ Kidney doctor (4)

☐ Nurse (5)

☐ Online support groups (6)

☐ Partner (10)

☐ Primary healthcare provider (e.g., family physician, nurse practitioner, primary care physician) (7)

☐ Someone else (please specify) (8) ________________________________

☐ Nobody (9)
Q41 Where did you learn about periods and kidney disease (click all that apply)?

- Books/magazines/newspapers (2)
- Educational websites (e.g., gynecology foundation websites, kidney foundation websites) (1)
- Kidney doctor (3)
- Movies/podcasts/radio/television (4)
- Other healthcare providers (5)
- Other people living with kidney disease (7)
- Social media (e.g., Facebook, Instagram, TikTok, Twitter, YouTube) (6)
- Somewhere else (please specify) (8) ________________________________
- Nowhere (9)

End of Block: Yes Period Stopped

Start of Block: No, IDK Period Stopped

Q42 Periods can be very predictable (i.e., you know exactly when the next one will occur), highly unpredictable (i.e., you don’t know when the next one will occur) or some pattern in between. How predictable is the start of your period?

- Very predictable (I can predict it within 0-4 days) (1)
- Predictable (I can predict it within 5-7 days) (2)
- Usually unpredictable (3)
- Always unpredictable (4)
- I don't know (5)

--------------------------------------------------------------------------------------------------------------------------

75
Display This Question:

*If Periods can be very predictable (i.e., you know exactly when the next one will occur), highly unp... = Usually unpredictable*

*Or Periods can be very predictable (i.e., you know exactly when the next one will occur), highly unp... = Always unpredictable*

Q43 Individuals whose periods are becoming more irregular may experience or have experienced new symptoms. Have you experienced any of these new symptoms (click all that apply)?

- □ Chills (1)
- □ Hot flashes (2)
- □ Irregular periods (3)
- □ Loss of breast fullness (4)
- □ Mood changes (5)
- □ Night sweats (6)
- □ Sleep problems (7)
- □ Thinning hair and/or dry skin (8)
- □ Vaginal dryness (9)
- □ Weight gain and slowed metabolism (10)
- □ None of these apply to me (11)
If Periods can be very predictable (i.e., you know exactly when the next one will occur), highly unp... = Usually unpredictable

Or Periods can be very predictable (i.e., you know exactly when the next one will occur), highly unp... = Always unpredictable

Q44 Have you ever been **on** menopausal hormone therapy?

- Yes (1)
- No (2)
- I don't know (3)

Q45 Have you ever been **offered** menopausal hormone therapy?

- Yes (1)
- No (2)
- I don't know (3)

Q46 How many non-bleeding days do you usually have between your periods?

- Number of days (1) __________________________________________
- I don't know (2)
Q47 How many days do you usually bleed?

- [ ] Number of days (1) ________________________________
- [ ] I don't know (2)

Q48 Which period products do you use (click all that apply)?

- [ ] Pad (1)
- [ ] Pantyliner (2)
- [ ] Period cup (3)
- [ ] Period underwear (4)
- [ ] Reusable cloth pad (5)
- [ ] Tampon (6)
- [ ] Something else (please specify) (7) ________________________________
- [ ] None (8)

Q49 Do you ever use at least 2 period products together at the same time (e.g., tampon and pad together)?

- [ ] Yes (1)
- [ ] No (2)
- [ ] I don't know (3)
Q50 I am able to afford period products when I need them:

- Always (1)
- Most times (2)
- Sometimes (3)
- Rarely (4)
- Never (5)

Q51 Tell us about your bleeding (click all that apply):

- During my period, I need to change my period product (e.g., pad, tampon, etc.) at least once an hour for several hours in a row (1)
- Sometimes, I need to wear multiple period products (e.g., multiple pads, pad and tampon, etc.) at the same time to control flow (2)
- Sometimes, I need to wake up in the middle of the night to change my period product (e.g., pad, tampon, etc.) (3)
- I pass blood clots at least the size of a quarter during my period (4)
- My period bleeding interferes with daily activities (5)
- None of these apply to me (6)
Q52 Who do you talk to about your periods (click all that apply)?

- Family members (1)
- Friends (2)
- Gynecologist (3)
- Kidney doctor (4)
- Nurse (5)
- Online support groups (6)
- Partner (10)
- Primary healthcare provider (e.g., family physician, nurse practitioner, primary care physician) (7)
- Someone else (please specify) (8) ____________________________________________
- Nobody (9)

____________________________________________________________________________
Q53 Who do you wish you could talk to about your periods (click all that apply)?

☐ Family members (1)
☐ Friends (2)
☐ Gynecologist (3)
☐ Kidney doctor (4)
☐ Nurse (5)
☐ Online support groups (6)
☐ Partner (10)
☐ Primary healthcare provider (e.g., family physician, nurse practitioner, primary care physician) (7)
☐ Someone else (please specify) (8) ________________________________
☐ Nobody (9)

______________________________________________________________________________
Q54 Where do you learn about periods and kidney disease (click all that apply)?

☐ Books/magazines/newspapers (2)

☐ Educational websites (e.g., gynecology foundation websites, kidney foundation websites) (1)

☐ Kidney doctor (3)

☐ Movies/podcasts/radio/television (4)

☐ Other healthcare providers (5)

☐ Other people living with kidney disease (7)

☐ Social media (e.g., Facebook, Instagram, TikTok, Twitter, YouTube) (6)

☐ Somewhere else (please specify) (8) ________________________________

☐ Nowhere (9)

End of Block: No, IDK Period Stopped

Start of Block: Part 2 of 6: Tell us about your periods

Q89 Do you have spotting (bleeding that is lighter than a full period that occurs before your next period)?

☐ Yes (1)

☐ No (2)

☐ I don't know (3)

Q55 Is there anything else you would like to tell us?

___________________________________________________________________________
Q56
**Part 3 of 6: Tell us about your CURRENT experience with birth control**

Are you *currently* pregnant or breastfeeding?

- Yes (1)
- No (2)
- I don't know (3)

Q58 Are you currently having sex that has the potential to result in pregnancy?

- Yes (1)
- No (2)
- I don't know (3)
Q59 Are you actively trying to get pregnant now?

- Yes (1)
- No (2)
- I don't know (3)

Display This Question:
If Are you actively trying to get pregnant now? = Yes
Or Are you actively trying to get pregnant now? = I don't know

Q90 How long have you been trying to get pregnant?

▼ 1 month or less (1) ... I don't know (14)

Display This Question:
If Are you actively trying to get pregnant now? = Yes
Or Are you actively trying to get pregnant now? = I don't know

Q60 Are you currently receiving fertility treatment?

- Yes (1)
- No (2)
- I don't know (3)
Q61 Are you **currently** using any birth control?

- Yes (1)
- No (2)
- I don't know (3)

---

**Display This Question:**

If Are you currently using any birth control? = Yes

Or Are you currently using any birth control? = I don't know

---

Q88 What is the reason you are using birth control (click all that apply)?

- To prevent pregnancy (1)
- To manage my periods (2)
- Other reason(s) (please specify) (4) ________________________________
- I don't know (3)

---

**Display This Question:**

If Are you currently using any birth control? = Yes

Or Are you currently using any birth control? = I don't know
Q62 Which type(s) are you currently using (click all that apply)? For how many years (if you don't know, then you may skip the text box)?

☐ Abstinence (years) (20) ______________________________________________

☐ Cervical cap (years) (1) _____________________________________________

☐ Cervical sponge (years) (2) __________________________________________

☐ Combined birth control pill (years) (3) _________________________________

☐ Copper intrauterine device (IUD) (years) (4) ___________________________

☐ Diaphragm (years) (5) _______________________________________________

☐ Female condom (years) (6) ___________________________________________

☐ Hormonal intrauterine device (IUD) (years) (7) _________________________

☐ Implant (years) (8) _________________________________________________

☐ Injectable (years) (9) _______________________________________________

☐ Male condom (years) (10) ___________________________________________

☐ Patch (years) (11) _________________________________________________

☐ Progestin-only pill/minipill (years) (12) _______________________________

☐ Rhythm method (years) (21) _________________________________________

☐ Salpingectomy (years) (13) _________________________________________

☐ Spermicide (years) (14) _____________________________________________

☐ Tubal ligation (years) (15) _________________________________________
Display This Question:

If Are you currently using any birth control? = No

Q83 Why are you not using birth control (click all that apply)?

- Cost (1)
- Fear (2)
- Healthcare provider's advice (3)
- I am not having sex (9)
- I am trying to get pregnant (10)
- Influence of family (4)
- Influence of friends (5)
- Influence of social media (6)
- Religion (7)
- Other reason(s) (please specify) (8) _________________________________
Q63 Who do you talk to about birth control (click all that apply)?

☐ Family members (1)

☐ Friends (2)

☐ Gynecologist (3)

☐ Kidney doctor (4)

☐ Nurse (5)

☐ Online support groups (6)

☐ Partner (10)

☐ Primary healthcare provider (e.g., family physician, nurse practitioner, primary care physician) (7)

☐ Someone else (please specify) (8) ______________________________________

☐ Nobody (9)
Q64 Who do you wish you could talk to about birth control (click all that apply)?

