Received: 30 June 2021 | Revised: 14 September 2021 | Accepted: 23 September 2021

DOI: 10.1002/ppul.25703

REVIEW

WILEY

Optimizing sexual and reproductive health across the lifespan in people with cystic fibrosis

Natalie E. West MD, MHS[1] | Traci M. Kazmerski MD, MS[2,3] | Jennifer L. Taylor-Cousar MD, MSCS[4] | Vin Tangpricha MD, PhD[5] | Kelsie Pearson MBA[6] | Moira L. Aitken MD, FRCP[7] | Raksha Jain MD, MSc[8]

[1]Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA

[2]Department of Pediatrics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[3]Center for Women's Health Research and Innovation (CWHRI), University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[4]Departments of Medicine and Pediatrics, National Jewish Health, Denver, Colorado, USA

[5]Department of Medicine, Division of Endocrinology, Metabolism & Lipids, Emory University, Atlanta, Georgia, USA

[6]Cystic Fibrosis Foundation Therapeutics Development Network, Seattle Children's Hospital, Seattle, Washington, USA

[7]Department of Medicine, University of Washington, Seattle, Washington, USA

[8]Department of Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Correspondence
Raksha Jain, MD, MSC, Department of Medicine University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd. Mail code 8558, Dallas, TX 85390, USA.
Email: Raksha.Jain@utsouthwestern.edu

Funding information
Cystic Fibrosis Foundation, Grant/Award Numbers: WEST19Y3, KAZMER19Y3, TAYLOR19Y3, AITKEN19Y3, JAIN19Y3

Abstract

With improved therapies, people with cystic fibrosis are living longer and healthier lives and increasingly have questions surrounding their sexual and reproductive health. This article will summarize the important issues of which providers should be aware during the lifespan of people with cystic fibrosis, including puberty, adulthood, and menopause. A wide range of sexual and reproductive health topics are addressed such as puberty, transgender and gender nonbinary identities, contraception, sexually transmitted infections, hypogonadism, sexual functioning, cyclical hemoptysis, and urinary incontinence. We discuss gaps in knowledge and current evidence as well as management strategies to optimize care. Our goal is to support providers to enable them to give comprehensive care throughout the lifespan of people with cystic fibrosis.

KEYWORDS
cystic fibrosis, hypogonadism, menopause, puberty, sexual and reproductive health

1 | INTRODUCTION

Cystic fibrosis (CF) was once thought to be exclusively a disease of childhood. With improved care management and therapies, people with CF are living longer and healthier lives with life expectancy now nearing 50 years.[1] Most notably, therapies that target the underlying cause of disease, CF transmembrane conductance regulator (CFTR) modulators, are dramatically increasing survival as well as quality of life. Improved life expectancy is allowing many people with CF to consider future goals including family planning, thus leading to more

questions surrounding their sexual and reproductive health (SRH). In this article, we will discuss the phases of SRH of men and women with CF and highlight some of the unique challenges both genders face during puberty, their reproductive years, and, in women, menopause. Family planning, pregnancy, and fertility are discussed in the companion paper included in this issue entitled "Family-building and Parenting Considerations for People with Cystic Fibrosis.[2]"

1.1 | Puberty

Puberty is commonly defined as the physiological and morphological changes that occur within the growing child as the gonads change from an infantile to adult state, but also marks an important point in social and biologic changes for an adolescent. The added complexity of a chronic illness on puberty can complicate this time of transition for adolescents. Puberty in the general US population typically occurs between ages 8 and 13 years in females and 9 and 14 years in males.[3] Formerly, CF was associated with delayed puberty.[4,5] Early studies of CF showed delayed pubertal progression, age of menarche, skeletal maturity, and growth spurt.[6,7] A study from 1984 showed that 28% of males between the ages of 14 and 18 years had delays in pubertal development.[5] In 1997, a group demonstrated that the mean age at menarche for CF females was 14.9 ± 1.4 years, which was significantly later than in healthy controls 13.0 ± 1 years.[4] The impact of early diagnosis/newborn screening on pubertal growth is unclear, but a study within a single state, Wisconsin in 2016, showed that diagnosis by newborn screening versus diagnosis by symptoms led to earlier and sustained linear growth through puberty and better adult height.[8] Life expectancy has significantly improved in the past few decades largely due to improved therapies.[1] In line with this change, the delay in pubertal onset has improved for the majority of adolescents with CF, potentially due to improved nutrition and overall health.[9,10] Given that indices of puberty such as menarche and Tanner staging are not captured in the US Cystic Fibrosis Foundation Patient Registry (CFFPR) and similar patient registries, a 2014 study used peak height velocity to estimate age of puberty.[11] The authors found the average age of puberty to be 13.2 ± 2.2 years in males and 11.2 ± 2.0 years in females, which correlate with pubertal age reported in the general population.[11–13] The impact of CFTR modulators on puberty onset is not yet known.

Puberty is associated with worsening health status in CF. A few years after undergoing puberty, the rate of pulmonary exacerbations (PEx) increased in adolescent males and females but in females to a greater extent than what was seen in males.[11] Numerous epidemiologic studies in CF support a sex disparity in outcomes between males and females with CF.[14–16] The CFFPR study by Sutton et al. tracked the rate of PEx 10 years before puberty and 10 years postpuberty and found the rate of PEx postpuberty increased in females at 1.17 ± 1.35 per year in females versus 0.95 ± 1.27 in males ($p < 0.001$) despite controlling for morphometrics, comorbidities, and microbiologic variables, potentially supporting a role for sex hormones in the disease process.[11] In a French cohort, children with CF were shown to have a normal age of onset of puberty and pubertal growth spurt, with a low peak height velocity.[17] Pubertal growth contributed less to final adult height, and neither body mass index (BMI) nor lung function as measured by forced expiratory volume over one second (FEV_1) was associated with a significant effect on pubertal height gain. It is important to note that youth with more severe lung disease, poorly controlled CF-related diabetes (CFRD) and CF-related liver disease (CFRLD) are still at risk for malnutrition and may remain at risk for delayed puberty, and therefore, require close monitoring to ensure growth and pubertal development.[18]

Sex hormones may play a role in the disparity in outcomes observed between males and females with CF by impairing mucociliary clearance and immune response, as well as by increasing inflammation and bacterial virulence. Studies show worsening airway infection and inflammation in association with increased levels of estrogen.[19] Estrogen hinders the innate immune response to bacterial infections, which predominate PEx in people with CF. Finally, in vitro studies show that 17β-estradiol can decrease mucociliary clearance by increasing mucin production, by reducing movement of cilia, and by altering airway surface liquid, thereby creating thicker mucous.[19]

When care providers are discussing the potential impact of the hormonal changes of puberty on CF with adolescents, they should also discuss fertility. While discussions of male infertility should ideally begin at diagnosis with the parents of boys with CF, this conversation should at least occur in early adolescence in people with CF, to ensure that males with CF are aware of the high rates of male infertility due to congenital bilateral absence of the vas deferens (CBAVD).[20] Education on this important issue should be provided by the CF pediatric team as men who were first told at >20 years of age were more likely to report being "very upset" by the lack of information compared to those told at <16 years of age.[20]

Finally, it is also important to note that emotional changes associated with puberty can be challenging for all adolescents and, therefore, medical and psychosocial guidance is crucial in the prepubertal and pubertal period for a healthy transition to adulthood.[18,21] In this context, adolescents are commonly focused on their appearance and body image. An Australian survey found that symptoms (coughing, flatulence, steatorrhea, and digital clubbing) and signs (pubertal delay, short stature, and low body mass) seen commonly in CF were extremely distressing and isolating for adolescents, especially if the signs and symptoms caused visible differences compared to their peers.[22] CF care teams must be prepared to address the physiologic consequences of puberty and the direct psychosocial impacts of those changes as people with CF transition through puberty.

