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Gynecologic health care for females with cystic fibrosis

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ABSTRACT

As females with cystic fibrosis (CF) increasingly reach their reproductive years, gynecologic issues have become an important area of clinical care and research. First, females with CF may have disease-specific gynecologic problems, including cyclic pulmonary symptoms, vaginal yeast infections, and urinary incontinence. Next, contraceptive methods are thought to be overall safe and effective, however further research is needed to confirm this and to understand the lower rates of uptake among females with CF compared to the general population. Further, females with CF have reduced fertility, although the etiology of this is unknown and under investigation. While assisted reproductive technologies may help achieve pregnancy, decision-making around parenthood remains complex. Finally, while patients and providers agree on the importance of sexual and reproductive health care, females with CF underutilize basic preventive services such as cervical cancer screening, and better approaches are needed to bridge the gap with gynecology. In this review, we discuss the current state of gynecologic care for females with CF, as well as clinical and research opportunities for improvement.

Introduction

As the adult population with cystic fibrosis (CF) continues to grow, issues of sexual and reproductive health (SRH) have become increasingly prominent. Adolescent and adult females living with CF face both routine as well as unique SRH concerns, which continue to evolve with advances in CF and reproductive care. In this review of gynecologic health care, we discuss disease-specific gynecologic concerns, contraception, fertility, preventive care, and integration of these services for females with CF.

CF disease-specific gynecologic concerns

Females with CF experience a variety of SRH concerns. In this section, we will review common gynecologic issues that reproductive-age females with CF experience, including delayed puberty, menstrual irregularities, cyclicality of pulmonary symptoms, vulvovaginal candidiasis, and urinary incontinence. Research on the menopausal transition and post-menopausal gynecologic health is still lacking for females with CF.

Delayed puberty

Puberty was reported to be delayed in females with CF in older studies with mean age of menarche ranging from 14.2 to 14.9 years [1–5]. However, more recent studies found a closing of this gap. In an Australian study, bone age, but not Tanner pubertal stage or age of menarche, differed between adolescents with CF and controls [6]. Similarly, data from the French CF registry showed that the age of pubertal onset in girls with CF was similar to reference data, although their peak height velocity was lower [7]. More recently, Kazmerski et al. reported that mean age of menarche was slightly delayed in a survey of American females with and without CF (13.1 ± 1.3 vs. 12.4 ± 0.05 years); 29% of those with CF reported a perceived delay in puberty compared to their peers [8]. Delayed menarche and puberty may be associated with poor communication with parents about SRH, as well as other psychosocial issues, among adolescents with CF [9,10].

Menstrual irregularities

Older reports documented high prevalence (>50%) of menstrual irregularities including oligomenorrhea, primary or secondary