- [ ] Family members (1)
- [ ] Friends (2)
- [ ] Gynecologist (3)
- [ ] Kidney doctor (4)
- [ ] Nurse (5)
- [ ] Online support groups (6)
- [ ] Partner (10)
- [ ] Primary healthcare provider (e.g., family physician, nurse practitioner, primary care physician) (7)
- [ ] Someone else (please specify) (8) ______________________________________
- [ ] Nobody (9)
Q65 Where do you learn about birth control and kidney disease (click all that apply)?

☐ Books/magazines/newspapers (2)

☐ Educational websites (e.g., gynecology foundation websites, kidney foundation websites) (1)

☐ Kidney doctor (3)

☐ Movies/podcasts/radio/television (5)

☐ Other healthcare providers (4)

☐ Other people living with kidney disease (7)

☐ Social media (e.g., Facebook, Instagram, TikTok, Twitter, YouTube) (6)

☐ Somewhere else (please specify) (8) ____________________________

☐ Nowhere (9)

Q66 Is there anything else you would like to tell us?

________________________________________________________________

________________________________________________________________

________________________________________________________________

________________________________________________________________

________________________________________________________________

Page Break

End of Block: Part 3 of 6: Tell us about your birth control
Q67  
**Part 4 of 6: Tell us about your gynecology history**  
Have you ever been diagnosed with (click all that apply):

- [ ] Cancer of the female reproductive organs (1)
- [ ] Endometriosis (2)
- [ ] History of infertility (actively trying to conceive for 12 months or longer without success) (8)
- [ ] Polycystic ovarian syndrome (PCOS) (3)
- [ ] Premature menopause/premature ovarian failure/primary ovarian insufficiency (POF/POI) (4)
- [ ] Uterine fibroids or polyps (5)
- [ ] Other (please specify) (9) ________________________________
- [ ] I don't know (6)
- [ ] None of these apply to me (7)

Q68 Have you had your uterus removed?

- [ ] Yes (1)
- [ ] No (2)
- [ ] I don't know (3)
Q69 Have you had your ovary/ies removed?
   ○ Yes (1)
   ○ No (2)
   ○ I don't know (3)

Display This Question:
   If Have you had your ovary/ies removed? = Yes
   Or Have you had your ovary/ies removed? = I don't know

Q70 How many ovaries?
   ○ 1 (1)
   ○ 2 (2)
   ○ I don't know (3)

Q71 Is there anything else you would like to tell us?

________________________________________________________________
________________________________________________________________
________________________________________________________________
________________________________________________________________
________________________________________________________________

Page Break

End of Block: Part 4 of 6: Tell us about your gynecology history
Q72  
**Part 5 of 6: Tell us about your medical history**  
Have you ever needed a blood transfusion?

- Yes (1)
- No (2)
- I don't know (3)

Q73 Are you currently on a blood thinner (e.g., aspirin, heparin, oral anti-coagulants, warfarin)?

- Yes (1)
- No (2)
- I don't know (3)

Q74 Have you ever received (click all that apply):

- [ ] Chemotherapy (1)
- [ ] Immunosuppressive medications (e.g., cyclophosphamide, Cytoxan, methotrexate, mycophenolate mofetil (MMF), CellCept) (2)
- [ ] Lupron (leuprolide) (3)
- [ ] Radiation to the pelvis or abdomen (4)
- [ ] I don't know (5)
- [ ] None of these apply to me (6)
Q75 Is there anything else you would like to tell us?

________________________________________________________________
________________________________________________________________
________________________________________________________________
________________________________________________________________
________________________________________________________________

Page Break

End of Block: Part 5 of 6: Tell us about your medical history

Start of Block: Part 6 of 6: Tell us about yourself
Q76
Part 6 of 6: Tell us about yourself
How do you primarily identify?

- Black (1)
- Caribbean (2)
- Central Asian (4)
- East Asian (5)
- Indigenous (6)
- Latinx (7)
- Middle Eastern or North African (8)
- Pacific Islander (9)
- South Asian (10)
- Southeast Asian (11)
- White (3)
- I prefer to self-identify as (12) ______________________________________________
- I prefer not to say (13)

Q77 What was the sex on your birth certificate?

- Female (1)
- Intersex (2)
- Male (3)
- I prefer not to say (4)
Q78 What best describes your current gender identity (i.e., who you are in your day-to-day life)?

- Agender (I don’t identify as having a gender identity) (1)
- Cis man (I identify as a man and my sex at birth is male) (6)
- Cis woman (I identify as a woman and my sex at birth is female) (10)
- Demigender (I feel partially connected to a particular gender identity) (2)
- Gender fluid (my gender identity varies over time) (4)
- Gender-nonconforming (in terms of appearance and/or behavior, I don’t adhere to the traditional gender expectations) (5)
- Genderqueer (I don’t identify as a man nor woman, but somewhere in between, beyond, or a combination of gender identities) (3)
- Non-binary (I don’t fit into traditional gender categories) (7)
- Transgender man (I identify as a man and my sex at birth is female) (8)
- Transgender woman (I identify as a woman and my sex at birth is male) (13)

Display This Choice:
If Part 6 of 6: Tell us about yourself How do you primarily identify? = Indigenous

- Two-spirit (I identify as an Indigenous person who has both a feminine and masculine spirit) (9)
- I prefer to self-identify as (11) ____________________________________________
- I prefer not to say (12)

Q79 Is there anything else you would like to tell us?

________________________________________________________________________
Thank you for completing the survey. Would you like to be contacted to participate in a future telephone interview to discuss how kidney disease affects periods and birth control among female patients? All telephone conversations will be audio-recorded, and all comments will be transcribed and used in combination with your survey responses.

- Yes (1)
- No (2)

This is the end of the survey. You now have the option of entering a draw for a chance to win 1 in 10 Amazon gift cards ($50 CAD). Would you like to enter the draw?

- Yes (1)
- No (2)
Display This Question:

If Future Telephone Interview Thank you for completing the survey. Would you like to be contacted to... = Yes

Or Prize Draw This is the end of the survey. You now have the option of entering a draw for a chance... = Yes

Q83 Please provide your telephone number and/or email address.

☐ Telephone number (1) ________________________________

☐ Email address (2) ________________________________

End of Block: Future Telephone Interview, Prize Draw
<table>
<thead>
<tr>
<th>Item Category</th>
<th>Checklist Item</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Describe survey design</td>
<td>This is a global web-based survey targeting people with CKD (any stage) who were born with a uterus and are 18-50 years of age to describe self-assessed menstruation and contraceptive use. A snowball sampling method of recruitment will be used.</td>
</tr>
<tr>
<td><strong>IRB (Institutional Review Board) approval and informed consent process</strong></td>
<td>IRB approval</td>
<td>This study will be approved by the University of Calgary Conjoint Health Research Ethics Board (REB21-0326).</td>
</tr>
<tr>
<td></td>
<td>Informed consent</td>
<td>All participants will provide informed consent before beginning the survey by selecting the option indicating that they understand the information and consent to voluntary participation. The e-consent form will be the first page of the survey outlining who the principal investigator is, background information, purpose of the study, what participation entails, the estimated time length of the survey, nature of the questions, confidentiality, and data storage.</td>
</tr>
<tr>
<td></td>
<td>Data protection</td>
<td>All data will be kept confidential and stored securely. A secure online survey platform called Qualtrics will be used. All data are encrypted and stored directly on its secure servers. Researcher access to the survey data is password-protected and the transmission is encrypted. Survey responses cannot be linked to participants’ computer. Only members of the research team will have access to the data, and all data will be analyzed in aggregate. A unique identifier code will be used in place of participants’ name. Identifying data will be stripped from all results derived from this study.</td>
</tr>
<tr>
<td><strong>Development and pre-testing</strong></td>
<td>Development and testing</td>
<td>The survey will be developed by reviewing relevant literature and obtaining input from patients, nephrologists, and gynecologists. Qualtrics paid translation services will initially be used to translate the survey into 15 languages and a language assistance plan will be developed to make corrections and ensure cultural safety. An assessment of the face validity, clarity, length, and</td>
</tr>
</tbody>
</table>
The completeness of the survey will be performed through semi-structured interviews (pre-testing) with stakeholders. The survey will be finalized based on collective feedback.