1.2 | Transgender and gender nonbinary identities in CF care

Gender-diverse individuals with CF have unique needs, and providers should be aware of health disparities as well as the gender-affirming care that is available.[23] A list of commonly used transgender terminology is available in Table1.[24] The assessed prevalence of transgender and gender nonbinary (TGGNB) identities increased over the past decade,

TABLE 1 Commonly used gender terminology

Gender diverse	Umbrella term used to describe gender identities that demonstrate a diversity of expression beyond the binary framework
Sex assigned at birth	Classification of people as male, female, or another sex assigned at birth often based on physical anatomy at birth and/or karyotyping
Cisgender	Term used for someone who identifies as their sex assigned at birth (not trans)
Gender identity	One's internal sense of being male, female, both, neither or other gender(s)
Transgender	Umbrella term for many gender identities for those who do not identify with their sex assigned at birth
Transwoman	Generally describes someone assigned male at birth who identifies as a woman
Transman	Generally describes someone assigned female at birth who identifies as a man
Nonbinary	Preferred term for all genders other than female/male or woman/man. Not all nonbinary people identify as trans and not all transpeople identify as nonbinary
Sexual orientation	A person's identity in relation to the gender(s) to which they are sexually attracted (heterosexual, homosexual)

and was likely underreported previously.[25] A recent study from a large US-based cohort from three Kaiser Permanente healthcare systems found that the number of adults with a TGGNB identity increased from roughly 10–20 per 100,000 individuals in 2006 to roughly 40–75 per 100,000 individuals in 2014.[25] A recent study found that nearly 10% of youth in one US urban school district identify as gender-diverse.[26] Similar rates of increased prevalence of TGGNB people seeking medical attention have occurred in Europe.[27] The increasing number of TGGNB individuals seeking healthcare is likely due to increased awareness among the medical community, societal acceptance of different gender identities, and availability of medical guidelines.[28–30]

A multispecialty approach is necessary, especially in youth, to support TGGNB with CF in their transition.[30] In youth, the Endocrine Society recommends that the team includes professionals that have experience in the diagnosis of gender dysphoria and in social transitioning of transgender youth. For youth and adults, gender affirming hormone therapy (GAHT) is often the cornerstone of treatment for those TGGNB people seeking a gender transition.[31] With the increasing number of TGGNB people presenting for healthcare, clinicians should be aware of the potential impact of gender affirmation hormone therapies on CF care. In transgender women, GAHT is associated with increased risk of pulmonary embolism and cerebrovascular disease.[32] In transgender men, GAHT is associated with polycythemia.[33] One case report of a transgender woman (assigned male at birth) with CF undergoing estrogen therapy found worsened lung function and increasing frequency of PEx after 1 year of estrogen therapy.[34] Another case report of a transgender woman with CF reported the new appearance of *Pseudomonas aeruginosa* in sputum but relatively stable pulmonary function after 1 year of estrogen therapy.[35] These two case reports highlight a potential clinical concern of which providers taking care of TGGNB people with CF should be aware.

Other nonhormonal gender affirming care may impact care of patients with CF.[36] Most transgender men will bind their chests with commercial binders to better conform their appearance to their gender identity.[37] The majority of transgender men using chest binders will experience back pain, shoulder pain, chest pain, bad posture, and shortness of breath due to chest binding in their lifetime.[37] Use of chest binding during pulmonary function tests may decrease lung volumes.[38] The impact of chest binding on high-frequency chest wall oscillation is unknown. Transgender women may seek silicone breast implants from unlicensed professionals which have been associated with silicone metastasis to lung and distant organs.[39]

There remain many unknowns regarding the care of people with CF and TGGNB identities. These unknowns include which reference database (male or female) should be used for pulmonary function testing or bone mineral density measurements. Using the affirmed gender for the reference group in spirometry will significantly change interpretation and potentially lead to missed diagnoses.[40] Finally, other unknowns in people with CF include the impact of chest binding in transmasculine individuals on pulmonary function,[36] and the interaction with the initiation of GAHT on highly effective modulator therapy (HEMT), such as elexacaftor/tezacaftor/ivacaftor (ETI) and ivacaftor.

1.3 | Contraception

While the majority of women with CF plan to have children at some point, reports indicate that 25%–50% of pregnancies are unplanned.[41–43] However, limited data exist surrounding the use of contraception in CF.[44,45] The United States Medical Eligibility Criteria for Contraception Use contains evidence-based guidelines regarding contraception use in CF,[46] but, importantly, the interplay of disease-specific risk factors, such as medication interactions, gastrointestinal absorption, CFRLD, CFRD, bone health, and frequent use of intravenous access devices for antibiotics, may complicate contraception decisions for women with CF.

Types of contraception used by women with CF vary greatly. In a recent study published in 2020, investigators surveyed 150 women from three different CF centers to understand contraceptive use.[43] Combined hormonal contraceptives were used most commonly (42%) followed by barrier methods such as condoms (34%), followed by long-acting reversible contraceptive methods such as intrauterine devices (IUDs) (27%).[43] Twenty-four percent reported no method of contraception and, importantly, 50% of those who became pregnant reported unplanned pregnancies.[43] With the advent of HEMT, such

as ETI and ivacaftor, fertility is anticipated to increase in women with CF likely due to thinning of cervical mucus, possible increased mucociliary transport, and improved conditions for sperm capacitation in the female reproductive tract.[47–49] Therefore, conversations surrounding contraception and understanding of the benefits and risks to contraception for people with CF are increasingly important.

Combined hormonal contraceptives (containing estrogen and progesterone) include pills, patches, and vaginal rings. Such methods are commonly contraindicated in women with pulmonary hypertension and decompensated cirrhosis secondary to increased risk of thrombosis.[46,50] Malabsorption of oral medications due to pancreatic enzyme insufficiency may theoretically decrease the effectiveness of oral contraceptive pills (OCPs). Data on contraceptive efficacy are limited but a small study of pharmacokinetics of orally administered hormones in women with CF versus controls suggests similar plasma levels.[51] Questions are outstanding regarding patch contraception and whether absorption of hormones through the skin of people with CF with abnormal sweat glands is similar to that of the general population. Standard preparations of the combined OCPs are associated with a two to three-times increased risk of venous thromboembolism, which is of particular importance for those with implantable vascular access devices (associated with a 5%–14% risk of venous thromboembolism alone), commonly used in people with CF.[50,52]

Medications commonly used in CF can interact with hormonal contraceptives. This interaction is of particular concern in women with CF, who require antibiotics frequently throughout their reproductive years. Few articles in the literature suggest antibiotic use is a true contraindication to hormonal contraception and most antibiotics typically used for CF PEx do not pose known pharmacokinetic contraindications[44]; however, these concerns have not been researched specifically in the CF population. A few special circumstances include treatment of nontuberculous mycobacteria, which often includes rifampin and rifabutin. These drugs can interfere with the effectiveness of hormonal contraceptives.[53] Importantly, the CFTR modulator lumacaftor/ivacaftor affects metabolism and reduces the efficacy of oral hormonal contraceptives and product information recommends avoidance of all forms of hormonal contraception.[53] Other CFTR modulators, including ivacaftor, tezacaftor/ivacaftor, and ETI, do not have this interaction.[53–55] Of note, in people with CF who recently started ETI, there is a higher incidence of rash in women than in men which occurs more frequently in women on hormonal contraceptives than those not on hormonal contraceptives.[56] The rash often resolves without intervention.

The hormonal injection, depot medroxy-progesterone acetetate (DMPA), typically lasts 3 months before an additional dose is required. This dosing schedule makes it a convenient contraceptive option, but it is associated with accelerated, but potentially reversible, loss of bone mineral density.[50] DMPA may also be useful in the treatment of underweight women with CF as it can cause weight gain.[57] Long-acting reversible contraceptives, such as copper and hormonal IUDs and hormonal implants, are highly effective and reversible methods with increasing use in the general population.[50] For many women with CF, these methods are safe to use. Hormonal IUDs may theoretically be affected by use of lumacaftor/ivacaftor and, thus, are not recommended according to the US prescribing information; however, the copper IUD is an effective option for women taking this medication.[53]

Women with CF report low rates of contraceptive counseling and rarely discuss this aspect of care at their CF care center visits.[42,44,58] Given the unique considerations outlined above, contraceptive options along with risks and benefits should be discussed in the context of the CF care model with coordinated decisions with women's health providers. Importantly, selection of a contraceptive method should take into consideration both the women's preferences and priorities as well as the impact on their CF health status.

