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REVIEW

Female Reproductive and Gynecologic Considerations in Chronic Kidney Disease: Adolescence and Young Adulthood

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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.

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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.[1] Although the most common causes of kidney disease at a global level are hypertension and diabetes,[2,3] childhood onset of kidney disease is most frequently due to congenital abnormalities and hereditary disorders.[4–7] 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.[8] Furthermore, compared with the adult population, glomerulonephritides are a more common cause of CKD in children, particularly in the adolescent population after puberty.[4,8]

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CKD in the female population is often accompanied by abnormal uterine bleeding, sexual dysfunction, reduced fertility, and higher risk pregnancies.[9,10] 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.[11] According to the North American Pediatric Renal Trials and Collaborative Studies database, adolescents represent the largest group of pediatric kidney transplant recipients.[12] Although CKD is associated with increased abnormal uterine bleeding,[13–15] kidney transplantation, at least in the adult population, may restore uterine bleeding.[15,16] Kidney transplantation guidelines[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.[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.

Methods

For the purpose of providing a summary on female reproductive and gynecologic health among adolescents with CKD, the first author (DHC) searched 2 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.

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,[21] and a healthy menstrual cycle lasts 24 to 38 days with bleeding occurring for ≤8 days (on average, 5 days).[22] Details regarding the healthy menstrual cycle are outlined elsewhere.[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).[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.[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.[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.[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.[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.[29] When comparing participants with and without menstrual disturbances, prolactin levels were higher in those with menstrual disturbances.[29]

Kidney Disease and Age of Menarche

Menarche is the first occurrence of uterine bleeding and the beginning of the female reproductive lifespan.

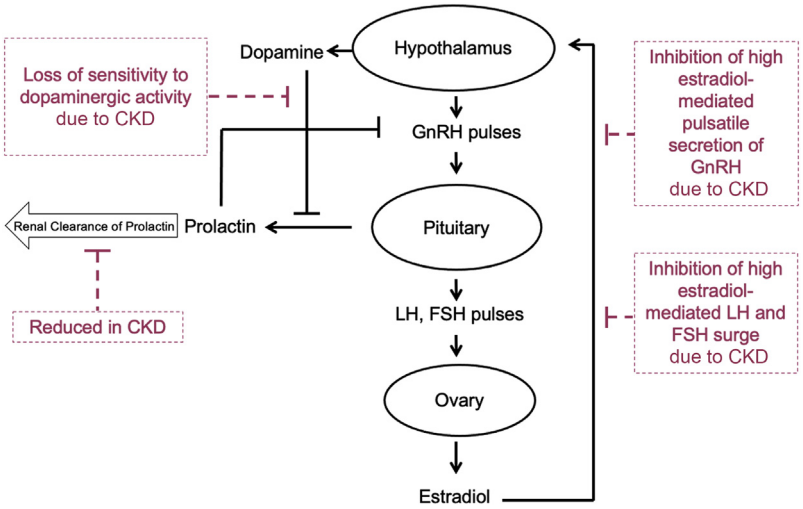

Figure 1. Hypothalamic-pituitary-ovarian axis in females with kidney disease. From Ahmed SB, Ramesh S. Sex hormones in women with kidney disease. Nephrology Dialysis Transplantation, 2016, volume 31, issue 11, pages 1787–1795 © The Author(s). Published by Oxford University Press on behalf of the ERA-EDTA. All rights reserved.[26] CKD, chronic kidney disease; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

Among healthy adolescents, the median age of menarche is approximately 12 to 13 years.[30,31] Multiple factors are associated with the onset of menarche in the general population. An inverse association between body mass index,[32–34] height, and weight[35] with age of menarche has been found. Earlier menarche is reported among those living with anyone other than a family consisting of 2 biological parents,[33,36–38] though study results vary regarding the impact of low socioeconomic status on early[36,38,39] and late[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.[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.[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.*[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.[44]

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.[31] Nevertheless, in a study of 75 nephrologists (95% pediatric, 5% adult) practicing in the United States and Puerto Rico, Vasylyeva *et al.*[45] 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.