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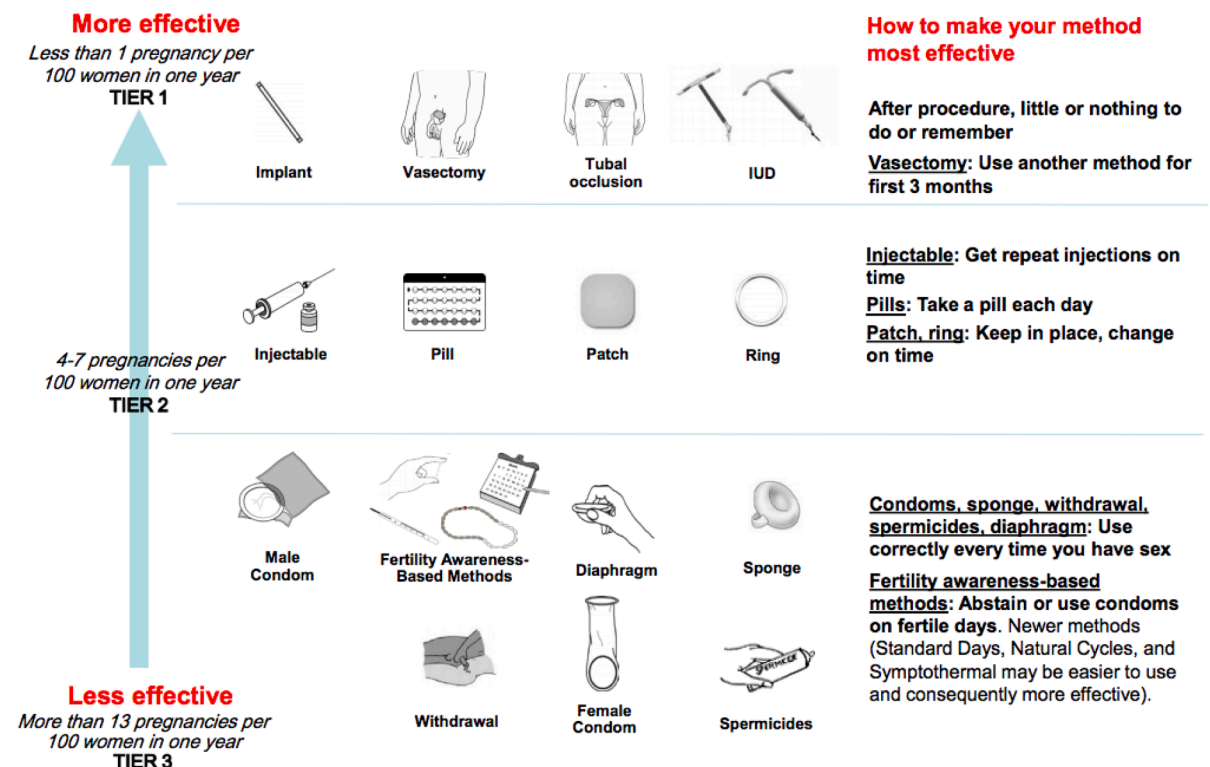


Fig. 1. Typical effectiveness of contraceptive methods.

amenorrhea, and abnormal uterine bleeding in females with CF [4,11]. Regular menses was associated with better lung function and higher body mass index and percentage body fat [11]. Unfortunately, current estimates of the prevalence of menstrual irregularities are lacking.

Cyclicity of pulmonary symptoms in women with CF

Estrogen has been implicated as a factor that modulates crucial components of CF lung physiology including inflammation, infection, and transepithelial ion transport [12,13]. Pulmonary exacerbation frequency can vary with the menstrual cycle, peaking at the same time as endogenous estradiol levels do mid-cycle [14]. In addition, research has shown that endogenous estradiol levels are significantly higher in females with CF experiencing pulmonary exacerbations than at baseline, and among females with CF using oral contraceptives, this pattern is absent [14]. Estradiol is thus suspected to influence pulmonary physiology, and may account for sex differences in pulmonary disease morbidity [15].

Catamenial (perimenstrual) hemoptysis has been reported in females with CF, although its prevalence is unknown [16,17]. It is either a clinical manifestation of thoracic endometriosis, a rare condition in which endometrial tissue implants in the thoracic cavity, or a result of bronchial artery bleeding secondary to hormonally-mediated fluctuations in airway inflammation or infection. Management strategies often include hormonal contraceptives, as well as pro-coagulants (vitamin K, tranexamic acid), anti-inflammatories (prednisone, azithromycin), and bronchial artery embolization for poorly controlled cases; CFTR modulators have also been known to improve these symptoms [17,18]. The cyclicity of pulmonary exacerbations and hemoptysis in some females with CF highlights the importance of obtaining a menstrual history from these patients.

Vulvovaginal candidiasis

Females with CF are at increased risk of vulvovaginal candidiasis

because of frequent use of systemic antibiotics and corticosteroids, as well as the high prevalence of diabetes. In a recent U.S. survey of 188 young females with CF, 49% reported ever having a yeast infection and 19% reported at least one yeast infection annually [8]. An Australian study reported that one-quarter of females with CF had monthly episodes of vulvovaginal candidiasis [19].

Urinary incontinence

Urinary incontinence (UI) is common among adult females with CF, with an estimated prevalence ranging from 30% to 76% [20–22]. In a survey of young females with CF aged 15–24, 16% reported a history of UI with a mean age of onset at 16 years [8]. Some studies have found an association between disease severity (%FEV1 and pulmonary exacerbation frequency), while others have not [23,24].

