



## CF and male health: Sexual and reproductive health, hypogonadism, and fertility

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### ABSTRACT

Over 30,000 people in the United States are diagnosed with cystic fibrosis (CF), and over 50% of those with CF are male. Men with CF face specific and sometimes difficult sexual and reproductive health (SRH) issues, including infertility and hypogonadism. Male infertility affects over 95% of men with CF, with obstructive azoospermia resulting from congenital bilateral absence of the vas deferens being the primary cause of infertility. SRH education for males with CF represents an important opportunity for clinical improvement, as the majority of men with CF know that their disease impacts their fertility, however the depth of this understanding varies significantly. Hypogonadism is a clinical syndrome that affects men with low testosterone level, a common finding among men with CF that has clinical implications and can significantly affect quality of life. Better understanding of SRH attitudes, the prevalence of hypogonadism, and management of infertility in men with CF should remain future research priorities.

### Introduction

Over 30,000 people in the United States are diagnosed with cystic fibrosis (CF), and over 50% of those with CF are male [1]. Most men with CF often have congenital absence of the bilateral vas deferens (CABVD) which poses a challenge for reproduction. It is reported that 95% of men with CF have CABVD [2]. In addition, men with CF may have inadequate spermatogenesis for fertility. It is known that CFTR is expressed in sperm, and recent reports found that CFTR mutation actually compromises spermatogenesis [3]. Finally, hypogonadism may also occur which impact many facets of sexual and reproductive health (SRH). A cross-sectional study of young men with CF found hypogonadism in roughly 25% of participants [4], while other studies have found the prevalence of hypogonadism to be closer to 45% [5].

Historical surveys have shown that men with CF have been dissatisfied with their SRH discussions and care [6]. Given that more than 80% of men with CF surveyed in the past have expressed a desire to have children [6], early discussions about CF and infertility should become part of regular care provision. There are significant gaps in knowledge regarding the overall prevalence of hypogonadism in men and the

impact of treatment of hypogonadism in men. Additionally, we know very little about how these gaps in SRH knowledge impact the quality of life in men with CF. Very little is known about the impacts of highly effective modulator therapies (HEMT) on hypogonadism or fertility.

Given the gaps in knowledge in SRH concerns in men with CF, the purpose of this review was to highlight key areas of concern regarding CF and men's health. The literature review focuses on 2 main areas of SRH: infertility and hypogonadism. Also included in the review are literature regarding experiences and attitudes of men seeking SRH counseling. Finally, the review provides information of the impact of HEMT on these areas and provide future areas of research.

### Male infertility

Infertility affects nearly 98% of men with CF [7]. The less than 2% who remain fertile [7] tend to carry mild CFTR mutations such as 3849 + 10 kb C-T [8–10]. The primary cause of infertility in men with CF is obstructive azoospermia (OA) resulting from congenital bilateral absence of the vas deferens (CBAVD) [11–13]. CBAVD is thought to develop in utero due to CFTR mutations [14]. Abnormalities in the tail

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and body of the epididymis have also been noted. [11] It is important to note that spermatogenesis does occur in men with CF [9,11,13] given its implication for assisted reproduction, but most men with CF have lower ejaculate volume [15]. Men with CF may also have compromised spermatogenesis, potentially related to CFTR gene expression in sperm [3]. Evaluation for men with CF who are seeking fertility may include gonadotropin and testosterone levels [15], transrectal ultrasonography [16], and semen analysis, which typically reveals azoospermia [17].

**Options for management**

Advances in reproductive technology have enabled men with CF to conceive biological offspring [17–18]. Before considering fertility treatment, it is recommended that partners be screened for the CFTR gene mutation and that they both undergo genetic counseling [7]. This may be followed by sperm extraction from either the testicle or the epididymis. Methods for sperm extraction from the testicle include testicular sperm extraction (TESE) and percutaneous testicular sperm aspiration (TESA). Sperm may be extracted from the epididymis using either microsurgical epididymal sperm aspiration (MESA) or percutaneous epididymal sperm aspiration (PESA) [7,15,19]. Percutaneous techniques may be performed in an outpatient setting under local anesthesia while open techniques reliably produce a large volume of sperm that can be used for cryopreservation. Table 1 outlines the advantages and disadvantages of each method. Once sperm is harvested, it is injected into an oocyte, a procedure termed intracytoplasmic sperm injection (ICSI) [19]. Compared to conventional in vitro fertilization which requires large numbers of sperm, this method requires only a single sperm [19] and is well-suited to conditions associated with azoospermia, such as CF. Assuming successful sperm retrieval, the source (testicular vs. epididymal) does not appear to significantly impact IVF/ICSI outcomes [20].