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.[22] 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.[46] Abnormal uterine bleeding is also associated with absenteeism in school and work.[47–49] In the general population of reproductive-aged women, the estimated prevalence of abnormal uterine bleeding is at least 10% to 30%,[50] whereas heavy menstrual bleeding affects 30% of women throughout their reproductive lifespan.[51] Heavy menstrual bleeding is defined as the loss of ≥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 ≥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.[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.[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 ≥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.[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.[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.[13,14,24] In a small study of 17 women aged 18 to 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.[13] In a cross-sectional study of women <55 years of age with kidney failure treated with hemodialysis and peritoneal dialysis,[14] 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.[24,55] This may be especially relevant for those in need of a kidney transplant, given the risk of sensitization.[24]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,[15] 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.[56] 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.[53,56–58] 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.[57,59] It is important to note, however, that estrogen-containing options increase thrombotic risk.[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.[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.[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,[60] whereas only 15% reported discussing menstrual irregularities with their patients.[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.

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,[62] serving as a socioeconomic, cultural, and political barrier. CKD is associated with significant socioeconomic disparities,[63,64] and period poverty only exacerbates the economic toll of CKD. Menarche and menstrual management are fundamental aspects in adolescent female health,[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 well-being.[66] Period poverty results in some young people to miss up to a fifth of their school year.[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 well-being and quality of life.[68,69] Finally, although there are no studies focusing on period poverty among menstruating individuals with CKD, socioeconomic position and country income level and may also influence one's access to safe menstrual products and hygiene management facilities.[63,64,70–72]

Kidney Disease and Sexual Activity and Function

Adolescents with CKD tend to experience later onset of puberty[68] and initiate sexual intercourse at a later age compared with the general age-matched population.[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 gender or using alcohol or illicit drugs during gender were comparable in the 2 groups.[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.[74] In the United States, almost 30% of high school students reported being sexually active,[75,76]

with nearly 50% of young females reporting sexual dysfunction.[77] 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.[78] In a cross-sectional study of 106 women under the age of 50 years,[79] 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,[16] 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.[78,80,81] 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.[78,79,81,82]

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,[83,84] and it is estimated that 1 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.[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.[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 years 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.[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.[88,89] The incidence of syphilis in the adult kidney failure population is >3× higher than in the general population, and many affected patients had late-stage syphilis.[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.[91] 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.[92] 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.[93] 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%).[45] Increasing the dialogue on sexual activity and STIs among adolescents with CKD is important to providing better care, considering the immunosuppressed states of patients.

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,[94] 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.[73] Although the oral contraceptive pill is the second most common contraceptive used by adolescents in the general population in high-income countries,[75,95] 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,[96–98] increased blood pressure,[99,100] venous thromboembolism, arterial thrombosis,[101] and cervical cancer,[59,102] in part owing to activation of the renin-angiotensin-aldosterone system,[82,96,99,100,103] 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.[59,104] 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.[105,106] 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.[60] In contrast, nearly two-thirds of nephrologists caring for adolescents with CKD report being very confident or confident providing contraceptive counseling,[45] 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[122] and are safe in CKD.[123] Although a clinical practice guideline on pregnancy and kidney disease exists,[114,115] 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,[124] neonatal and long-term complications for fetuses exposed to angiotensin receptor blockers,[125] and an elevated incidence of structural malformations with mycophenolate mofetil exposure during pregnancy[126] highlight the need for effective contraception when pregnancy is not desired.