<table>
<thead>
<tr>
<th><strong>Recruitment process and description of the sample having access to the questionnaire</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Open survey versus closed survey</strong></td>
<td>This is an open survey that will be sent via targeted email to kidney patient groups and kidney-based foundations and organizations around the world for dissemination among their members. The survey will also be broadly disseminated via social media platforms (Twitter, Facebook), where anyone who is online and/or has an account can access the publicly available survey.</td>
<td></td>
</tr>
<tr>
<td><strong>Contact mode</strong></td>
<td>Kidney patient groups and kidney-based foundations and organizations will be sent a scripted recruitment request via email to disseminate the survey among their members. This email will include a link to the survey on Qualtrics.</td>
<td></td>
</tr>
<tr>
<td><strong>Advertising the survey</strong></td>
<td>The survey will be advertised upon receiving permission from the various kidney patient groups and kidney-based foundations and organizations to disseminate the survey on their weekly/monthly emails, newsletters, websites, and social media platforms (Twitter, Facebook). A banner ad will be posted on social media outlining the nature of eligible participants, topics covered, incentive, as well as the link and QR code to the online survey.</td>
<td></td>
</tr>
</tbody>
</table>

<p>| <strong>Survey administration</strong> | <strong>Web/email</strong> | Key stakeholders will be sent a targeted email with the survey information and link that will be disseminated to their members via email (mailing lists) and posted on social media. It will also be found on the websites of these kidney groups and organizations. |
| | <strong>Context</strong> | The survey will be available globally to anyone who has internet access. The websites in which the survey will be advertised are intended for patients with kidney disease. It is likely that most website visitors search for educational resources. Using websites as a vehicle of survey dissemination may impact the sample as patients without internet access or who are uncomfortable |</p>
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandatory/voluntary</td>
<td>Participation is completely voluntary, and all participants will be aware of this.</td>
</tr>
<tr>
<td>Incentives</td>
<td>Participants will be aware that they have a chance to win 1 in 10 Amazon gift cards ($50 CAD) in a draw of all participants who complete the survey.</td>
</tr>
<tr>
<td>Time/date</td>
<td>The survey will remain open from May to July 2021.</td>
</tr>
<tr>
<td>Randomization of items or questionnaires</td>
<td>Items will not be randomized or alternated.</td>
</tr>
<tr>
<td>Adaptive questioning</td>
<td>Depending on certain responses, some participants may have follow-up questions, resulting in a longer time to complete the survey, though this will reduce the number and complexity of questions for others.</td>
</tr>
<tr>
<td>Number of items</td>
<td>There will be 6 parts of the survey, each focusing on a different outcome. The number of questions per page is currently unknown.</td>
</tr>
<tr>
<td>Number of screens (pages)</td>
<td>The number of screens (pages) is currently unknown.</td>
</tr>
<tr>
<td>Completeness check</td>
<td>To check completeness, a combination of literature review and consultation with experts in the field will be done and consensus will be reached. To ensure participants have not merely skipped a question, options such as “I don’t know”, “I prefer not to say”, and “None of these apply to me” will be provided.</td>
</tr>
<tr>
<td>Review step</td>
<td>Respondents will be able to review/change their answers using a “Back” button.</td>
</tr>
<tr>
<td><strong>Response rates</strong></td>
<td></td>
</tr>
<tr>
<td>Unique site visitor</td>
<td>Potential respondents will be provided with a link and QR code to the survey’s online portal (an electronic questionnaire via Qualtrics). The Prevent Ballot Box Stuffing option on Qualtrics will prevent respondents from re-taking the survey.</td>
</tr>
<tr>
<td>View rate</td>
<td>N/A</td>
</tr>
<tr>
<td>Participation rate</td>
<td>The participation rate will be determined by counting the unique number of respondents who agreed to participate in the survey by providing informed consent, divided by visitors who simply visited/viewed the informed consent page.</td>
</tr>
</tbody>
</table>
## Completion rate
The completion rate, to assess for attrition, will be determined by counting the number of respondents who submitted the last page of the survey, divided by the number of people who agreed to participate by submitting the first page (informed consent).

## Preventing multiple entries from the same individual
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cookies used</td>
<td>The Prevent Ballot Box Stuffing option on Qualtrics will prevent respondents from re-taking the survey multiple times by placing a cookie on their browser after submitting a response.</td>
</tr>
<tr>
<td>IP check</td>
<td>N/A</td>
</tr>
<tr>
<td>Log file analysis</td>
<td>N/A</td>
</tr>
<tr>
<td>Registration</td>
<td>As this is an open survey, there is no participant registration.</td>
</tr>
</tbody>
</table>

## Analysis
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Handling of incomplete questionnaires</td>
<td>Incomplete questionnaires may not be included for analysis, depending on the number of respondents. Only responses completed within a reasonable timeframe (based on pre-testing) will be analyzed.</td>
</tr>
<tr>
<td>Questionnaires submitted with an atypical timestamp</td>
<td>The cut-off point will be determined from pre-testing. Any survey submitted sooner than that will not be analyzed.</td>
</tr>
<tr>
<td>Statistical correction</td>
<td>If we obtain an unrepresentative sample, methods of statistical correction (e.g., weighting of responses) will be used.</td>
</tr>
</tbody>
</table>
2.11 Supplemental Figures

**Supplemental Figure 1.** Period products used among participants with current menses. Numbers add up to more than 100% as participants were able to submit multiple responses.
Supplemental Figure 2. Reasons for not using contraception. Numbers add up to more than 100% as participants were able to submit multiple responses.
Chapter 3: Manuscript (In-Progress) – Menstruation and Reproductive Hormones in Kidney Failure

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¹Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; ²Libin Cardiovascular Institute, Calgary, Alberta, Canada; and ³Alberta Kidney Disease Network, Calgary, Alberta, Canada

3.1 Abstract

Kidney failure disrupts the hypothalamic-pituitary-ovarian axis, resulting in reproductive hormone abnormalities. It is not fully understood if these disturbances impact menstruation in females living with kidney failure treated with dialysis. Therefore, this study aimed to (1) describe menstruation and changes in menstrual patterns with chronic kidney disease (CKD) progression, and (2) assess associations between reproductive hormones and menstrual patterns among females with kidney failure. Females aged 18-50 years were recruited from dialysis clinics around Calgary, Alberta, Canada. Using a self-administered survey, demographic, kidney health, and menstrual health histories were recorded. Blood samples were collected to measure follicle-stimulating hormone, luteinizing hormone, estradiol, progesterone, testosterone, prolactin, sex hormone binding globulin, and anti-Müllerian hormone levels. Descriptive and bivariate analyses were performed as appropriate. Twenty-seven females [n=23 hemodialysis (age 36 (IQR: 31,44) years), n=4 peritoneal dialysis (age 38 (IQR: 30,45) years)], largely
identifying as white cisgender women were included. In the hemodialysis group, 52% reported absent menstrual bleeding during dialysis, though only 17% reported this during CKD and 9% before CKD diagnosis (p=0.01); however, there was no difference in proportions across timepoints in the peritoneal dialysis group (25% each) (p=0.92). In the hemodialysis group, 48% described heavy menstrual bleeding during dialysis; this proportion did not differ during CKD (65%) and before CKD diagnosis (70%) (p=0.20). Among participants on peritoneal dialysis, 25% described heavy menstrual bleeding during dialysis, which did not significantly differ during CKD (25%) and before CKD diagnosis (50%) (p=0.91). All the hormone levels did not differ between those with absent and present menstrual bleeding during dialysis, nor did it differ between those with heavy and normal menstrual bleeding. Among females with dialysis-dependent kidney failure, proportions of absent and heavy menstrual bleeding were high. No associations between reproductive hormone levels and menstrual status were observed, underscoring the uncertainty around how kidney disease affects female reproductive health.

3.2 Introduction

Kidney failure affects 0.1% of the global population, though in Canada, the prevalence is expected to double over the next 20 years. Studies have found that chronic kidney disease (CKD) disproportionately affects more females than males as this population has a notably lower survival rate and quality of life. Therefore, there is an important need to understand the sex-specific factors that tend to yield these negative outcomes. The menstrual cycle and reproductive hormones [e.g., gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), hormone (LH), estrogen, progesterone, prolactin, anti-Müllerian hormone (AMH)] are worth considering when investigating kidney disease in females given the
key role the kidneys play in regulating such hormones.\textsuperscript{27} In kidney disease, disruption of the hypothalamic-pituitary-ovarian axis is thought to result in an abnormal reproductive hormone profile, where people with kidney failure tend to have the most severe disruptions.\textsuperscript{14,24,26,151} Unfortunately, there is limited research on abnormal uterine bleeding, which is the disruption of a healthy menstrual cycle by volume, regularity, frequency, and/or duration of menses, and how it relates to various hormone levels in the setting of kidney failure.\textsuperscript{14,24,151,152} While existing literature suggests a high prevalence of abnormal uterine bleeding and hormone levels that stray from typical ranges,\textsuperscript{14,24,151,152} these are small-scale and older studies, hence, updated research on this topic is necessary. Therefore, the objectives of this exploratory, cross-sectional study were to (1) describe self-assessed menstruation and changes in menstrual patterns with CKD progression, and (2) explore the association between reproductive hormone profile and menstrual status among reproductive-aged female living with kidney failure.

3.3 Methods

3.3.1 Survey Development

The survey (Supplemental File A) was adapted from a previously developed interview guide for this study. Additionally, it was informed by existing literature and consulting with people with female sex assigned at birth living with kidney disease (n=6) representing 3 different countries and a team of multidisciplinary experts [nephrologist (n=2), gynecologist (n=1), general internist (n=1), endocrinologist (n=1), family physician (n=1), in-center hemodialysis nurse (n=1), home hemodialysis nurse (n=1), nocturnal hemodialysis nurse (n=1), peritoneal dialysis nurse (n=1), non-dialysis CKD nurse (n=1), nephrology research nurse manager (n=1)]. Pretesting to assess the face validity, clarity, length, and completeness of the survey was performed through semi-
structured interviews or by obtaining written feedback from all 17 collaborators. After updating the survey, it was then pilot tested to ensure the questions and items were coherent and relevant.  