1.4 | Sexually transmitted infections (STIs) and genital candidiasis

People with CF generally engage in the same types of sexual behaviors and activities as their peers without CF, including number of sexual partners, age of sexual debut, and performance and receipt of oral, vaginal, and anal sex.[59–63] However, STIs in people with CF are understudied. This population is expected to have a normal response to most STIs; however, those with hepatitis B and C infections risk a poorer prognosis, especially in the setting of concomitant CFRLD. Young women with CF report a similar prevalence of STIs, but lower rates of STI screening compared to the general population.[61] Men with CF report suboptimal condom use with one-third disclosing their assumption that they did not need to use condoms during adolescence, due to presence of known male infertility associated with CF.[59]

A recent study from France documented a high proportion of abnormal pap smears and cervical dysplasia among transplanted and nontransplanted women with CF.[64] Unfortunately, the same research team found that cervical screening among women with CF is suboptimal with only 55% reporting a previous Pap smear.[65] Adolescent and young adult women with CF and the general US population report obtaining the human papillovirus (HPV) immunization at nearly equal rates (44% vs. 43%).[66] Among 9- to 17-year-old females attending French pediatric CF centers, 31% had received the HPV vaccine with two-thirds receiving the prescription from their CF center.[67] As people with CF can be considered for organ transplantation and immunosuppression is associated with a heightened risk of cervical dysplasia, routine cervical, and STI screening and HPV vaccination is crucial for this population.[68]

Genital candidiasis is also a significant and often distressing problem for both men and women with CF.[61,69–71] Incidence of candidiasis has been associated with long-term antibiotic use, but CFRD, immunosuppression, and corticosteroid use are additional risk factors.[70] Treatment with typical topical or oral antifungal medications is largely effective. However, if the person is currently taking a CFTR modulator, dosing adjustments are required for metabolism effects and interactions with azole therapy.[53–55,72]

1.5 | Hypogonadism

Hypogonadism in boys typically presents as delayed puberty (see Section 1.1) and in men with symptoms of sexual dysfunction, fatigue, and decreased quality of life.[73] In either age group, screening for hypogonadism and a referral to endocrinology is a reasonable approach. Men with CF are at risk of developing hypogonadism due to recurrent illness, stress, lower nutritional status, and medications such as glucocorticoids or opiates.[74] The prevalence of hypogonadism in men with CF is not known due to lack of published studies and standardized screening protocols. A cross-sectional study conducted in 2003 found approximately a quarter of men with CF had serum testosterone levels 2 standard deviations below reference men.[75] However, this study only measured a single morning testosterone value to classify participants.

In the absence of guidelines, men with CF who have symptoms of hypogonadism (poor libido, erectile dysfunction, decreased muscle mass and/or strength) or low bone density should be screened for low testosterone.[76] Serum total testosterone should be measured between 7 and 10 am in the morning and on two separate occasions.[77] Also, it is important to utilize laboratories that participate in the Centers for Disease Control and Prevention (CDC) Hormone Standardization Program as proficiency in measuring testosterone at the lower levels may vary between laboratories.[78] In the evaluation of low testosterone, the Endocrine Society recommends distinguishing between primary (hypothalamic/pituitary) versus secondary (testicular) disease in the etiology of the hypogonadism.[77]

After establishing a diagnosis and etiology of hypogonadism, treatment of hypogonadism in CF should be individualized. Potentially reversible causes of low testosterone should target the primary cause (prolactinoma, medications, illness, nutritional status, etc.). When hypogonadism is due to stress or illness (hypothalamic hypogonadism), serum testosterone levels may recover when health stabilizes. However, in some cases, testosterone levels may remain chronically low and initiation of testosterone therapy may be indicated to reverse symptoms of hypogonadism and/or improve bone health.[79] However, long-term data are limited in CF regarding the impact of testosterone therapy on improving SRH, increasing bone density, and reducing fractures in men with CF.[74] It is important to discuss the impact of testosterone therapy on fertility potential as testosterone therapy will reduce spermatogenesis.[76] Considering potential long-term risks of testosterone therapy, the duration of testosterone therapy needs to be individualized.[80] Furthermore, we do not know the impact of HEMT on restoring testosterone levels in hypogonadal men with CF. Despite these limitations in our knowledge, it is clear that men with CF desire more discussions surrounding SRH concerns and thus care providers should routinely initiate such conversations.[59]

Women with CF are at risk for low estrogen levels due to the same factors listed for men with CF. Low estrogen levels in women with CF can present as primary or secondary amenorrhea, low bone density, infertility, and decreased sexual health. Unlike in men with CF, hypogonadism in women with CF is diagnosed clinically as opposed to measurement of serum sex hormone concentrations. Few studies have reported the prevalence of hypogonadism in women with CF; however, early studies suggested that the majority of premenopausal women with CF have menstrual irregularities.[81,82] Wu et al. found that very few women with CF receive estrogen therapy and those who do receive estrogen therapy benefit with improved bone density.[83] Studies are needed to better characterize circulating sex steroid hormone concentrations in women with CF.

Evidence connecting female sex hormones and CF disease outcomes has prompted questions about the use of contraception as a treatment modality for women with CF. In a retrospective analysis of women attending a single CF center in the United Kingdom between 1981 and 2010, Kernan et al. showed no difference in clinical outcome measures in 57 women exposed to combined hormonal contraceptive pills versus matched nonexposed controls over a 5-year period as well as no difference when analyzing intrapatient effect on women with CF who had exposure to OCPs followed by nonexposure over a 3-year period.[84] Another study showed an association with fewer PEx in women on OCPs than those who were not.[85] In another recently published study, higher levels of sputum inflammatory markers were associated with elevated 17β-estradiol levels and this inflammation was attenuated by the initiation of combined OCPs therapy that suppressed endogenous estrogen levels.[86] Data on the effects of various types of contraception on CF health are lacking and further research is ongoing (NCT 04568980).

1.6 | Sexual functioning

There are aspects of CF-related directly to CFTR dysfunction and its downstream consequences that may impair sexual function in people with CF such as dyspareunia related to vaginal dryness, body image resulting from testosterone deficiency, and low body weight, and coughing and dyspnea during intercourse. In a survey of women with CF (not peer-reviewed) conducted in 2020, nearly 80% of female respondents ($n = 39$) stated that they believe that CF plays a significant role in their sexual function.[87] Although prevalence of reported sexual dysfunction in people with CF varies by age (and thus likely by disease severity and concomitant comorbidities) rates as high as 43% in women and 65% in men are reported.[61,88]

For the majority of men with CF, based on CBAVD, the content of ejaculate is azoospermic, low volume, acidic, and primarily composed of prostatic fluid.[89] While use of CFTR modulators is not believed to restore the vas deferens in men with CF, the action of modulators on the CFTR channels present in the male reproductive tract could lead to increased ejaculate volume.[90] A case series recently described the onset of acute testicular pain in seven men with CF following initiation of ETI. The pain onset occurred within 2 weeks of starting therapy and was hypothesized to be related to increased reproductive tract CFTR function.[48]

While CBAVD and low ejaculate volume do not impair sexual function in men with CF, the occurrence of testosterone deficiency can have a multitude of effects. In small studies of men with CF, 28%–45% of participants had mild-moderate testosterone deficiency.[75,91] Testosterone deficiency can adversely impact libido, depress mood, and cause

fatigue. Further, body image changes such as loss of body and facial hair and diminished muscle mass may also impair libido.

Based on interviews of women with CF, negative body image based on weight, surgical scars, and implantable medical devices may affect the libido of women with CF.[87] Although women with CF have anatomy that is similar to that of women without CF, dysfunctional CFTR in the reproductive tract of women with CF contributes to thick cervical mucus and likely to decreased vaginal lubrication.[90,92] Dyspareunia (genital or pelvic pain temporally related to sexual intercourse) can occur as a result of vaginal dryness, vulvodynia (peri-vulval pain), vaginal infection, or vaginismus (spontaneous contraction of vaginal wall muscles). In a survey of young women with CF, 16% of respondents with history of vaginal penetration reported that dyspareunia occurred at least half the time.[61] No data are yet available for the impact of ETI on sexual function in women with CF.