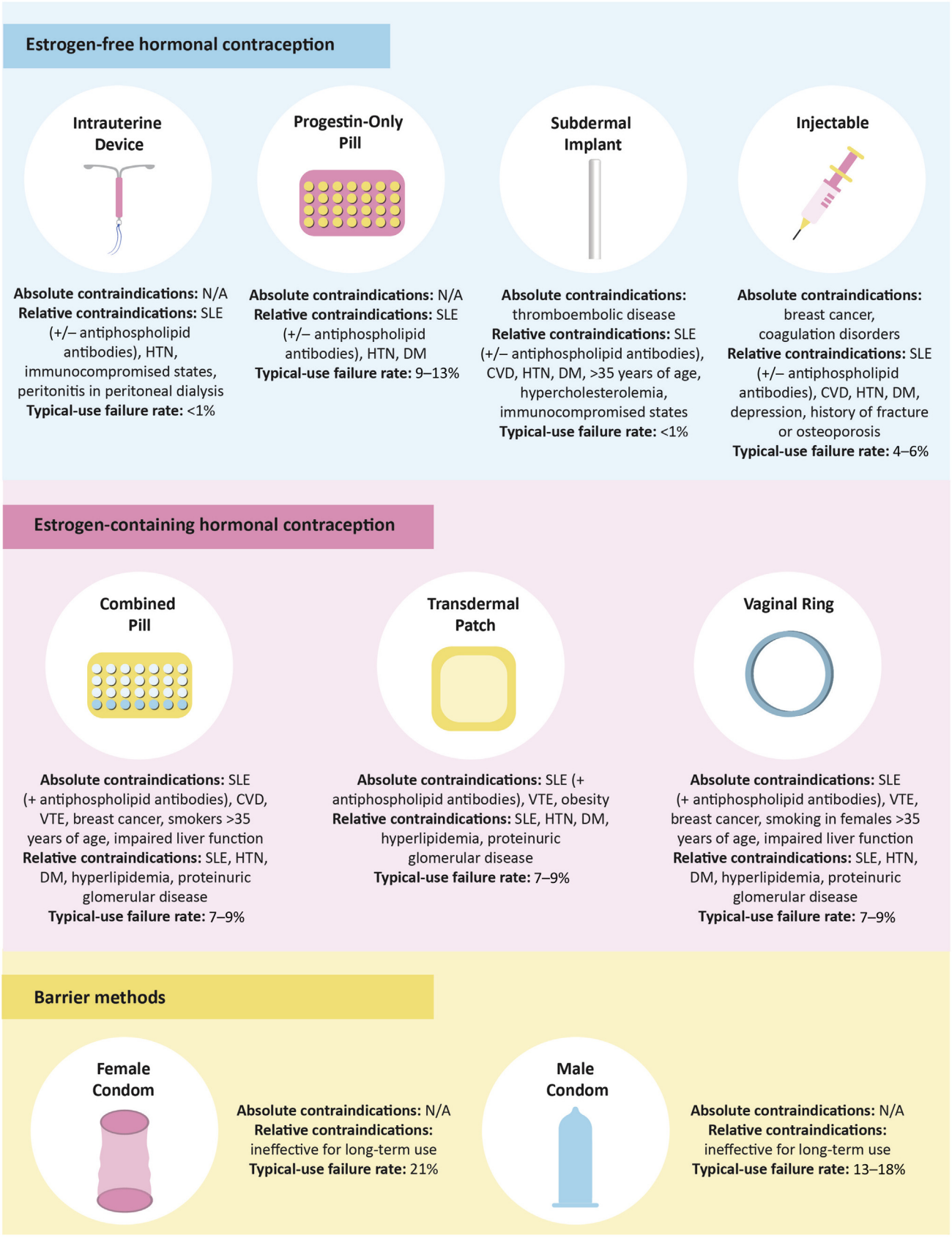

Figure 2. Contraceptive options and considerations for adolescent females with kidney disease. (Adapted from Ahmed *et al.*,[82] Attini *et al.*,[115] Sachdeva,[101] Watnick,[104] and Wiles and Lightstone[102]). CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; N/A, not available; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.