CF patients with UI report that coughing, laughing, sneezing, physical activity, airway clearance, and spirometry most often trigger UI [20,24], suggesting that the most common form of UI in this population is stress incontinence. Stress UI is recognized as a complication of chronic lung disease, with involuntary leakage of urine at times of increased intra-abdominal pressure due to weakened pelvic floor muscles. Some patients report that UI limits effective airway clearance and chest physiotherapy [20], negatively impacts exercise regimens [20,21], and affects their social lives and intimate relationships [25].

Patients underreport UI to parents and healthcare providers [25], and currently there is no standard approach to identify UI in females with CF. Forty-four percent of patients are unaware of UI treatment options [24], which may include the following. Pelvic floor exercises are the least invasive option, though may be difficult to integrate into daily routines [26,27]. Vaginal pessaries are support devices that compress the urethra against the pubic symphysis to reduce UI and are a non-surgical treatment option [28]. Surgical management may be considered when conservative approaches fail [29] and urethral sling procedures have been used for females with CF who did not respond to pelvic floor muscle strengthening [30].

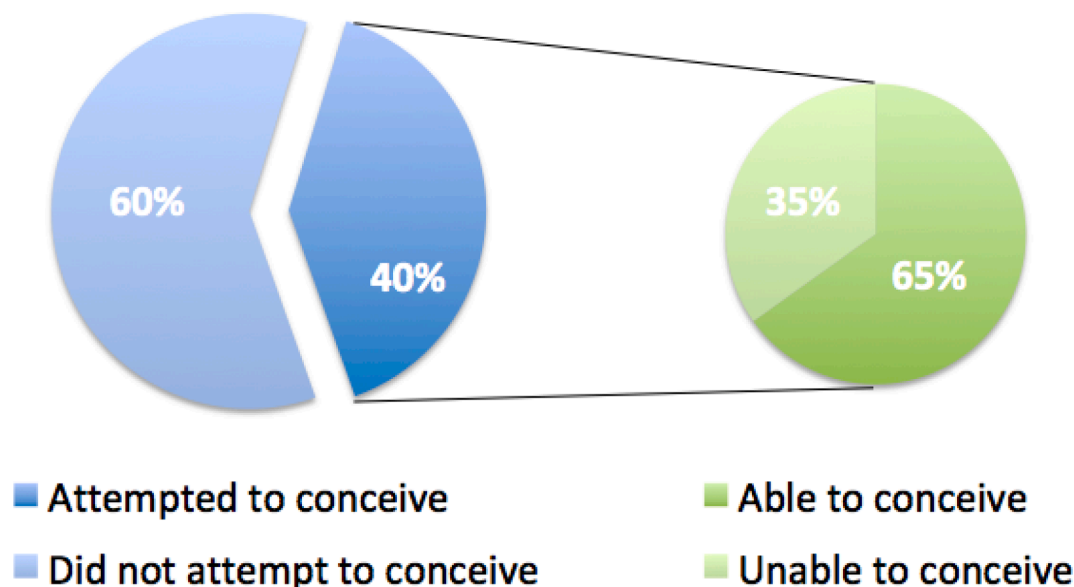


Fig. 2. Conception rates among 605 women with cystic fibrosis from a retrospective multi-site study.

Contraception for females with CF

Rates of sexual activity among females with CF are comparable to that of the general population, and approximately one-quarter of pregnancies in females with CF are unintended [31,32]. Pregnancy can carry significant risks, including preterm delivery, gestational diabetes, nutritional deficiency, and increased pulmonary exacerbations, as well as increased physical demands of lactation and parenting after pregnancy [33]. Thus, contraception is crucial to optimizing health and pregnancy timing.

Hormonal contraception in particular may serve a dual role, with a protective effect on CF disease in addition to its contraceptive function. As described in the previous section, pulmonary symptoms may vary with the menstrual cycle, and hormonal contraception that suppresses ovulation, such as the etonogestrel implant, depot medroxyprogesterone acetate (DMPA, Depo-Provera) injection, combined oral contraceptive pill (OCP), transdermal patch, and vaginal ring, may help eliminate these fluctuations. Chotirmall et al. used Irish registry data to show that females with CF who use OCPs require significantly lower antibiotic use compared to those who do not [14]. The etonogestrel implant has been shown to successfully treat recurrent perimenstrual pulmonary exacerbations, with subsequent recovery of impaired lung function [34].