For both men and women with CF, severity of lung disease and associated symptoms such as cough, hemoptysis, and exercise intolerance may interfere with the enjoyment of intercourse. Aguiar et al. administered the CF (CFQ) and sexual satisfaction (SSQ) questionnaires and 6 min walk tests (6MWT) to 52 adults with CF.[93] There were positive correlations between CFQ and SSQ scores and 6MWT performance. To combat cough and breathlessness during sexual activity, the British Lung Foundation offers specific recommendations such as breathing control techniques, airway clearance, and medication use for symptom control before sexual activity, and low energy sexual positions.[94]

1.7 | Cyclical hemoptysis

Catamenial hemoptysis, the expectoration of blood during menses, occurs in less than 6% of the general female population,[95] and is also reported by women with CF. While hemoptysis is a well-known complication in people with CF and occurs in approximately 9% of individuals with CF over a 5-year time period,[96] studies examining catamenial hemoptysis in women with CF are limited. Clinical history of hemoptysis occurring at the same time as the menstrual cycle is the most helpful for diagnosis of probable pulmonary endometrial tissue, while CT scan and bronchoscopy are not specific.[97] Dysregulated inflammation of the airway driven by fluctuations in hormones is thought to be the etiology of catamenial hemoptysis in CF.[86] Significant hemoptysis may require treatment with bronchial artery embolization, and is recommended by CF guidelines for unstable massive hemoptysis.[96] However, efficacy of bronchial artery embolization ranges from 75% to 93%, and hemoptysis recurs in approximately 40% of people.[98] Caution must be taken as embolization can precipitate respiratory failure in end-stage lung disease and lead to a more urgent need for lung transplant evaluation.[99] Catamenial hemoptysis can be treated by optimizing vitamin K supplementation, and consideration of a trial with OCPs or Gonadotropin-releasing hormone analogs. Case reports suggest that there is some degree of response to initiation of OCPs.[100]

Improvement of catamenial hemoptysis after initiation of HEMT, including ETI, has been reported,[100] which is thought to result from decreased airway inflammation and decreased rates of PEx from the improvement in CFTR protein function enabled by these therapies.[56] Treatment with chronic macrolide therapy, for which many women with CF are prescribed, may also further improve hemoptysis by decreasing inflammation.

In summary, catamenial hemoptysis can be managed by vitamin K supplementation, trial of OCPs, use of CFTR modulators if eligible, anti-inflammatories, consider bronchial artery embolization when hemoptysis is massive, and surgical resection of the involved lung if the former does not resolve hemoptysis.

1.8 | Urinary incontinence (UI)

UI is common in people with CF, with prevalence ranging from 5% to 15% for men and 15%–76% for women.[101,102] Common triggers of

TABLE 2 Sexual and reproductive health model of health assessment over the lifespan for CF care providers and collaborating care providers

Adolescence	Adulthood	Late adulthood
Assess pubertal development, hormones, and hypogonadism		
Openly discuss gender identity and sexual preferences		
Discuss fertility and contraception		
Counsel on STI prevention		
	Discuss sexual functioning; address any concerns	
	Discuss parenthood and reproductive options	
	Evaluate urinary incontinence	
		Evaluate peri-menopause symptoms

Abbreviation: STI, sexually transmitted infection.

TABLE 3 Research on topics related to sexual and reproductive health in CF, funded by the CF Foundation*,[119]

	Potentially beneficial collaborations	Related cystic fibrosis Foundation-funded studies
Body image	Psychiatry, psychology, mental health, and social workers	In need of funded investigation
Contraception	Family planning, obstetrics/gynecology	-Impact of hormone contraception on exacerbations (PI: Godfrey, University of Washington) -MENstrual Sympto TRacking to Understand and Assess (women) Living with CF (PI: Godfrey, University of Washington)
Fertility—male and female	Obstetrics/gynecology, urology	-Cervical mucus quality in women on/off modulator with healthy controls (PI: Roe, University of Pennsylvania) -Fertility Preservation in Men with Cystic Fibrosis Pre-lung Transplantation (PI: Ladores, University of Alabama-Birmingham)
Gender transition and gender affirming care	Endocrinology	In need of funded investigation
Menopause	Endocrinology	In need of funded investigation
Pregnancy	Obstetrics/gynecology, maternal fetal medicine	-Evaluation of Predictors Of Maternal-fetal Outcomes in CF (PIs: Jain, University of Texas Southwestern; Taylor-Cousar, National Jewish Health) -MyVoice: CF (A reproductive goals decision aid for women with CF) (PI: Kazmerski, University of Pittsburgh) -MAYFLOWERS (Maternal and Fetal Outcomes in the Era of Modulators) (CFF Therapeutics Diagnostics Network; NCT04828382)
Parenthood		-Qualitative parenthood study ongoing (PIs: Taylor-Cousar, National Jewish Health; Kazmerski, University of Pittsburgh) -HOPe CF (**H**ealth **O**utcomes in **P**arents with CF), (PIs: Georgiopoulos, Massachusetts General Hospital; Taylor-Cousar, National Jewish Health; Kazmerski, University of Pittsburgh; Jain, University of Texas Southwestern)
Sex hormones, clinical outcomes, sex disparity, puberty	Endocrinology	-Sex differences in response to highly effective modulator therapy (PI: Jain, University of Texas Southwestern) -Association of sex hormones with respiratory health in women with CF (PI: Montemayor, Johns Hopkins University) -Sex differences in pulmonary exacerbations in cystic fibrosis patients (PI: Montemayor, Johns Hopkins University, *funded by the NIH*)
Sexual and reproductive health services	Mutlidiscliplinary	-Sexual and reproductive health in adult women with cystic fibrosis (PI: Kazmerski, University of Pittsburgh)
Urinary incontinence	Urology	-Urinary incontinence (PI: Bradly, West, Johns Hopkins University; Kazmerski, University of Pittsburgh)

Abbreviations: CFF, cystic fibrosis Foundation; NIH, National Institutes of Health.
*Above studies are funded by the CF Foundation.

UI include coughing, physical activity, laughing, sneezing, and somewhat unique to people with CF: performing airway clearance and spirometry. In general, UI is categorized as (1) stress UI related to effort or physical exertion including coughing, (2) urgency UI related to loss of urine associated with urgency, or (3) a combination of both, mixed incontinence. The majority of women with CF experience stress UI secondary to frequent coughing and need to perform airway clearance. UI can interfere with the ability of people with CF to perform airway clearance, exercise, or do effective spirometry, with approximately 40% of women with CF reporting a deleterious impact on their ability to effectively complete airway clearance.[103] Men with CF with UI report higher rates of anxiety and depression.[102] UI in both men and women in CF are associated with a decreased quality of life,[104] and therefore, diagnosis of UI and management are essential.

Evaluation and treatment of constipation, urinary tract infections, and CFRD are key to ensure those issues are not contributing to UI. Physical therapists are a necessary resource to evaluate and manage UI in people with CF, and there is evidence that exercises to strengthen pelvic floor muscles improve UI.[105] Less invasive options for therapy include bladder training, intravaginal mechanical devices, and disposable and absorbent pads. Referral to urogynecology may be necessary for more severe UI that does not resolve with physical therapy. Surgical options include mid-urethal slings for stress UI,[106] or botulinum toxin injections for urgency UI, but guidelines advise trials of noninvasive therapies initially.[107]

Despite the frequency of UI being quite high in people with CF, there is no data on subjective and objective measures of UI in CF. Research is ongoing to better characterize UI in women with CF, as well as identifying the most appropriate treatment options, given the unique triggers of significant cough and their need for effective airway clearance.

1.9 | Menopause

Menopausal transition among females classically starts in the fifth decade of life.[108,109] However, menopausal features that may be unique to women with CF have not yet been well-characterized. Menopausal symptoms include irregular menstrual cycles, hot flashes, sleep disturbance, depression, mood changes, vaginal dryness, dyspareunia, and sexual dysfunction. Menopause has been categorized into stages (STages of Reproductive Aging Workshop, STRAW).[24] Signs and symptoms usually appear within the 4 years before a woman's last menstrual period. The use of HEMT is anticipated to markedly increase CF women's longevity and add to the number of postmenopausal women with CF.

Currently, there is only limited information available regarding the age at which women with CF experience menopausal symptoms. Relatively little is documented regarding the treatment of menopause symptoms specific to women with CF, and, to date, information from women without CF is commonly extrapolated, such as the benefits and risks of hormone replacement therapy (HRT) to alleviate menopausal symptoms.[110] In women without CF, the benefits of HRT for those aged 50–59 years may include a trend toward less bone fractures, improved diabetes control, and all-cause mortality, but there could also be a trend toward increased risk of cerebrovascular accidents, deep vein thrombosis, and pulmonary embolism. Thus, to determine the best approach to care for peri- or postmenopausal women with CF, the risks and benefits of HRT in women with CF needs further study.