### 3.3.2 Survey Dissemination

Included participants were those born with a uterus, aged 18-50 years, and had dialysis-dependent kidney failure. Exclusion criteria comprised of those who were pregnant or breastfeeding, had a kidney transplant, had acute kidney injury, or were undergoing fertility treatment. Additionally, participants were excluded if they had polycystic ovarian syndrome or primary ovarian insufficiency, underwent surgical menopause (i.e., oophorectomy, hysterectomy), had a history of pelvic/abdominal radiation, chemotherapy, or gonadotoxic medication use (e.g., cyclophosphamide), or if they were unable to provide informed consent. The survey was available in English and all participants received a Tim Hortons gift card ($10 CAD) upon survey completion. An informative recruitment poster was created and shared across the Southern Alberta Kidney Care dialysis units and clinics in Calgary, Alberta, Canada (Foothills Hemodialysis Unit, Northwest Hemodialysis Unit, Peter Lougheed Hemodialysis Unit, Sheldon M. Chumir Hemodialysis Unit, Sheldon M. Chumir Home Hemodialysis and Peritoneal Dialysis Clinics, South Calgary Hemodialysis Unit, Sunridge Hemodialysis Unit). Minimally disruptive, prearranged educational in-services to dialysis nurses at each location were provided to streamline the identification of potential participants such that nurses were able to identify eligible participants and obtain consent to contact. A convenience sampling method of recruitment was utilized, aiming to recruit 10 participants each on hemodialysis and peritoneal dialysis. Given the exploratory nature of this descriptive study, the sample size represented a
reasonable number of participants anticipated to provide meaningful data. The recruitment period began on 14 September 2021 and ended on 14 April 2022.

3.3.3 Data Collection and Analysis

Ethics approval was obtained from the University of Calgary Conjoint Health Research Ethics Board (ethics ID REB19-0822) and participation in the study was voluntary. After obtaining consent to contact, dialysis nurses received written informed consent from eligible participants. At routine hemodialysis sessions, participants completed the self-administered survey and for those on peritoneal dialysis, the survey was completed either in clinic or at home, where the surveys were mailed out to them. Demographic (e.g., age, ethnicity, sex assigned at birth, current gender identity), medical history (e.g., kidney, gynecologic, hematologic), and menstruation (e.g., menarche, menstruation, menopause) information were collected. For the menstrual outcomes, responses were collected regarding participants’ menstrual cycles during dialysis, during CKD, and before CKD diagnosis. Dialysis nurses and trained phlebotomists completed the blood requisition forms and obtained samples including the hormones FSH, LH, estradiol, progesterone, testosterone, prolactin, sex hormone binding globulin (SHBG), and AMH. For participants with current menses, the samples were timed to their menstrual cycle and consistently collected in the early follicular phase (i.e., between days 1-7 of the menstrual cycle). Standardizing blood collection to the menstrual cycle ensured that bloodwork for all participants with menses is drawn at approximately the same time. For those who did not have current menses, samples were collected at any time. Data were analyzed with descriptive statistics [median (IQR), proportions, percentages] given the exploratory nature of this study. Statistical analyses were performed using the Mann-Whitney U test to compare reproductive hormone
levels between those with absent and present menstrual bleeding as well as those with heavy and normal menstrual bleeding. Pearson’s chi-squared test was also used to assess for any differences in the prevalence of absent and heavy menstrual bleeding during dialysis, during CKD, and before CKD diagnosis. Finally, linear regression analyses were completed to determine an association between age and various reproductive hormone levels. P<0.05 was considered statistically significant for all analyses.

3.4 Results

3.4.1 Demographics

While a total of 30 participants completed the study, 3 were eliminated based on exclusion criteria. Of the remaining 27 participants, 23 were receiving either in-center, home, or nocturnal hemodialysis and 4 were being treated with peritoneal dialysis. Table 4 summarizes participant demographic characteristics. In both hemodialysis and peritoneal dialysis groups, most people identified as white, female, and cisgender women. Diabetes was the most common cause of CKD and while nearly half the participants in each group needed a blood transfusion, the majority did not have a bleeding disorder. Table 5 outlines participants’ reproductive health history. In terms of gynecologic diagnoses, most hemodialysis and peritoneal dialysis participants were healthy. Of those who had been pregnant, most have not experienced pregnancy complications in both groups. Additionally, while about a quarter of participants in each group experienced infertility, only 2 people in the hemodialysis group received fertility treatment and only 1 hemodialysis and peritoneal dialysis participant reported that their nephrologist had discussed fertility and pregnancy with them.
3.4.2 Menstruation

Menstrual characteristics among participants on hemodialysis and peritoneal dialysis are described in Table 6. Before CKD, during CKD, and during dialysis, the prevalence of absent menstrual bleeding significantly increased throughout this time period in the hemodialysis group (p=0.01), although there was no significant difference for the peritoneal dialysis group (p=0.92). Figure 11 supports these results for both the hemodialysis (panel A) and peritoneal dialysis (panel B) groups. Figure 12 depicts the predictability of menses during dialysis, during CKD, and before CKD. For the hemodialysis group during dialysis, most participants reported that their periods were “usually unpredictable”, whereas during CKD, asides from being “unsure”, the majority reported that they were “predictable”, and before CKD, most reported that they were “very predictable” (Figure 12, panel A). Among the peritoneal dialysis group, asides from half the participants reporting that they were “unsure” how predictable their periods were during dialysis and CKD, a quarter reported their periods were “very predictable” and “predictable” during dialysis (Figure 12, panel B). During CKD, peritoneal dialysis participants responded that their periods were equally “very predictable” and “usually unpredictable”, whereas before CKD, participants equally reported that they were “very predictable”, “usually unpredictable”, and “always unpredictable”. Table 6 further outlines menopause among participants, where only people on hemodialysis reported experiencing menopause, while Table 7 focuses on these 9 participants. Of these participants who were <40 years of age and/or currently experiencing these symptoms, none reported having discussions about hormone replacement therapy with their nephrologist, kidney care team, or family doctor, nor received it. In terms of the clinical indicators of heavy menstrual bleeding, Table 8 summarizes the proportion of participants on hemodialysis and peritoneal dialysis who reported changing their period product more than once
per hour for several hours, had to use multiple period products at once, had to wake up at night to change their period product, passed blood clots the size of a quarter, and whose periods interfered with their daily activities during dialysis, during CKD, and before CKD. Overall, almost half the hemodialysis group experienced at least one of the indicators of heavy menstrual bleeding during dialysis, compared to most during CKD and before CKD, although this was not statistically significant (p=0.20). Additionally, a quarter of those on peritoneal dialysis reported at least one of the clinical indicators of heavy menstrual bleeding during dialysis and during CKD compared to half before CKD, but this was again, not significant (p=0.90). This information is also displayed in Figure 13, panels A and B.

3.4.3 Female Reproductive Hormones

Reproductive hormone levels were evaluated based on dialysis modality (Table 9). When considering the reported point estimate compared to the reference range, LH, FSH, estradiol, progesterone, SHBG, and AMH levels were healthy in both hemodialysis and peritoneal dialysis groups. However, testosterone levels in the hemodialysis group were lower than the reference range and for both groups, prolactin levels were higher than normal. When comparing hormone levels in those with absent versus present menstrual bleeding using the Mann-Whitney U test, none of the values were significantly different between groups (p=0.7 LH, p=0.3 FSH, p=0.2 estradiol, p=0.4 progesterone, p=0.9 testosterone, p=0.3 prolactin, p=0.1 SHBG, p=0.8 AMH; Table 10). Similarly, in Table 11, there were no significant differences in any of the hormone levels between those with heavy menstrual bleeding and those without (p=0.2 LH, p=0.99 FSH, p=0.97 estradiol, p=0.5 progesterone, p=0.5 testosterone, p=0.5 prolactin, p=0.5 SHBG, p=0.7 AMH). When assessing for potential relationships between age and hormone levels, Figure 14,
panels A, C, D, F, and G show that respectively, LH, estradiol, progesterone, prolactin, and SHBG levels were not associated with age. However, in Figure 14, panels B, E, and H, FSH is positively associated with age \((p=0.04)\), while testosterone \((p<0.01)\) and AMH \((p<0.01)\) are negatively associated with age.

3.5 Discussion

This cross-sectional, exploratory study updates the literature on self-assessed menstruation and changes in menstrual patterns with CKD progression, in addition to investigating the association between reproductive hormone profile and menstrual status among young females with dialysis-dependent kidney failure. While the prevalence of absent menstrual bleeding significantly increased from before being diagnosed with CKD until being treated with hemodialysis, this did not differ for those receiving peritoneal dialysis. In terms of predictability of menses before CKD, during CKD, and during dialysis, participants in the hemodialysis group reported their periods to be trending towards decreased predictability throughout the course of their kidney disease, though, there is no clear pattern in the peritoneal dialysis group. There were 9 participants, all of which were being treated with hemodialysis, who reported experiencing menopause. However, none reported having discussions about hormone replacement therapy during their kidney care, thus none reported ever receiving it. Finally, the prevalence of heavy menstrual bleeding did not significantly change during dialysis, during CKD, and before CKD in both hemodialysis and peritoneal dialysis groups.