Kidney Disease and Fertility

Reduced fertility has been observed in the female CKD population compared with the general population,[10] postulated secondary to multiple factors, including a reduction in ovarian reserve.[9,127–129] Individuals with female biology are born with a finite number of ovarian follicles,[130] and anti-Müllerian hormone (AMH), produced by preantral and small antral ovarian follicles, is the gold standard measure of ovarian reserve.[131,132] As a woman's ovarian reserve naturally depletes with age, AMH levels also decline.[130] 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.[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.[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.[45,60,61]

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

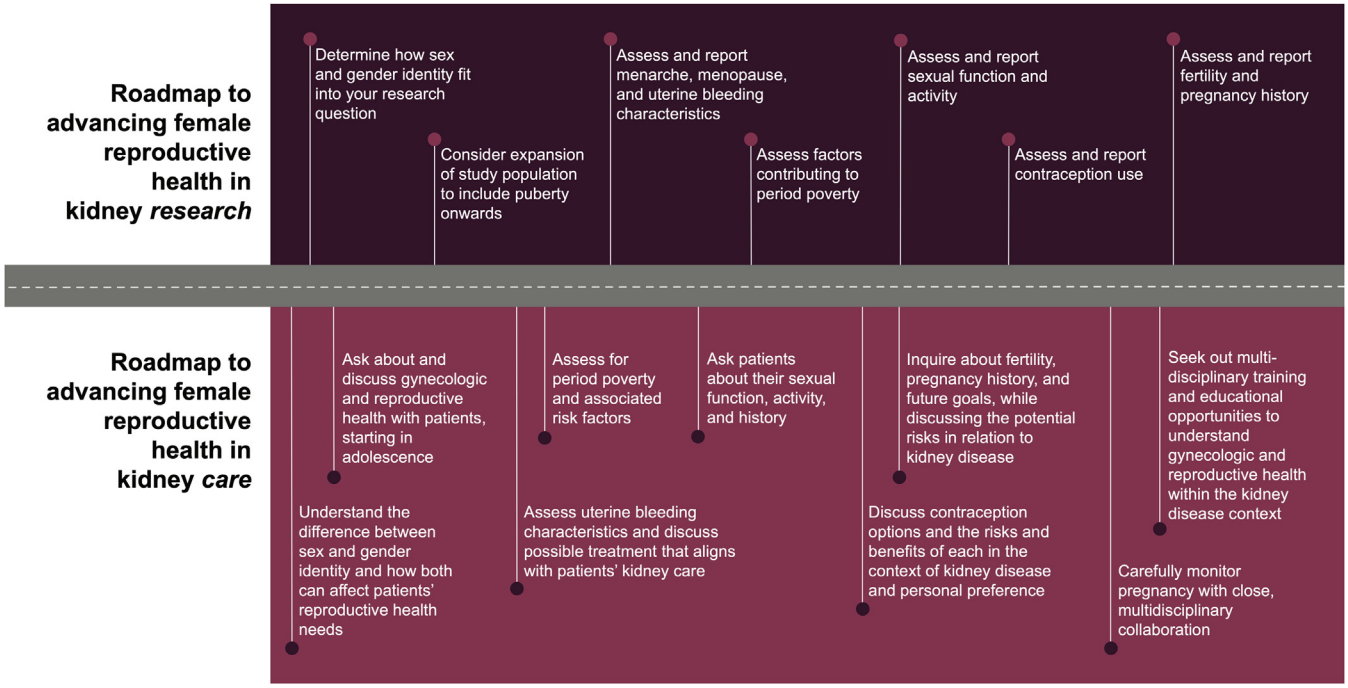

Figure 3. Roadmap to advancing female reproductive health in kidney research and care.

proportion of this group.[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.[141] Despite this important consideration, information regarding the reproductive care of transgender boys and nonbinary individuals within the CKD context is lacking.

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.

DISCLOSURE

All the authors declare no competing interests.

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