HRT can include estrogen versus estrogen/progesterone combination supplementation aimed at alleviating menopausal symptoms such as hot flashes and vaginal dryness. Estrogens can be given orally, subcutaneously, or vaginally. When given orally, estrogens undergo hepatic metabolism and increase hepatic production of several proteins including clotting factors. Importantly, women with CF may have altered hepatic metabolism, due to CF, and due to CFTR modulator treatments, thus, altering serum estrogen levels. Estrogen can also be used transdermally, sometimes with the addition of progestin. Topical forms of estradiol are available in a variety of forms including gels, aerosols, and pumps for the treatment of vasomotor symptoms. Administration of low-dose vaginal estrogen can be safely used to treat vaginal atrophy.

2 | CONCLUSION

SRH is an increasingly important topic as people with CF live longer and healthier lives. Both general and disease-specific SRH concerns are understudied and generally unaddressed in traditional CF care.[74,111] Many people with CF view their subspecialist as a “de facto” primary care provider and, thus, may rely on the CF team for SRH counseling and referrals. Prior research among CF providers demonstrates a lack of standardization regarding SRH care and counseling for people with CF and many barriers to optimal care provision.[112–115] Not surprisingly, both men and women with CF express dissatisfaction with SRH care provision in the current CF care model.[20,59,116] The majority of women with CF desire tailored SRH discussions related to their CF initiated by their CF provider in early adolescence.[117] In a prior multicenter survey of men with CF, one-third identified that they would first like to hear about SRH concerns (specifically fertility) from their CF team, one-third from parents, and the remainder from a combination of parents, healthcare providers, and educational materials.[116] A model of health assessments that can be performed over the lifespan of people with CF can be used as a guide (Table 2).

Due to significant gaps in counseling and care provision, people with CF report low rates of SRH care utilization.[20,65,66,103] Indeed, both adolescent and adult women with CF from the US report markedly lower rates of contraception use, cervical screening, pregnancy testing, and screening for STIs than the general population.[66,103] A contemporary study from France echoed this suboptimal SRH care utilization among women with CF, with 45% lacking routine Pap smears and 25% lacking gynecologic follow up.[65] Regarding men with CF, an Australian survey found that only a quarter reported ever receiving a “sexual health checkup.”[20] A minority of women with CF receive or discuss SRH care in the CF setting, although the majority desire such conversations.[42,66] Similarly, only half of men with CF report hearing about fertility concerns from their preferred source.[20,59]

The impact of the approval and increased use of HEMT on SRH care needs and outcomes remains to be seen. However, due to the positive impact on health and longevity, it is expected that people with CF will increasingly face SRH concerns and decisions. Optimizing SRH care as the face of CF changes is imperative to meet these emerging needs throughout the lifespan. A recent French study documented the successful integration of women's SRH care provision in CF care through provision of gynecologic consultation in the CF clinic.[118] Similar explorations into collaborations between SRH care providers and the CF team are needed.

SRH in CF is an exciting area of research as the quantity and quality of life for people with CF continues to improve. Clinical care and research must evolve on these topics to adequately address and manage SRH concerns throughout the lifespan. A call for research in multiple areas is supported by the CF Foundation[119] (Table 3), and a group of CF Foundation-sponsored physicians, researchers, and people with CF have joined to form the CF Therapeutics Development Network Women's Health Research Working Group to target questions specific to SRH for both men and women with CF. Additionally, the group has outlined research priorities in men with CF.[74] The goal of this group is to facilitate and conduct well-designed studies related to SRH that will provide data to improve the lives of people with CF.

ACKNOWLEDGMENT

Natalie E. West, Traci M. Kazmerski, Jennifer L. Taylor-Cousar, Moira L. Aitken, and Raksha Jain receive grant support from the Cystic Fibrosis Foundation (WEST19Y3, KAZMER19Y3, TAYLOR19Y3,

AITKEN19Y3, JAIN19Y3) to support the Women's Health Research Working Group in Cystic Fibrosis.

AUTHOR CONTRIBUTIONS

Natalie West: conceptualization (lead); writing original draft (lead); writing review and editing (lead). **Traci Kazmerski**: conceptualization (equal); writing original draft (equal); writing review and editing (equal). **Jennifer Taylor-Cousar**: conceptualization (equal); writing original draft (equal); writing review and editing (equal). **Vin Tangpricha**: writing original draft (equal); writing review and editing (equal). **Kelsie Pearson**: conceptualization (equal); writing original draft (equal). **Moira L. Aitken**: conceptualization (equal); writing original draft (equal); writing review and editing (equal). **Raksha Jain**: conceptualization (lead); writing original draft (lead); writing review and editing (lead).

ORCID

Natalie E. West http://orcid.org/0000-0002-0025-2422
Traci M. Kazmerski http://orcid.org/0000-0002-3916-8260
Jennifer L. Taylor-Cousar http://orcid.org/0000-0002-5436-9722
Raksha Jain http://orcid.org/0000-0002-2407-7374

REFERENCES

1. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry, 2019 Annual Data Report. Bethesda, Maryland; 2020.
2. Kazmerski TM, West NE, Jain R, et al. Family-building and parenting considerations for people with cystic fibrosis. *Pediatr Pulmonol*. 2021:ppul.25620. https://doi.org/10.1002/ppul.25620
3. National Institutes of Health. About puberty and precocious puberty. https://www.nichd.nih.gov/health/topics/puberty/conditioninfo
4. Johannesson M, Gottlieb C, Hjelte L. Delayed puberty in girls with cystic fibrosis despite good clinical status. *Pediatrics*. 1997;99(1):29-34. https://doi.org/10.1542/peds.99.1.29
5. Landon C, Rosenfeld RG. Short stature and pubertal delay in male adolescents with cystic fibrosis. Androgen treatment. *American Journal of Diseases of Children (1960)*. 1984;138(4):388-391. https://doi.org/10.1001/archpedi.1984.02140420054017
6. Mahaney MC, McCoy KS. Developmental delays and pulmonary disease severity in cystic fibrosis. *Hum Biol*. 1986;58(3):445-460
7. Sproul A, Huang N. Growth patterns in children with cystic fibrosis. *J Pediatr*. 1964;65:664-676. https://doi.org/10.1016/s0022-3476(64)80151-7
8. Zhang Z, Lindstrom MJ, Farrell PM, Lai HJ. Wisconsin cystic fibrosis neonatal screening group. pubertal height growth and adult height in cystic fibrosis after newborn screening. *Pediatrics*. 2016;137(5):e20152907. https://doi.org/10.1542/peds.2015-2907
9. Buntain HM, Greer RM, Wong JCH, et al. Pubertal development and its influences on bone mineral density in Australian children and adolescents with cystic fibrosis. *J Paediatr Child Health*. 2005;41(7):317-322. https://doi.org/10.1111/j.1440-1754.2005.00635.x
10. Kelly A, Schall JI, Stallings VA, Zemel BS. Deficits in bone mineral content in children and adolescents with cystic fibrosis are related to height deficits. *J Clin Densitom*. 2008;11(4):581-589. https://doi.org/10.1016/j.jocd.2008.07.002
11. Sutton S, Rosenbluth D, Raghavan D, Zheng J, Jain R. Effects of puberty on cystic fibrosis related pulmonary exacerbations in women versus men. *Pediatr Pulmonol*. 2014;49(1):28-35. https://doi.org/10.1002/ppul.22767
12. Iuliano-Burns S, Mirwald RL, Bailey DA. Timing and magnitude of peak height velocity and peak tissue velocities for early, average, and late maturing boys and girls. *Am J Hum Biol*. 2001;13(1):1-8. https://doi.org/10.1002/1520-6300(200101/02)13:1%3C1::AID-AJHB1000%3E3.0.CO;2-S
13. Abbassi V. Growth and normal puberty. *Pediatrics*. 1998;102(2 Pt 3):507-511.
14. Rosenfeld M, Davis R, FitzSimmons S, Pepe M, Ramsey B. Gender gap in cystic fibrosis mortality. *Am J Epidemiol*. 1997;145(9):794-803. https://doi.org/10.1093/oxfordjournals.aje.a009172
15. Harness-Brumley CL, Elliott AC, Rosenbluth DB, Raghavan D, Jain R. Gender differences in outcomes of patients with cystic fibrosis. *J Womens Health (Larchmt)*. 2014;23(12):1012-1020. https://doi.org/10.1089/jwh.2014.4985
16. Montemayor K, Psoter KJ, Lechtzin N, et al. Sex differences in treatment patterns in cystic fibrosis pulmonary exacerbations. *J Cyst Fibros*. 2021. Accessed June 7, 2021. https://doi.org/10.1016/j.jcf.2021.05.012 https://www.cysticfibrosisjournal.com/article/S1569-1993(21)00163-6/abstract
17. Bournez M, Bellis G, Huet F. Growth during puberty in cystic fibrosis: a retrospective evaluation of a French cohort. *Arch Dis Child*. 2012;97(8):714-720. https://doi.org/10.1136/archdischild-2011-301069
18. Goldsweig B, Kaminski B, Sidhaye A, Blackman SM, Kelly A. Puberty in cystic fibrosis. *J Cyst Fibros*. 2019;18(Suppl 2):S88-S94. https://doi.org/10.1016/j.jcf.2019.08.013
19. Lam GY, Goodwin J, Wilcox PG, Quon BS. Sex disparities in cystic fibrosis: review on the effect of female sex hormones on lung pathophysiology and outcomes. *ERJ Open Res*. 2021;7(1):00475-2020. https://openres.ersjournals.com/content/7/1/00475-2020. https://doi.org/10.1183/23120541.00475-2020
20. Sawyer SM, Farrant B, Wilson J, et al. Sexual and reproductive health in men with cystic fibrosis: consistent preferences, inconsistent practices. *J Cyst Fibros*. 2009;8(4):264-269. https://doi.org/10.1016/j.jcf.2009.05.005
21. Withers AL. Management issues for adolescents with cystic fibrosis. *Pulm Med*. 2012;2012:134132. https://doi.org/10.1155/2012/134132
22. Allan JL, Townley RR, Phelan PD. Family response to cystic fibrosis. *Aust Paediatr J*. 1974;10(3):136-146. https://doi.org/10.1111/j.1440-1754.1974.tb01105.x
23. Kidd KM, Sequeira GM, Voss RV, et al. Caring for gender diverse youth with cystic fibrosis. *J Cyst Fibros*. 2020;19(6):1018-1020. https://doi.org/10.1016/j.jcf.2020.03.003
24. Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab*. 2012;97(4):1159-1168. https://doi.org/10.1210/jc.2011-3362
25. Zhang Q, Rechler W, Bradlyn A, et al. Changes in size and demographic composition of transgender and gender non-binary population receiving care at integrated health systems. *Endocr Pract*. 2021;27(5):390-395. https://doi.org/10.1016/j.eprac.2020.11.016
26. Kidd KM, Sequeira GM, Douglas C, et al. Prevalence of gender-diverse youth in an urban school district. *Pediatrics*. 2021;147(6). https://doi.org/10.1542/peds.2020-049823
27. Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam cohort of gender dysphoria study (1972-2015): trends in prevalence, treatment, and regrets. *J Sex Med*. 2018;15(4):582-590. https://doi.org/10.1016/j.jsxm.2018.01.016
28. Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med*. 2019;381(25):2451-2460. https://doi.org/10.1056/NEJMcp1903650
29. Safer JD, Tangpricha V. Care of the transgender patient. *Ann Intern Med*. 2019;171(10):775-776. https://doi.org/10.7326/L19-0535
30. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903. https://doi.org/10.1210/jc.2017-01658
31. Chantrapanichkul P, Stevenson MO, Suppakitjanusant P, Goodman M, Tangpricha V. Serum hormone concentrations in