There are few studies that focus on abnormal menstruation within the kidney failure population although, these tend to be older and smaller in size.\(^{14,24,151,152}\) For instance, one study consisting
of 17 premenopausal females with dialysis-dependent kidney failure determined that only 1 participant experienced regular menses, suggesting a prevalence of abnormal menstruation of 94% in this population. Another study of 95 females undergoing kidney replacement therapy found heavy and absent menstrual bleeding to also be common, with 50 and 33 participants experiencing them, respectively. Additional research focusing on 75 reproductive-aged females on hemodialysis found that three quarters of their sample had menstrual disturbances, again largely attributed to absent menstrual bleeding. We are aware of only one study that clearly explores the prevalence of abnormal menses throughout the progression of CKD. The authors determined that of the 76 female participants on dialysis, 58% reported an absence of menses and 59% of those who still had menstrual cycles reported irregular bleeding, while 64% had heavy flows with blood clots. However, before initiating dialysis, 37% had absent menstrual bleeding, with 75% of participants reporting regular menses and 38% experiencing heavy flows with blood clots. These results align with our findings of the hemodialysis group, as the prevalence of absent menstrual bleeding significantly increased throughout participants’ progression to dialysis-dependent CKD; however, this difference may be attributed to participants’ age, especially if these timepoints spanned a wide range in their lives. In terms of the prevalence of heavy menstrual bleeding, our study found no significant difference throughout the progression of CKD, which differs from a previous study that revealed more people to experience heavy bleeding during dialysis compared to before. The underlying mechanisms and reasons for these differences are unclear, nonetheless, it is important to acknowledge the small sample size that may have yielded these non-significant results.
To our knowledge, this study was the first to evaluate a comprehensive variety of reproductive hormones within the dialysis-dependent kidney failure population to this extent. Our results show that reproductive hormone levels in females with kidney failure are comparable to the ranges of the healthy population. An exception was prolactin in the peritoneal dialysis group, in which the point estimate and spread were above the healthy range. Although studies have previously reported hyperprolactinemia in the presence of CKD, where reduced renal clearance and increased production of prolactin may be responsible, our results must be interpreted with caution due to the limited sample size. Further our findings contradict other literature that have found changes in hormone levels in the setting of CKD. In a multicenter study of reproductive-aged females on hemodialysis, those with abnormal menses had lower mean serum progesterone levels compared to the healthy range while estradiol levels varied in participants depending on the type of abnormal uterine bleeding. Mean FSH and LH levels were also elevated in this group compared to the controls. However, an older study of 17 females with kidney failure found that while estradiol, progesterone, and FSH levels were similar to the healthy population in the follicular phase, estradiol levels do not increase midcycle to trigger the LH surge, despite LH levels being slightly higher in the follicular phase compared to the controls. Therefore, our research highlights that factors asides from hormones and the hypothalamic-pituitary-ovarian axis may be at play with respect to females’ menstrual status. Our linear regression analyses found that FSH is positively associated with age, where 16% of the variation can be attributed to age, whereas testosterone and AMH were negatively associated with age as respectively 35% and 41% of the variation was due to age. These results coincide with what tends to occur in the general population, thus, the wide age range captured in our sample could potentially be obscuring the relationship between hormone levels and menstrual
profiles. Further, our study shows similar reproductive hormone levels in absent compared to present menstrual bleeding, similar to the comparison between heavy and normal menstrual bleeding. This contradicts what we expected to find given that abnormal menstruation has previously been associated with disruptions in the hypothalamic-pituitary-ovarian axis in CKD. Ultimately, we recommend that further research be done to understand how despite having healthy hormone levels, abnormal uterine bleeding can still manifest in people with kidney failure. Finally, our study reveals a high prevalence of early menopause, particularly in the hemodialysis group. Menopause is defined as the absence of a menstrual period for >12 months, and in the general population occurs at an average age of 51 years. Among females being treated with dialysis, the average age of menopause was reported as 47 years, which is important since early menopause is associated with a higher incidence of cardiovascular disease and mortality. However, there is difficulty assessing menopause status in females with CKD as cessation of menses may be attributed to the kidney disease itself (i.e., functional menopause). A prospective cohort study of females with dialysis-dependent kidney failure noted that while in the general population, hormone levels can be useful to determine menopause status rather than evaluating menses, authors highlighted challenges using this classification system within the kidney failure population. Therefore, it still remains unclear how menopause status can be elucidated in our sample.

Our study has several limitations and strengths. First, the small sample size may have limited the power of this study to detect truly significant differences and relationships; however, the results will serve as the foundation for further comprehensive work in this area. Next, while serum hormone levels were collected only at one point throughout the study, single measurements have
previously shown to be reliable indicators of long-term reproductive hormone levels.\textsuperscript{187,188}

Additionally, this study was the first to our knowledge, to examine a diversity of reproductive hormones in females with kidney failure to this extent,\textsuperscript{151} including SHBG and testosterone, in addition to including people being treated with peritoneal dialysis. Convenience sampling is another a limitation of the study as it may have hindered the generalizability of our results, given that our sample largely consisted of white cisgender women. Nonetheless, it is important to recognize that the exploratory nature of this project is hypothesis-generating and will aid in the development of future studies that will capture a greater diversity of participants. The self-reported nature of the data for the survey portion of the study must also be acknowledged as recall bias may have been present especially as participants had to remember their experiences before they were being treated with dialysis and even before they had CKD; however, previous studies found recall of certain menstrual characteristics reliable and valid.\textsuperscript{46,164,166,167} Finally, using the term “period” instead of “uterine bleeding” in the survey is a limitation given its non-medical, gendered connotation. Although terms such as “uterine bleeding”, “bleeding from your uterus”, and “bleeding from your vagina” are more accurate, participants may have had difficulty truly understanding their meanings.

This study of reproductive-aged females with kidney failure on dialysis shows that there is a high prevalence of abnormal uterine bleeding, particularly absent and heavy menstrual bleeding, despite having generally healthy levels of reproductive hormones. This is especially important to recognize in kidney failure since abnormal menstruation has previously been associated with increased cardiovascular risk.\textsuperscript{46} Further, our results describe a lack of difference between all studied hormone levels when comparing those with absent and present menstrual bleeding and
those with heavy and normal menstrual bleeding. Unfortunately, we are unaware of any physiological mechanisms that could possibly explain these results, though we emphasize the importance of pursuing further research to understand these novel, sex-specific findings.

3.6 Disclosure

All the authors declare no competing interests.

3.7 Acknowledgments

We gratefully acknowledge RB, ND, KF, AG, LH, JH, GH, KJ, HL, JK, EO, LP, NS, JZ, and all study participants for their contributions. DHC is supported by graduate scholarships from the Canadian Institutes of Health Research, University of Calgary, and Libin Cardiovascular Institute.
### 3.8 Tables

**Table 4.** Participant demographic characteristics by dialysis modality. Hemodialysis includes in-center, home, and nocturnal hemodialysis. Values are medians (IQR) where relevant. \(^a\)22 responses included; \(^b\)21 response included; \(^c\)1 response included; \(^d\)26 responses included; \(^e\)3 responses included. AKI, acute kidney injury; AVF, arteriovenous fistula; AVG, arteriovenous graft; CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; CVC, central venous catheter; DM, diabetes mellitus; GN, glomerulonephritis; HD, hemodialysis; HTN, hypertension; N/A, not applicable; PD, peritoneal dialysis; PDC, peritoneal dialysis catheter; PKD, polycystic kidney disease.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pooled (n=27)</th>
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<th>PD (n=4)</th>
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<td>36 (IQR: 31,44)</td>
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</table>
**Table 5. Reproductive health history.** Hemodialysis includes in-center, home, and nocturnal hemodialysis. Values are medians (IQR) where relevant.  

*a* 16 responses included;  
*b* 13 responses included;  
*c* 3 responses included;  
*d* 11 responses included;  
*e* 9 responses included;  
*f* 2 responses included;  
*g* 12 responses included;  
*h* 10 responses included;  
*i* 7 responses included.  

CKD, chronic kidney disease; HD, hemodialysis; N/A, not applicable; PD, peritoneal dialysis.

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Table 6. Menstrual characteristics (for menstruation only: *p<0.05). Hemodialysis includes in-center, home, and nocturnal hemodialysis. Values are medians (IQR) where relevant. *a25 responses included; b21 responses included; c19 responses included; d17 responses included; e2 responses included; f15 responses included; g13 responses included; h18 responses included; i3 responses included; j9 responses included. CKD, chronic kidney disease; HD, hemodialysis; HRT, hormone replacement therapy; N/A, not applicable; PD, peritoneal dialysis.