According to the Centers for Disease Control, which issues guidance regarding contraceptive safety in the setting of specific medical conditions, all contraceptive methods are safe to use, and none are contraindicated in CF [35]. Fig. 1 shows currently available contraceptive methods. However, there are co-existing conditions and issues that may modify one's choice of contraception in the setting of CF. For example, CF carries an elevated risk of thrombosis [36] and exogenous estrogen in contraceptive methods such as the combined OCP, the transdermal patch, and the vaginal ring is contraindicated in the setting of a history of venous thromboembolism, complicated organ transplant, or diabetes with long-term cardiovascular sequelae [35]. Pancreatic insufficiency raises a theoretical concern for malabsorption of the OCP in the small intestines; however, no studies specifically examine its absorption in patients with pancreatic insufficiency or CF, but non-oral methods of contraception may be preferable in this setting.

Some limited data do exist on contraception and bone health in CF. A survey study of 150 females with CF linked participants' reported contraceptive history to clinical outcomes from the CF Foundation Patient Registry [37]. In this study, use of DMPA was associated with 5 times greater odds of osteoporosis compared to never use, after adjusting for

BMI. Although the sample size was small (only 11 DMPA users), these findings are consistent with evidence of DMPA's temporary impairment of bone health in the general population [38]. In a cross-sectional assessment of bone health via DEXA scan, 12 females with CF who were using a combined OCP had significantly lower bone mineral density at the spine compared to 37 females with CF who were not [39]. Further research is needed to understand the relationship between exogenous estrogen and bone disease in CF.

Medication interactions are a common consideration when initiating contraception. The only known antibiotic that interacts with hormonal contraception is rifampin, a potent hepatic enzyme inducer that decreases hormonal contraceptive efficacy [35]. This is not a common antibiotic choice for those with CF and thus antibiotics do not often pose any conflicts. Similarly, elexacaftor, tezacaftor, and ivacaftor do not exhibit interactions with hormonal contraception and thus there are no concerns about concurrent use [40]. On the other hand, lumacaftor, like rifampin, is a strong hepatic enzyme inducer and can impact hormonal contraceptive efficacy. Therefore, an alternative or secondary method of contraception is encouraged [41].

Contraceptive uptake is lower in patients with CF than in the general population, with only half of females with CF using any form of contraception [32]. The most common methods are the OCP and condoms [32,42], although a recent survey indicates growing use of intrauterine devices [37]. Qualitative interviews with females with CF reveal that contraceptive decision-making can be complicated as they weigh possible health effects and medication interactions, and contraception is often a lower priority amidst their other health considerations [43,44]. In addition, females with CF often believe they cannot become pregnant, and most rely on their CF team for their primary care [43,44]. These fertility concerns and issues of gynecologic care access likely impact uptake of contraception and will be addressed in the following sections.

Fertility among females with CF

Pregnancy rates are lower among females with CF compared with the general population: approximately 35 vs 100 pregnancies per 1,000 females per year [45,46]. Subfertility is seen in animal models of CF as well: mice with CFTR gene mutations have fewer pregnancies and fewer offspring per pregnancy; 29% experienced infertility over a 5-month study period [47]. While females with CF attempt pregnancy at lower rates than in the general population (40% in a retrospective study of 605 patients), one-third of those who do experience infertility [48,49]