transgender individuals receiving gender-affirming hormone therapy: a longitudinal retrospective cohort study. *Endocr Pract*. 2021; 27(1):27-33. https://doi.org/10.4158/EP-2020-0414

32. Getahun D, Nash R, Flanders WD, et al. Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. *Ann Intern Med*. 2018;169(4):205-213. https://doi.org/10.7326/M17-2785
33. Antun A, Zhang Q, Bhasin S, et al. Longitudinal changes in hematologic parameters among transgender people receiving hormone therapy. *J Endocr Soc*. 2020;4(11):bvaa119. https://doi.org/10.1210/jendso/bvaa119
34. Lam GY, Goodwin J, Wilcox P, Quon BS. Worsening pulmonary outcomes during sex reassignment therapy in a transgender female with cystic fibrosis (CF) and asthma/allergic bronchopulmonary aspergillosis: a case report. *BMC Pulm Med*. 2020;20(1):234. https://doi.org/10.1186/s12890-020-01272-x
35. Shaffer L, Bozkanat K, Lau M, et al. Gender-affirming hormone therapy in cystic fibrosis–a case of new pseudomonas infection. *Respir Med Case Rep*. 2021;32:101353. https://doi.org/10.1016/j.rmcr.2021.101353
36. Peitzmeier S, Gardner I, Weinand J, Corbet A, Acevedo K. Health impact of chest binding among transgender adults: a community-engaged, cross-sectional study. *Cult Health Sex*. 2017;19(1):64-75. https://doi.org/10.1080/13691058.2016.1191675
37. Peitzmeier SM, Silberholz J, Gardner IH, Weinand J, Acevedo K. Time to first onset of chest binding-related symptoms in transgender youth. *Pediatrics*. 2021;147(3):e20200728. https://doi.org/10.1542/peds.2020-0728
38. Cumming R, Sylvester K, Fuld J. Understanding the effects on lung function of chest binder use in the transgender population. *Thorax*. 2016;p:71-A227.
39. Turner GA, Amoura NJ, Strah HM. Care of the transgender patient with a pulmonary complaint. *Ann Am Thorac Soc*. 2021; 18(6):931-937. https://doi.org/10.1513/AnnalsATS.202007-801CME
40. Haynes JM, Stumbo RW. The impact of using non-birth sex on the interpretation of spirometry data in subjects with air-flow obstruction. *Respir Care*. 2018;63(2):215-218. https://doi.org/10.4187/respcare.05586
41. Fair A, Griffiths K, Osman LM. Attitudes to fertility issues among adults with cystic fibrosis in Scotland. The Collaborative Group of Scottish Adult CF Centres. *Thorax*. 2000;55(8):672-677. https://doi.org/10.1136/thorax.55.8.672
42. Gatiss S, Mansour D, Doe S, Bourke S. Provision of contraception services and advice for women with cystic fibrosis. *J Fam Plann Reprod Health Care*. 2009;35(3):157-160. https://doi.org/10.1783/147118909788708075
43. Godfrey EM, Mody S, Schwartz MR, et al. Contraceptive use among women with cystic fibrosis: A pilot study linking reproductive health questions to the Cystic Fibrosis Foundation National Patient Registry. *Contraception*. 2020;101(6):420-426. https://doi.org/10.1016/j.contraception.2020.02.006
44. Roe AH, Traxler S, Schreiber CA. Contraception in women with cystic fibrosis: a systematic review of the literature. *Contraception*. 2016;93(1): 3-10. https://doi.org/10.1016/j.contraception.2015.07.007
45. Whiteman MK, Oduyebo T, Zapata LB, Walker S, Curtis KM. Contraceptive safety among women with cystic fibrosis: a systematic review. *Contraception*. 2016;94(6):621-629. https://doi.org/10.1016/j.contraception.2016.05.016
46. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep*. 2016; 65(3):1-103. https://doi.org/10.15585/mmwr.rr6503a1
47. Taylor-Cousar JL. CFTR modulators: impact on fertility, pregnancy, and lactation in women with cystic fibrosis. *J Clin Med*. 2020;9(9). https://doi.org/10.3390/jcm9092706
48. Rotolo SM, Duehlmeyer S, Slack SM, Jacobs HR, Heckman B. Testicular pain following initiation of elexacaftor/tezacaftor/ivacaftor in males with cystic fibrosis. *J Cyst Fibros*. 2020;19(5): e39-e41. https://doi.org/10.1016/j.jcf.2020.04.017
49. Kazmerski TM, West NE, Jain R, Uluer A, Georgiopoulos ML, Taylor-Cousar JL Family-building and Parenting considerations for people with cystic fibrosis. Pediatr Pulmon. 2021. in press.
50. WHO. Medical eligibility criteria wheel for contraceptive use. Accessed June 18, 2021. http://www.who.int/reproductivehealth/publications/family_planning/mec-wheel-5th/en/
51. Stead RJ, Grimmer SF, Rogers SM, et al. Pharmacokinetics of contraceptive steroids in patients with cystic fibrosis. *Thorax*. 1987; 42(1):59-64. https://doi.org/10.1136/thx.42.1.59
52. Deerojanawong J, Sawyer SM, Fink AM, Stokes KB, Robertson CF. Totally implantable venous access devices in children with cystic fibrosis: incidence and type of complications. *Thorax*. 1998;53(4): 285-289. https://doi.org/10.1136/thx.53.4.285
53. USPI Lumacaftor Ivacaftor. https://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf
54. USPI Tezacaftor Ivacaftor. https://pi.vrtx.com/files/uspi_tezacaftor_ivacaftor.pdf
55. USPI Elexacaftor Tezacaftor Ivacaftor. https://pi.vrtx.com/files/uspi_elexacaftor_tezacaftor_ivacaftor.pdf
56. Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med*. 2019;381(19):1809-1819. https://doi.org/10.1056/NEJMoa1908639
57. Kissner DG. Role of progestational agents in the treatment of undernourished patients with cystic fibrosis. *Pediatr Pulmonol*. 2000;29(3): 244. https://doi.org/10.1002/(sici)1099-0496(200003)29:33.0.co;2-#
58. Plant BJ, Goss CH, Tonelli MR, McDonald G, Black RA, Aitken ML. Contraceptive practices in women with cystic fibrosis. *J Cyst Fibros*. 2008;7(5):412-414. https://doi.org/10.1016/j.jcf.2008.03.001
59. Sawyer SM, Farrant B, Cerritelli B, Wilson J. A survey of sexual and reproductive health in men with cystic fibrosis: new challenges for adolescent and adult services. *Thorax*. 2005;60(4):326-330. https://doi.org/10.1136/thx.2004.027599
60. Korzeniewska A, Grzelewski T, Jerzyńska J, et al. Sexual and reproductive health knowledge in cystic fibrosis female patients and their parents. *J Sex Med*. 2009;6(3):770-776. https://doi.org/10.1111/j.1743-6109.2008.01049.x
61. Kazmerski TM, Sawicki GS, Miller E, et al. Sexual and reproductive health behaviors and experiences reported by young women with cystic fibrosis. *J Cyst Fibro*. 2018;17(1):57-63. https://doi.org/10.1016/j.jcf.2017.07.017
62. Sawyer SM, Phelan PD, Bowes G. Reproductive health in young women with cystic fibrosis: knowledge, behavior and attitudes. *J Adolesc Health*. 1995;17(1):46-50. https://doi.org/10.1016/1054-139X(94)00096-W
63. Britto MT, Garrett JM, Dugliss MA, et al. Risky behavior in teens with cystic fibrosis or sickle cell disease: a multicenter study. *Pediatrics*. 1998; 101(2):250-256. https://doi.org/10.1542/peds.101.2.250
64. Rousset-Jablonski C, Reynaud Q, Nove-Josserand R, et al. Study conducted in Lyon France. High proportion of abnormal pap smear tests and cervical dysplasia in women with cystic fibrosis. *Eur J Obstet Gynaecol Reprod Biol*. 2018;221:40-45. https://doi.org/10.1016/j.ejogrb.2017.12.005
65. Rousset Jablonski C, Reynaud Q, Perceval M, et al. Contraceptive practices and cervical screening in women with cystic fibrosis. *Hum Reprod*. 2015;30(11):2547-2551. https://doi.org/10.1093/humrep/dev217
66. Kazmerski TM, Sawicki GS, Miller E, et al. Sexual and reproductive health care utilization and preferences reported by young women with cystic fibrosis. *J Cystic Fibros*. 2018;17(1):64-70. https://doi.org/10.1016/j.jcf.2017.08.009