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<td>Skipped question n (%)</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>2 (50)</td>
</tr>
<tr>
<td><strong>During CKD:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>13 (48)</td>
<td>11 (48)*</td>
<td>2 (50)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>5 (19)</td>
<td>4 (17)*</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>N/A n (%)</td>
<td>6 (22)</td>
<td>6 (26)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>2 (7)</td>
<td>1 (4)</td>
<td>1 (25)</td>
</tr>
<tr>
<td><strong>Before CKD:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>18 (67)</td>
<td>16 (70)*</td>
<td>2 (50)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>3 (11)</td>
<td>2 (9)*</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>N/A n (%)</td>
<td>3 (11)</td>
<td>3 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>2 (7)</td>
<td>1 (4)</td>
<td>1 (25)</td>
</tr>
<tr>
<td><strong>Length of periods (days):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>During dialysis:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>3 (11)</td>
<td>3 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>18 (67)</td>
<td>16 (70)</td>
<td>2 (50)</td>
</tr>
</tbody>
</table>

Intermenstrual bleeding:

<p>| <strong>During dialysis:</strong>             |               |           |          |
| Yes n (%)                        | 3 (11)        | 3 (13)    | 0 (0)    |
| No n (%)                         | 18 (67)       | 16 (70)   | 2 (50)   |</p>
<table>
<thead>
<tr>
<th></th>
<th>During CKD:</th>
<th>Before CKD:</th>
<th>Menopause:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsure n (%)</td>
<td>2 (7)</td>
<td>2 (9)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>4 (15)</td>
<td>2 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>3 (11)</td>
<td>3 (13)</td>
<td>9 (39)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>17 (63)</td>
<td>16 (70)</td>
<td>39 (IQR: 28,44)</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>6 (22)</td>
<td>3 (13)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>5 (19)</td>
<td>5 (22)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>16 (59)</td>
<td>13 (57)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>6 (22)</td>
<td>5 (22)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of last menstrual period (years)</td>
<td>39 (IQR: 28,44)</td>
<td>39 (IQR: 28,44)</td>
<td>N/A</td>
</tr>
<tr>
<td>No n (%)</td>
<td>15 (56)</td>
<td>13 (57)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Unsure n (%)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>2 (50)</td>
</tr>
</tbody>
</table>
Table 7. Participants reporting menopause on hemodialysis (in-center, home, and nocturnal hemodialysis). Vasomotor symptoms include hot flashes, night sweats, and heart palpitations. \(^a^6\) responses included; \(^b^1\) response included; \(^c^2\) responses included; \(^d^3\) responses included. HRT, hormone replacement therapy; VMS, vasomotor symptoms.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Participants (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years n (%)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>≥40 years n (%)</td>
<td>5 (56)</td>
</tr>
<tr>
<td><strong>VMS</strong></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>1 (11)</td>
</tr>
<tr>
<td><strong>Discussions of HRT with health care professionals of those &lt;40 years of age and/or currently experiencing VMS</strong></td>
<td></td>
</tr>
<tr>
<td>Nephrologist n (%)</td>
<td>0 (0)(^a)</td>
</tr>
<tr>
<td>Kidney care team n (%)</td>
<td>0 (0)(^a)</td>
</tr>
<tr>
<td>Family doctor n (%)</td>
<td>0 (0)(^a)</td>
</tr>
<tr>
<td><strong>Received HRT of those &lt;40 years of age and/or currently experiencing VMS</strong></td>
<td></td>
</tr>
<tr>
<td>Due to only &lt;40 years of age n (%)</td>
<td>0 (0)(^b)</td>
</tr>
<tr>
<td>Due to only VMS n (%)</td>
<td>0 (0)(^c)</td>
</tr>
<tr>
<td>Due to both &lt;40 years of age and VMS n (%)</td>
<td>0 (0)(^d)</td>
</tr>
</tbody>
</table>
Table 8. Clinical indicators of heavy menstrual bleeding (for none only: *p<0.05). Hemodialysis includes in-center, home, and nocturnal hemodialysis. CKD, chronic kidney disease; HD, hemodialysis; HMB, heavy menstrual bleeding; PD, peritoneal dialysis.

<table>
<thead>
<tr>
<th>HMB clinical indicators</th>
<th>During dialysis</th>
<th>During CKD</th>
<th>Before CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HD (n=23)</td>
<td>PD (n=4)</td>
<td>HD (n=23)</td>
</tr>
<tr>
<td>Change period product more than once per hour for several hours:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>3 (13)</td>
<td>1 (25)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>17 (74)</td>
<td>1 (25)</td>
<td>16 (70)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>3 (13)</td>
<td>2 (50)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Need to use multiple period products at once:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>2 (9)</td>
<td>1 (25)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>18 (78)</td>
<td>1 (25)</td>
<td>17 (74)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>3 (13)</td>
<td>2 (50)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Wake up at night to change period product:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>8 (35)</td>
<td>1 (25)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>12 (52)</td>
<td>1 (25)</td>
<td>15 (65)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>3 (13)</td>
<td>2 (50)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Pass quarter-sized blood clots:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>7 (30)</td>
<td>1 (25)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>13 (57)</td>
<td>1 (25)</td>
<td>14 (61)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>3 (13)</td>
<td>2 (50)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Bleeding interferes with daily activities:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>1 (4)</td>
<td>1 (25)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>19 (83)</td>
<td>1 (25)</td>
<td>16 (70)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>3 (13)</td>
<td>2 (50)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>None:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>9 (39)</td>
<td>1 (25)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>No n (%)</td>
<td>11 (48)</td>
<td>1 (25)</td>
<td>15 (65)</td>
</tr>
<tr>
<td>Skipped question n (%)</td>
<td>3 (13)</td>
<td>2 (50)</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>
Table 9. Reproductive hormone levels by dialysis modality. Hemodialysis includes in-center, home, and nocturnal hemodialysis. Values are medians (IQR). \^a25 responses included; \^b23 responses included; \^c2 responses included; \^d24 responses included; \^e22 responses included; \^f21 responses included. AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; HD, hemodialysis; IU, international unit; L, liter; LH, luteinizing hormone; nmol, nanomole; PD, peritoneal dialysis; pmol, picomole; SHBG, sex hormone binding globulin; µg, microgram.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Reference range</th>
<th>Pooled (n=27)</th>
<th>HD (n=23)</th>
<th>PD (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (IU/L)</td>
<td>1-13</td>
<td>7 (IQR: 4.2,61)^a</td>
<td>7 (IQR: 3.5,65)^b</td>
<td>9 (IQR: 6.11,9)^c</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>2-10</td>
<td>5.4 (IQR: 4.7)^a</td>
<td>6 (IQR: 4.41)^b</td>
<td>4.7 (IQR: 4.5,4)^c</td>
</tr>
<tr>
<td>Estradiol (pmol/L)</td>
<td>90-700</td>
<td>174.5 (IQR: 123,249)^d</td>
<td>171.5 (IQR: 120,263)^e</td>
<td>205 (IQR: 175,235)^f</td>
</tr>
<tr>
<td>Progesterone (nmol/L)</td>
<td>0-2.8</td>
<td>1.2 (IQR: 0.6,1.6)^a</td>
<td>1.4 (IQR: 0.5,1.7)^b</td>
<td>0.9 (IQR: 0.6,1.1)^c</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>0.5-2</td>
<td>0.3 (IQR: 0.2,1.3)^a</td>
<td>0.3 (IQR: 0.2,1.3)^b</td>
<td>1.7 (IQR: 1.2,2.2)^c</td>
</tr>
<tr>
<td>Prolactin (µg/L)</td>
<td>4-25</td>
<td>33 (IQR: 20,42)^a</td>
<td>31 (IQR: 19,47)^b</td>
<td>35.5 (IQR: 33,38)^c</td>
</tr>
<tr>
<td>SHBG (µg/L)</td>
<td>20-100</td>
<td>55 (IQR: 34,102)^b</td>
<td>59 (IQR: 34,102)^c</td>
<td>33 (IQR: 18,48)^c</td>
</tr>
<tr>
<td>AMH (pmol/L)</td>
<td>1.1-53.5</td>
<td>3.9 (IQR: 0.3,12.7)^d</td>
<td>3.5 (IQR: 0.2,11)^e</td>
<td>19.6 (IQR: 14.2,24.9)^f</td>
</tr>
</tbody>
</table>
Table 10. Reproductive hormone levels in absent compared to present menstrual bleeding (*p<0.05). Values are medians (IQR). a12 responses included; b10 responses included; c9 responses included; d11 responses included. AMH, anti-Müllerian hormone. FSH, follicle-stimulating hormone; IU, international unit; L, liter; LH, luteinizing hormone; nmol, nanomole; pmol, picomole; SHBG, sex hormone binding globulin; µg, microgram.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Absent menstrual bleeding (n=13)</th>
<th>Present menstrual bleeding (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (IU/L)</td>
<td>34 (IQR: 2.8,88.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7 (IQR: 4.2,13)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>6 (IQR: 4.9,61.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (IQR: 3.6)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Estradiol (pmol/L)</td>
<td>167.5 (IQR: 97.5,179)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>189 (IQR: 158,399)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Progesterone (nmol/L)</td>
<td>1 (IQR: 0.5,1.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5 (IQR: 0.8,1.6)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>0.3 (IQR: 0.2,1.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.3 (IQR: 0.2,1.3)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prolactin (µg/L)</td>
<td>35 (IQR: 23.5,106.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28 (IQR: 18,40)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SHBG (µg/L)</td>
<td>46 (IQR: 34,102)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>78 (IQR: 59,134)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>AMH (pmol/L)</td>
<td>2.6 (IQR: 0.2,19.9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.7 (IQR: 2.8,5.1)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Table 11. Reproductive hormone levels in heavy compared to normal menstrual bleeding (*p<0.05). Values are medians (IQR). \(^a\)11 responses included; \(^b\)9 responses included; \(^c\)10 responses included. AMH, anti-Müllerian hormone. FSH, follicle-stimulating hormone; IU, international unit; L, liter; LH, luteinizing hormone; nmol, nanomole; pmol, picomole; SHBG, sex hormone binding globulin; µg, microgram.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Heavy menstrual bleeding (n=12)</th>
<th>Normal menstrual bleeding (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (IU/L)</td>
<td>9 (IQR: 3.5,95.6)(^a)</td>
<td>7 (IQR: 2.7)(^b)</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>5 (IQR: 3.5,1.9)(^a)</td>
<td>6 (IQR: 4.6)(^b)</td>
</tr>
<tr>
<td>Estradiol (pmol/L)</td>
<td>181.5 (IQR: 48,318)(^c)</td>
<td>168 (IQR: 126,229)(^b)</td>
</tr>
<tr>
<td>Progesterone (nmol/L)</td>
<td>1.4 (IQR: 0.4,2.1)(^a)</td>
<td>1.4 (IQR: 0.5,1.5)(^b)</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>0.3 (IQR: 0.2,1.3)(^a)</td>
<td>0.4 (IQR: 0.2,1.6)(^b)</td>
</tr>
<tr>
<td>Prolactin (µg/L)</td>
<td>30 (IQR: 19,35)(^a)</td>
<td>33 (IQR: 25,67)(^b)</td>
</tr>
<tr>
<td>SHBG (µg/L)</td>
<td>68 (IQR: 52,102)(^b)</td>
<td>59 (IQR: 34,97)(^b)</td>
</tr>
<tr>
<td>AMH (pmol/L)</td>
<td>2.5 (IQR: 0.2,11.1)(^c)</td>
<td>3.7 (IQR: 2.8,11)(^b)</td>
</tr>
</tbody>
</table>
Figure 11. Lasagna plot of absent menstrual bleeding during dialysis, during CKD, and before CKD diagnosis among participants on (A) hemodialysis (n=23; p<0.05) and (B) peritoneal dialysis (n=4). “Unsure” represents skipped, not applicable, and unsure responses. CKD; chronic kidney disease.
Figure 12. Predictability of menses during dialysis, during CKD, and before CKD diagnosis among participants on (A) hemodialysis (n=23) and (B) peritoneal dialysis (n=4). “Unsure” represents skipped, not applicable, and unsure responses. CKD; chronic kidney disease.
Figure 13. Heavy menstrual bleeding during dialysis, during CKD, and before CKD diagnosis among participants on (A) hemodialysis (n=23) and (B) peritoneal dialysis (n=4). “Unsure” represents skipped, not applicable, and unsure responses. CKD; chronic kidney disease.
Figure 14. Linear regression plots of (A) LH (n=25), (B) FSH (n=25), (C) estradiol (n=24), (D) progesterone (n=25), (E) testosterone (n=25), (F) prolactin (n=25), (G) SHBG (n=23), and (H) AMH (n=24) levels by age among all participants. AMH, anti-Müllerian hormone. FSH, follicle-
stimulating hormone; IU, international unit; L, liter; LH, luteinizing hormone; nmol, nanomole; pmol, picomole; SHBG, sex hormone binding globulin; µg, microgram.
3.10 Supplemental Files