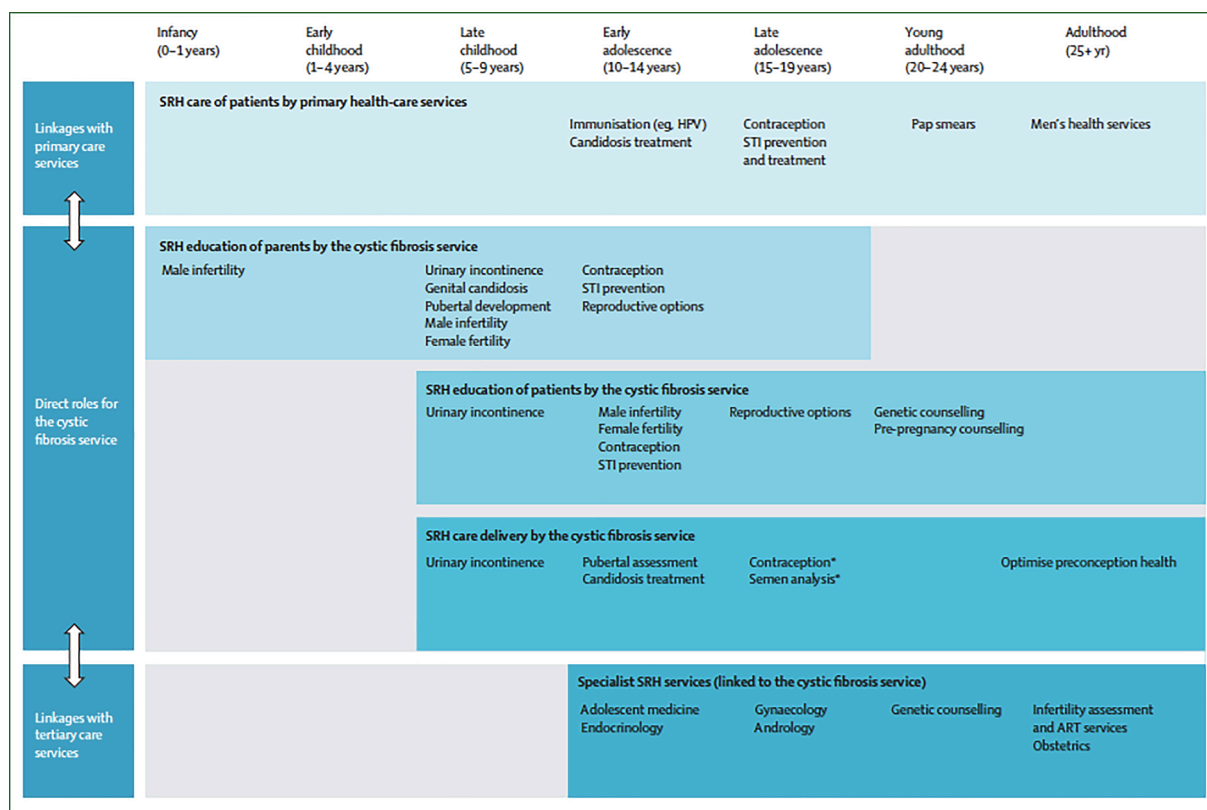


Fig. 3. A model of care delivery of sexual and reproductive health education and services across the life course for patients with cystic fibrosis.

(Fig. 2).

Multiple hypotheses for reduced fertility in CF exist. Chronic disease and malnutrition may suppress the hypothalamic-pituitary-ovary axis [11]. Ovarian dysfunction and decreased ovarian reserve have been documented in females with CF, however it is not known whether these are primary abnormalities or downstream endocrine effects [50,51]. Other proposed etiologies of infertility stem directly from malfunction of the CFTR protein, which is known to be expressed in the reproductive tract and may alter cervical mucus quality and uterine fluid pH, thereby impeding sperm penetration and fertilization [52-54].

With the recent advent of CFTR modulator therapy, it is crucial to understand any impact these medications may have on fertility. In animal models, elxacaftor and ivacaftor impair fertility at toxic doses, however have no such effect at normal human dose; tezacaftor and lumacaftor have not been shown to impact fertility at any dose [55]. Clinical data are lacking, but the report that 2% of females enrolled in ivacaftor clinical trials became pregnant, in addition to case reports of unintended pregnancy with use of modulators after an extended period of infertility, have led clinicians to suspect that modulators may actually improve fertility [56]. This possible trend needs to be quantified and better understood.

Preventive SRH care for females with CF

In addition to any disease-specific gynecologic care, females with CF need routine preventive SRH services, including cervical cancer and sexually transmitted infection (STI) screening. Despite this, studies in the U.S. and multiple other nations have repeatedly documented inadequate SRH education for CF females [57-60]. A recent survey of young females with CF in the U.S. showed that they receive less health care counseling on general contraception (9% vs 24%), emergency contraception (1% vs 4%), and STIs (9% vs 22%) than the general U.S. population [58].