67. Rousset-Jablonski C, Haesebaert J, Denis A, et al. Human papilloma virus vaccination among female patients attending french pediatric cystic fibrosis centers. *J Pediatr Adolesc Gynecol*. 2021;34(3):317-323. https://doi.org/10.1016/j.jpag.2020.12.004
68. Malouf MA, Hopkins PM, Singleton L, Chhajed PN, Plit ML, Glanville AR. Sexual health issues after lung transplantation: importance of cervical screening. *J Heart Lung Transplant* 2004;23(7):894-897. https://doi.org/10.1016/j.healun.2003.07.018
69. Sawyer SM, Bowes G, Phelan PD. Vulvovaginal candidiasis in young women with cystic fibrosis. *BMJ (Clinical research ed.)*. 1994;308(6944):1609. https://doi.org/10.1136/bmj.308.6944.1609
70. Webb AK, Woolnough E. Candida albicans infection in adults with cystic fibrosis. *J R Soc Med*. 2006;99(Suppl 46):13-16.
71. Chotirmall SH, Greene CM, McElvaney NG. Candida species in cystic fibrosis: a road less travelled. *Med Mycol*. 2010;48(Suppl 1):S114-S124. https://doi.org/10.3109/13693786.2010.503320
72. USPI Ivacaftor. https://pi.vrtx.com/files/uspi_ivacaftor.pdf
73. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism*. 2000;49(9):1239-1242. https://doi.org/10.1053/meta.2000.8625
74. Khan FN, Tangpricha V, Hughan KS, et al. Men's health in the modern era of cystic fibrosis. *J Cyst Fibros*. 2020. https://doi.org/10.1016/j.jcf.2020.12.013
75. Leifke E, Friemert M, Heilmann M, et al. Sex steroids and body composition in men with cystic fibrosis. *Eur J Endocrinol*. 2003;148(5):551-557. https://doi.org/10.1530/eje.0.1480551
76. Blackman SM, Tangpricha V. Endocrine disorders in cystic fibrosis. *Pediatr Clin North Am*. 2016;63(4):699-708. https://doi.org/10.1016/j.pcl.2016.04.009
77. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715-1744. https://doi.org/10.1210/jc.2018-00229
78. Cao ZT, Botelho JC, Rej R, Vesper H, Astles JR. Impact of testosterone assay standardization efforts assessed via accuracy-based proficiency testing. *Clin Biochem*. 2019;68:37-43. https://doi.org/10.1016/j.clinbiochem.2019.03.014
79. Yoon JC, Casella JL, Litvin M, Dobs AS. Male reproductive health in cystic fibrosis. *J Cyst Fibros*. 2019;18(Suppl 2):S105-S110. https://doi.org/10.1016/j.jcf.2019.08.007
80. Irwig MS, Fleseriu M, Jonklaas J, et al. Off-label use and misuse of testosterone, growth hormone, thyroid hormone, and adrenal supplements: risks and costs of a growing problem. *Endocr Pract*. 2020;26(3):340-353. https://doi.org/10.4158/PS-2019-0540
81. Stead RJ, Hodson ME, Batten JC, Adams J, Jacobs HS. Amenorrhoea in cystic fibrosis. *Clin Endocrinol*. 1987;26(2):187-195. https://doi.org/10.1111/j.1365-2265.1987.tb00776.x
82. Neinstein LS, Stewart D, Wang CI, Johnson I. Menstrual dysfunction in cystic fibrosis. *J Adolesc Health Care*. 1983;4(3):153-157. https://doi.org/10.1016/s0197-0070(83)80367-2
83. Wu M, Bettermann EL, Arora N, Hunt WR, McCracken C, Tangpricha V. Relationship between estrogen treatment and skeletal health in women with cystic fibrosis. *Am J Med Sci*. 2020;360(5):581-590. https://doi.org/10.1016/j.amjms.2020.06.005
84. Kernan NG, EWFW Alton, Cullinan P, Griesenbach U, Bilton D. Oral contraceptives do not appear to affect cystic fibrosis disease severity. *Eur Respir J*. 2013;41(1):67-73. https://doi.org/10.1183/09031936.00018712
85. Chotirmall SH, Smith SG, Gunaratnam C, et al. Effect of estrogen on pseudomonas mucoidy and exacerbations in cystic fibrosis. *N Engl J Med*. 2012;366(21):1978-1986. https://doi.org/10.1056/NEJMoa1106126 https://doi.org/10.1056/NEJMoa1106126
86. Holtrop M, Heltshe S, Shabanova V, et al. A Prospective study of the effects of sex hormones on lung function and inflammation in women with cystic fibrosis. *Ann Am Thorac Soc*. 2021;(18):1158-1166. https://doi.org/10.1513/AnnalsATS.202008-1064OC
87. Sexual and Reproductive Health Guide | CFReSHC. Accessed June 18, 2021. https://cfreshc.org/srh-guide/
88. Chambers R, Lucht A, Reihill A, Hough J. Prevalence and impact of pelvic floor dysfunction in an adult cystic fibrosis population: a questionnaire survey. *International Urogynecology Journal*. 2017;28(4):591-604. https://doi.org/10.1007/s00192-016-3152-z
89. Kaplan E, Shwachman H, Perlmutter AD, Rule A, Khaw KT, Holsclaw DS. Reproductive failure in males with cystic fibrosis. *N Engl J Med*. 1968;279(2):65-69. https://doi.org/10.1056/NEJM196807112790203
90. Tizzano EF, Silver MM, Chitayat D, Benichou JC, Buchwald M. Differential cellular expression of cystic fibrosis transmembrane regulator in human reproductive tissues. Clues for the infertility in patients with cystic fibrosis. *Am J Pathol*. 1994;144(5):906-914.
91. Elkin S, Burgess J, Kemp M, Hodson ME. Hypogonadism in adult males with cystic fibrosis. *Thorax*. 2000;55:A65.
92. Kopito LE, Kosasky HJ, Shwachman H. Water and electrolytes in cervical mucus from patients with cystic fibrosis. *Fertil Steril*. 1973;24(7):512-516.
93. Aguiar KCA, Marson FAL, Gomez CCS, et al. Physical performance, quality of life and sexual satisfaction evaluation in adults with cystic fibrosis: an unexplored correlation. *Rev Port Pneumol*. 2017;23(4):179-192. https://doi.org/10.1016/j.rppnen.2017.02.009
94. How do I stop myself getting out of breath during sex? British Lung Foundation, June 8, 2017. Accessed June 18, 2021. https://www.blf.org.uk/support-for-you/sex-and-breathlessness/suggestions
95. Papafragaki D, Concannon L. Catamenial pneumothorax: a case report and review of the literature. *J Womens Health (Larchmt)*. 2008;17(3):367-372. https://doi.org/10.1089/jwh.2007.0553
96. Flume PA, Mogayzel PJ, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: pulmonary complications: hemoptysis and pneumothorax. *Am J Respir Crit Care Med*. 2010;182(3):298-306. https://doi.org/10.1164/rccm.201002-0157OC
97. Augoulea A, Lambrinoudaki I, Christodoulakos G. Thoracic endometriosis syndrome. *Respiration; International Review of Thoracic Diseases*. 2008;75(1):113-119. https://doi.org/10.1159/000105102
98. Brinson GM, Noone PG, Mauro MA, et al. Bronchial artery embolization for the treatment of hemoptysis in patients with cystic fibrosis. *Am J Respir Crit Care Med*. 1998;157(6 Pt 1):1951-1958. https://doi.org/10.1164/ajrccm.157.6.9708067
99. Town JA, Monroe EJ, Aitken ML. Deaths related to bronchial arterial embolization in patients with cystic fibrosis: three cases and an institutional review. *Chest*. 2016;150(4):e93-e98. https://doi.org/10.1016/j.chest.2016.03.009
100. Bozkanat KM, West NE, Ladores S, et al. Catamenial haemoptysis in females with cystic fibrosis: a case series with review of management strategies. *Respirol Case Rep. 2021*. 2021;9(6). https://doi.org/10.1002/rcr2.755.e00755. Accessed May 13, 2021. https://onlinelibrary.wiley.com/doi/abs/10.1002/rcr2.755
101. Reichman G, De Boe V, Braeckman J, Michielsen D. Urinary incontinence in patients with cystic fibrosis. *Scand J Urol*. 2016;50(2):128-131. https://doi.org/10.3109/21681805.2015.1096826
102. Burge AT, Holland AE, Sherburn M, et al. Prevalence and impact of urinary incontinence in men with cystic fibrosis. *Physiotherapy*. 2015;101(2):166-170. https://doi.org/10.1016/j.physio.2014.11.001
103. Kazmerski TM, Stransky OM, Taylor-Cousar JL, et al. Sexual and reproductive health behaviors and experiences of adult women with cystic fibrosis. *Pediatr Pulmonol*. 2020;55S138:91. https://doi.org/10.1002/ppul.25089
104. Nankivell G, Caldwell P, Follett J. Urinary incontinence in adolescent females with cystic fibrosis. *Paediatr Respir Rev*. 2010;11(2):95-99. Accessed June 28, 2021. https://doi.org/10.1016/j.prrv.