File A: Participant survey

Periods, Birth Control, and Kidney Disease Survey

All the information you provide will be kept private and not given to anyone without your written consent. When researchers study your information, it will **not** be linked to your name.

**Please note if you do not know the answer to a question, you may write “I don’t know”**.

Date (D/M/Y): _________________________   Study ID: ________________________________
Age: ________________________________

Part 1 of 7: Tell us about your kidneys

What is the cause of your kidney disease? ________________________________
When were you diagnosed with kidney disease (M/Y)? ________________________________
When did you **first** start dialysis? ________________________________

What types of dialysis have you ever been on (check all that apply)?
- ☐ Hemodialysis in a clinic or hospital          When? ________________________________
- ☐ Home hemodialysis                          When? ________________________________
- ☐ Nocturnal hemodialysis                     When? ________________________________
- ☐ Peritoneal dialysis                         When? ________________________________

What is your current dialysis access?
- ☐ Arteriovenous fistula (AVF)
- ☐ Arteriovenous graft (AVG)
- ☐ Central venous catheter (CVC)
- ☐ Peritoneal dialysis catheter

Part 2 of 7: Tell us about your periods

How old were you when you **first** had your period (i.e., bleeding from your uterus that typically happens each month)? ____________
- ☐ Check this if you have **never** had your period (you may skip all questions of part 2)
Your periods NOW
Do you still get your periods?  Y  /  N  /  I don’t know
How many periods did you get in the last 1 year? ____________
Within the last 3 months, did you get a period?  Y  /  N  /  I don’t know
Within the last 12 months, did you get a period?  Y  /  N  /  I don’t know
If you think your period has stopped permanently, how old were you when it stopped? ________
Periods can be very predictable (i.e., you know exactly when the next one will occur), highly unpredictable (i.e., you don’t know when the next one will occur) or some pattern in between.
How predictable is the start of your period (check one)?
  □ Very predictable (I can predict it within 0-4 days)
  □ Predictable (I can predict it within 5-7 days)
  □ Usually unpredictable
  □ Always unpredictable
  □ I don’t know
How many non-bleeding days do you usually have between your periods? ____________
How many days do you usually bleed? ____________
Tell us about your bleeding (check all that apply):
  □ During my period, I need to change my period product (e.g., pad, tampon, etc.) at least once an hour for several hours in a row
  □ Sometimes, I need to wear multiple period products (e.g, multiple pads, pad and tampon, etc.) at the same time to control flow
  □ Sometimes, I need to wake up in the middle of the night to change my period product (e.g., pad, tampon, etc.)
  □ I pass blood clots at least the size of a quarter during my period
  □ My period bleeding interferes with daily activities
  □ None of these apply to me
Does bleeding occur between menstrual periods?  Y  /  N  /  I don’t know

Your periods BEFORE YOU WERE ON DIALYSIS BUT WHILE YOU HAD KIDNEY DISEASE (if you started dialysis at the same time you found out you had kidney disease, you may skip this section)
Did you still get your periods?  Y /  N /  I don’t know

How many periods did you get in 1 year? ____________

Periods can be very predictable (i.e., you know exactly when the next one will occur), highly unpredictable (i.e., you don’t know when the next one will occur) or some pattern in between.

How predictable was the start of your period (check one)?

☐ Very predictable (I could predict it within 0-4 days)

☐ Predictable (I could predict it within 5-7 days)

☐ Usually unpredictable

☐ Always unpredictable

☐ I don’t know

How many non-bleeding days did you usually have between your periods? ____________

How many days did you usually bleed? ____________

Tell us about your bleeding (check all that apply):

☐ During my period, I had to change my period product (e.g., pad, tampon, etc.) at least once an hour for several hours in a row

☐ Sometimes, I had to wear multiple period products (e.g., multiple pads, pad and tampon, etc.) at the same time to control flow

☐ Sometimes, I had to wake up in the middle of the night to change my period product (e.g., pad, tampon, etc.)

☐ I passed blood clots at least the size of a quarter during my period

☐ My period bleeding interfered with daily activities

☐ None of these applied to me

Did bleeding occur between menstrual periods?  Y /  N /  I don’t know

Your periods BEFORE YOU HAD KIDNEY DISEASE

Did you still get your periods?  Y /  N /  I don’t know

How many periods did you get in 1 year? ____________

Periods can be very predictable (i.e., you know exactly when the next one will occur), highly unpredictable (i.e., you don’t know when the next one will occur) or some pattern in between.

How predictable was the start of your period (check one)?

☐ Very predictable (I could predict it within 0-4 days)
Predictable (I could predict it within 5-7 days)
☐ Usually unpredictable
☐ Always unpredictable
☐ I don’t know

How many non-bleeding days did you usually have between your periods? __________

How many days did you usually bleed? __________

Tell us about your bleeding (check all that apply):
☐ During my period, I had to change my period product (e.g., pad, tampon, etc.) at least once an hour for several hours in a row
☐ Sometimes, I had to wear multiple period products (e.g, multiple pads, pad and tampon, etc.) at the same time to control flow
☐ Sometimes, I had to wake up in the middle of the night to change my period product (e.g., pad, tampon, etc.)
☐ I passed blood clots at least the size of a quarter during my period
☐ My period bleeding interfered with daily activities
☐ None of these applied to me

Did bleeding occur between menstrual periods? Y / N / I don’t know

Part 3 of 7: Tell us about your gynecology history

Have you ever been diagnosed with (check all that apply):
☐ Cancer of the female reproductive organs
☐ Endometriosis
☐ Uterine fibroids
☐ None of these apply to me

Have you ever had an operation on your vagina/cervix/uterus/fallopian tubes/ovaries?
☐ Y / N / I don’t know

Have you ever received radiation to the pelvis or abdomen?
☐ Y / N / I don’t know

Part 4 of 7: Tell us about your pregnancy history

How many times have you been pregnant? ____________
How many children have you had? ______________________

Have you had any miscarriages? Y / N If so, how many? _____

Have you had any pregnancy terminations (i.e., abortions)? Y / N If so, how many? _____

Have you ever had any of the following pregnancy complications (check all that apply):

☐ Gestational hypertension
☐ Gestational diabetes
☐ Preeclampsia
☐ Eclampsia
☐ None of these apply to me

Have you had any other pregnancy complications? ________________________________

Were any of your children born premature? Y / N / I don’t know

Have you ever tried to become pregnant, but couldn’t after 1 year of trying? Y / N

Have you ever received fertility treatment to become pregnant? Y / N

If so, what kind? ______________

Have you ever had a discussion about fertility and pregnancy with your kidney doctor?