Insufficient SRH education mirrors inadequate utilization of SRH

services in this population. Young females with CF in the U.S. report lower rates of STI screening (19% vs 34%), cervical cancer screening or pelvic exam (26% vs 57%), and history of contraceptive use (55% vs 74%) [8,58]. They report similar rates of human papilloma virus vaccination compared with the general population, although the majority remain unvaccinated [58]. Data from an older cohort of French females with CF similarly confirm low utilization of gynecologic healthcare, with only 55% reporting any history of cervical cancer screening [61], despite elevated rates of cervical dysplasia in the CF population, especially after transplant [62,63].

Integrating SRH care for females with CF

In the U.S., CF patients and providers alike recognize the importance of SRH and that health discussions should begin in early adolescence [64,65]. Females with CF often perceive CF physicians as their primary care providers and expect them to be the primary source of SRH information and care [66]. In a survey of 196 CF physicians, nurse practitioners, and physician assistants, 75% reported that SRH should be standardized within the CF care model, although discrepancies existed, with 62% of adult providers and only 29% of pediatric providers believing that the CF team should take a primary role in SRH [67]. However, multiple barriers exist to integrating SRH, most notably logistical challenges of limited time and difficulty obtaining patient privacy for those presenting with family members [67]. Importantly, many CF providers endorse a lack of SRH knowledge and a discomfort with these topics, leaving them insufficiently equipped in this domain [67,68].

In order to address these gaps, Frayman and Sawyer propose a formal integration of SRH into the CF care model with age-appropriate topics for CF females beginning as young as 5-9 years and progressing through adulthood, in partnership with specialist services such as gynecology beginning in late adolescence (Fig. 3) [64]. CF patients and their parents desire increased communication with their provider as well as SRH

educational resources [44,66]. On the provider end, practical interventions such as an electronic health template modification have been shown to improve documented conversations about sexual activity and contraception [69]. Provider SRH trainings may also be beneficial to improve ease with these topics, and inclusion of SRH outcomes in CF registry data may increase clinical and research attention in this area [66,67].

Partnership between the CF team and gynecology is integral to maximizing the uptake and quality of SRH care. Females with CF often act as an intermediary between their CF and obstetrics and gynecology teams due to differing areas of expertise and lack of communication, and prefer referrals to reproductive health providers with CF knowledge and experience [44]. At a French adult CF center, establishing a formal consult service with gynecologists trained in CF increased access to gynecologic care, cervical cancer screening, and use of contraception over a 3-year study period [70].

Future directions

Multiple studies on SRH for females with CF are currently underway, including:

- Association of Sex Hormones with Respiratory Health (Dr. Kristina Montemayor)
- Menstrual Symptom Tracking to Understand and Assess (Women) Living with Cystic Fibrosis (MENSTRUAL) (Drs. Sandra Sufian and Emily Godfrey)
- Urinary Incontinence in Cystic Fibrosis (Dr. Megan Bradley)
- CASE.4.CF: Assessment of Contraceptive Safety and Effectiveness in Cystic Fibrosis (Drs. Emily Godfrey and Moira Aitken)
- Cervical Mucus Quality in Women with CF On and Off of Triple Combination Therapy (Dr. Andrea Roe)
- Feasibility Trial of MyVoice:CF, a Reproductive Goals Decision Aid (Dr. Traci Kazmerski)

The results of these studies will shed light on the current state of SRH for females with CF and perhaps point a way forward for improved SRH communication, education, and care.

Conclusions

Females with CF need general, and sometimes complex, SRH care that addresses gynecologic disease prevention, contraception, fertility, and any disease-specific problems they may have. Further work is needed to increase CF provider comfort and knowledge surrounding these topics and to bridge the gap to gynecologic care.

CRedit authorship contribution statement

Andrea H. Roe: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Lina Merjaneh:** Investigation, Writing – original draft. **Rachael Oxman:** Investigation, Writing – original draft. **Kara S. Hughan:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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