2010.01.005 https://www.sciencedirect.com/science/article/pii/S1526054210000187
105. McVean RJ, Orr A, Webb AK, et al. Treatment of urinary incontinence in cystic fibrosis. *J Cyst Fibros*. 2003;2(4):171-176. https://doi.org/10.1016/S1569-1993(03)00088-2
106. Ford AA, Rogerson L, Cody JD, Aluko P, Ogah JA. Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev*. 2017;7:CD006375. https://doi.org/10.1002/14651858.CD006375.pub4
107. Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment 2019. *J Urol*. 2019;202(3):558-563. https://doi.org/10.1097/JU.0000000000000309
108. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas*. 1992;14(2):103-115. https://doi.org/10.1016/0378-5122(92)90003-m
109. Randolph JF, Crawford S, Dennerstein L, et al. The value of follicle-stimulating hormone concentration and clinical findings as markers of the late menopausal transition. *J Clin Endocrinol Metab*. 2006;91(8):3034-3040. https://doi.org/10.1210/jc.2006-0243
110. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(11):3975-4011. https://doi.org/10.1210/jc.2015-2236
111. Frayman KB, Sawyer SM. Sexual and reproductive health in cystic fibrosis: a life-course perspective. *Lancet Respir Med*. 2015;3(1):70-86. https://doi.org/10.1016/S2213-2600(14)70231-0
112. Sawyer SM, Tully MA, Colin AA. Reproductive and sexual health in males with cystic fibrosis: a case for health professional education and training. *J Adolesc Health*. 2001;28(1):36-40. https://doi.org/10.1016/s1054-139x(00)00172-5
113. Kazmerski TM, Borrero S, Sawicki GS, et al. Provider attitudes and practices toward sexual and reproductive health care for young women with cystic fibrosis. *J Pediatr Adolesc Gynecol*. 2017;30(5):546-552. https://doi.org/10.1016/j.jpag.2017.01.009
114. Kazmerski TM, Nelson EB, Newman LR, et al. Interprofessional provider educational needs and preferences regarding the provision of sexual and reproductive health care in cystic fibrosis. *J Cyst Fibros*. 2019;18(5):671-676. https://doi.org/10.1016/j.jcf.2019.01.015
115. Kazmerski TM, Tuchman LK, Borrero S, et al. Cystic fibrosis program directors' attitudes toward sexual and reproductive health in young women with CF. *Pediatr Pulmonol*. 2016;51(1):22-27. https://doi.org/10.1002/ppul.23321
116. Sawyer SM, Tully MA, Dovey ME, Colin AA. Reproductive health in males with cystic fibrosis: knowledge, attitudes, and experiences of patients and parents. *Pediatr Pulmonol*. 1998;25(4):226-230. https://doi.org/10.1002/(sici)1099-0496(199804)25:4%3C226.aid-ppul2%3E3.0.co;2-i
117. Kazmerski TM, Borrero S, Tuchman LK, et al. Provider and patient attitudes regarding sexual health in young women with cystic fibrosis. *Pediatrics*. 2016;137(6):e20154452. https://doi.org/10.1542/peds.2015-4452
118. Rousset-Jablonski C, Reynaud Q, Perceval M, et al. Improvement in contraceptive coverage and gynecological care of adult women with cystic fibrosis following the implementation of an on-site gynecological consultation. *Contraception*. 2020;101(3):183-188. https://doi.org/10.1016/j.contraception.2019.10.014
119. Research Priorities in the Health of Women with CF for 2021 RFA. https://www.cff.org/Research/Researcher-Resources/Therapeutics-Development-Network/Research-Priorities-in-the-Health-of-Women-With-CF-for-2021-RFA.pdf

How to cite this article: West NE, Kazmerski TM, Taylor-Cousar JL, et al. Optimizing sexual and reproductive health across the lifespan in people with cystic fibrosis. *Pediatric Pulmonology*. 2022;57:S89-S100. https://doi.org/10.1002/ppul.25703