Y / N / I don’t know

Did you know that your kidney disease can affect your fertility and pregnancy? Y / N

**Part 5 of 7: Tell us about your perimenopause history**

**Menopause Symptoms NOW**

Please circle if you have any of the following symptoms:

- Hot Flashes / Night Sweats / Difficulty Sleeping / Heart palpitations
- Difficulty concentrating / Irritability / Mood swings / Headaches
- Vaginal dryness / Vaginal itching / Abnormal vaginal discharge
- Vaginal infections / Pain during sexual activity

Are you on Hormone Replacement Therapy? Y / N / I don’t know

If so, when was it started? _________________

If so, what type is it? __________________________

Does your nephrologist discuss hormone therapy with you? Y / N

Does your nephrology team discuss hormone therapy with you? Y / N

Does your family doctor discuss hormone therapy with you? Y / N
Menopause Symptoms **BEFORE YOU WERE ON DIALYSIS BUT WHILE YOU HAD KIDNEY DISEASE** (if you started dialysis at the same time you found out you had kidney disease, you may skip this section)

Please circle if you had any of the following symptoms:

- Hot Flashes / Night Sweats / Difficulty Sleeping / Heart palpitations
- Difficulty concentrating / Irritability / Mood swings / Headaches
- Vaginal dryness / Vaginal itching / Abnormal vaginal discharge
- Vaginal infections / Pain during sexual activity

Were you on Hormone Replacement Therapy?  Y / N / I don’t know

If so, when was it started? ____________________

If so, what type was it? ____________________

Did your nephrologist discuss hormone therapy with you?  Y / N

Did your nephrology team discuss hormone therapy with you?  Y / N

Did your family doctor discuss hormone therapy with you?  Y / N

Menopause Symptoms **BEFORE YOU HAD KIDNEY DISEASE**

Please circle if you had any of the following symptoms:

- Hot Flashes / Night Sweats / Difficulty Sleeping / Heart palpitations
- Difficulty concentrating / Irritability / Mood swings / Headaches
- Vaginal dryness / Vaginal itching / Abnormal vaginal discharge
- Vaginal infections / Pain during sexual activity

Were you on Hormone Replacement Therapy?  Y / N / I don’t know

If so, when was it started? ____________________

If so, what type was it? ____________________

Did your family doctor discuss hormone therapy with you?  Y / N

**Part 6 of 7: Tell us about your medical history**

Have you ever needed a blood transfusion?  Y / N / I don’t know

Do you have any bleeding disorders?  Y / N / I don’t know
Have you ever received chemotherapy or immunosuppressive medications (e.g.,
cyclophosphamide, Cytoxan, methotrexate, mycophenolate mofetil (MMF), CellCept)?

Y / N / I don’t know
If so, which one? ___________________

Part 7 of 7: Tell us about yourself
Date of birth (D/M/Y): ___________________
How do you **primarily** identify (circle one)?

- Black
- Caribbean
- Central Asian
- East Asian
- Indigenous or Métis
- Latinx
- Middle Eastern or North African
- Pacific Islander
- South Asian
- Southeast Asian
- White
- I prefer to self-identify as: ______________
- I prefer not to say

Registered First Nations? Y / N  Nation:___________________________________
What was the sex on your birth certificate: Female / Intersex / Male / Prefer not to say
What best describes your **current** gender identity (check one)?

☐ Agender (I don’t identify as having a gender identity)
☐ Cis man (I identify as a man and my sex at birth is male)
☐ Cis woman (I identify as a woman and my sex at birth is female)
☐ Demigender (I feel partially connected to a particular gender identity)
☐ Gender fluid (my gender identity varies over time)
☐ Gender-nonconforming (in terms of appearance and/or behavior, I don’t adhere to the
  traditional gender expectations)
☐ Genderqueer (I don’t identify as a man nor woman, but somewhere in between,
  beyond, or a combination of gender identities)
☐ Non-binary (I don’t fit into traditional gender categories)
☐ Transgender man (I identify as a man and my sex at birth is female)
☐ Transgender woman (I identify as a woman and my sex at birth is male)
☐ Two-spirit (I identify as an Indigenous person who has both a feminine and masculine spirit)

☐ I prefer to self-identify as: ____________________________________________

☐ I prefer not to say

How do you see yourself (numbers do not have to add up to 5; 1 = not at all, 5 = very)?

Feminine 1 2 3 4 5
Masculine 1 2 3 4 5

How do you feel most people see you (numbers do not have to add up to 5; 1 = not at all, 5 = very)?

Feminine 1 2 3 4 5
Masculine 1 2 3 4 5
Chapter 4: Discussion

Kidney disease is increasing at a rapid rate$^{153,154,189}$ and affects $>13\%$ of the global population.$^{146}$ Menstrual abnormalities are common within the CKD population,$^{14,24,151,152}$ which is important to highlight as abnormal uterine bleeding has been associated with increased cardiovascular risk and premature mortality.$^{46}$ Therefore, these sex-specific factors may contribute to the low survival rates$^{144}$ and quality of life$^{145}$ previously described in females with CKD, making female reproductive health an important predictor of morbidity, mortality, and quality of life.$^{143}$

Pregnancy is also a high-risk condition especially in the setting of CKD, although studies have described low contraceptive use within this population.$^{14,94,159}$ The majority of research to date has primarily been limited to the kidney failure population, and so this work further expands on the current body of literature by including people across the spectrum of CKD.

Results from our first project suggest that the prevalence of menstrual abnormalities is high and contraceptive use is low among reproductive-aged females with CKD. Although the physiological mechanisms behind abnormal uterine bleeding in CKD is not fully understood, abnormal menses can fortunately be treated and result in an enhanced quality of life. An unplanned pregnancy poses risks to both the person living with CKD and their child; thus, contraception should be discussed as part of routine kidney care. To our knowledge, this is the first study to comment on period poverty in the setting of kidney disease. Understanding that CKD is already associated with significant socioeconomic disparities,$^{63,64}$ our results underscore the sex-specific challenges of accessing safe and clean period products on the existent financial barrier of CKD. Our second study supports findings from Project 1, as the prevalence of abnormal menstruation, particularly absent and heavy menstrual bleeding, was high in females.
with kidney failure. However, when examining reproductive hormone levels, we determined that participants largely fell within the healthy ranges of the general population, suggesting that factors aside from disruptions of the hypothalamic-pituitary-ovarian axis may be responsible for these findings. Unfortunately, we are unaware of possible explanations that could reconcile these findings; however, it is paramount that further research be done to understand these novel, sex-specific findings. Taken together, these complementary projects shed light on an important gap in the research and clinical care of females living with kidney disease, meaning that we have much to learn about how kidney disease affects female reproductive health.

The theme of World Kidney Day 2018 was “Kidneys & Women’s Health: Include, Value, Empower”,\textsuperscript{190} that highlighted the sex-based inequities in the care of people with CKD.\textsuperscript{191} For instance, while the prevalence of CKD is higher in females compared to males,\textsuperscript{146} less females are being treated with kidney replacement therapy, as there is lower awareness of CKD among this group in addition to unequal access to care.\textsuperscript{192,193} Additionally, menstruation, (hormonal) contraceptive use, and pregnancy are largely female-specific experiences that get complicated in the setting of kidney disease. However, with proper management and counselling, kidney health professionals can reduce these pre-existing barriers for their female patients and encourage greater life participation.\textsuperscript{194} Thus, while there are campaigns and efforts to reduce these sex-based inequities and raise awareness of female-specific issues in CKD, including gynecologic and reproductive health concerns, there is still much work that needs to be done in this area, whether it be advocating for equitable, sex-specific kidney care, improving education and training opportunities for kidney health professionals, or collaborating with patient partners in research to better inform the care of this population.
A paradigm shift is ultimately required to improve the multidimensional care of females living with CKD. Based on previous research, nephrologists have reported low confidence discussing female reproductive health issues, which not only highlights an important gap in the training and education of healthcare professionals but raises concerns in the quality of care that female patients have been receiving.\textsuperscript{45,60,61} Therefore, we recommend increased education for nephrologists on female reproductive health concerns such as, but not limited to menstruation, contraceptive use, sexual function and activity, and fertility within the kidney disease context as well as greater collaboration between the fields of nephrology and gynecology. As per future directions, this research highlights the need for greater teamwork between experts in kidney and female reproductive health; therefore, establishing multidisciplinary clinics with resources dedicated to examine the effectiveness of these clinics would be highly beneficial.\textsuperscript{195} If patients consistently show improved kidney, gynecologic, reproductive, and other health outcomes, there could be greater support for the implementation of this multidisciplinary approach around the world. Fortunately, as of now, there is increasing recognition of sex-specific considerations in the kidney disease context; however, we acknowledge that there is much more that needs to be done to advance female reproductive health in both kidney research and care.
Chapter 5: References


https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease


44. Kim HS, Ng DK, Matheson MB, et al. Delayed menarche in girls with chronic kidney
doi:10.1007/s00467-020-04559-7

to adolescent patients in nephrology clinics: a pediatric nephrology research consortium study.

the reproductive lifespan and risk of premature mortality: prospective cohort study. *BMJ*.
2020;371:m3464. doi:10.1136/bmj.m3464

008-0018-5

48. Lee LK, Chen PC, Lee KK, et al. Menstruation among adolescent girls in Malaysia: a cross-

doi:10.3111/13696998.2013.830974

of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding.

51. Market Opinion and Research International (MORI). Women’s health in 1990. [Research
study conducted on behalf of Parke-Davis Laboratories]. London: MORI; 1990.