Pregnancy rates after one or more rounds of ICSI are reported to be nearly 63% [17–18] with approximately 45–75% live births [17–18,21]. Despite its fairly high success rate, only a portion of men with CF are aware that fertility treatments are available [22].

**Impact of modulator therapy**

While highly effective CFTR modulator therapies (HEMT) hold promise for many aspects of CF care, they are not predicted to improve male fertility, as the primary defect responsible (CBAVD) is structural and occurs in utero [23]. As overall health improves, however, a higher proportion of men may desire fertility, underscoring the importance of

appropriately timed conversations about infertility and highlighting the role of multi-disciplinary teams to address individual concerns and provide resources for assisted reproductive techniques.

**Hypogonadism**

Hypogonadism refers to the clinical syndrome that affects men with low testosterone levels. Diagnosis of hypogonadism requires low morning total testosterone levels on two separate occasions outside of critical illness and while not taking any medications that could suppress testosterone levels [24]. In CF, hypogonadism tends to be multifactorial (Table 2). Chronic inflammation, recurrent infections, and regular glucocorticoid use are just some of the factors in men with CF that can lead to hypogonadism [15]. The exact prevalence of hypogonadism in men with CF remains unknown. However, a cross-sectional study of 40 men with CF noted that men with stable disease have reduced serum testosterone levels [4]. Hypogonadism can lead to decreased BMD, lower muscle mass, loss of energy, infertility, and impaired mood [24].

There are limited studies on hypogonadism in men with CF, so we do not fully understand the impact of hypogonadism on CF disease severity. We also do not know the impact of restoring CFTR function with highly effective modulator therapy on testosterone levels. In men with CF, it was noted that testosterone levels were strongly correlated with bone mineral density [4]. Specifically, the impact of testosterone levels on diaphragmatic strength, pulmonary function, muscle mass, and quality of life in men with CF ultimately remains unknown. There are no formal screening guidelines, however, if clinical suspicion is high, men with CF should be screened for hypogonadism and its root cause determined. Treatment involves testosterone replacement through topical formulations, intramuscular injections, patches, buccal tablets, subcutaneous pellets, or as a nasal gel [24].

**Table 2**  
Causes of Hypogonadism in Men with CF.

- Recurrent infections, chronic inflammation, and regular glucocorticoid use can cause HPA axis dysregulation and primary hypogonadism
- Lack of or impaired CFTR expression in GnRH-secreting hypothalamic cells, and Sertoli cells
- Other multifactorial causes such as substance abuse and organ failure

**Table 1**  
Methods for Sperm Extraction [20].

Method	Source	Technique	Advantages	Disadvantages
PESA	Epididymal	Percutaneous	<ul style="list-style-type: none"> <li>- Outpatient procedure with local anesthesia</li> <li>- Rapid recovery</li> <li>- Reproducible</li> <li>- Equipment/training in microsurgery not necessary</li> </ul>	<ul style="list-style-type: none"> <li>- Pain, hydrocele, infection, swelling</li> <li>- 25% unsuccessful on first attempt requiring TESE or TESA</li> </ul>
TESA	Testicular	Percutaneous	<ul style="list-style-type: none"> <li>- Outpatient procedure with local anesthesia</li> <li>- Rapid recovery</li> <li>- May be used in failed PESA (rescue TESA)</li> <li>- Higher retrieval rates than PESA</li> <li>- Diagnostic utility in OA (identifies presence or absence of spermatogenesis)</li> </ul>	<ul style="list-style-type: none"> <li>- Minimal tissue (insufficient for cryopreservation; often done on same day of egg retrieval)</li> <li>- Lower motility and quantity compared to successful PESA</li> </ul>
TESE	Testicular	Open	<ul style="list-style-type: none"> <li>- ~100% sperm retrieval rate in OA</li> <li>- Large volume sufficient for cryopreservation</li> <li>- May be used in men unable to produce epididymal sample</li> <li>- May be used when other methods unsuccessful</li> <li>- Diagnostic utility in OA</li> <li>- Popular amongst urologists due to familiarity with testicular biopsies</li> </ul>	Invasive
MESA	Epididymal	Open	<ul style="list-style-type: none"> <li>- ~100% retrieval rates in selected men with OA</li> <li>- Large volume of sperm</li> <li>- Diagnostic utility in OA</li> </ul>	<ul style="list-style-type: none"> <li>- Invasive</li> <li>- Requires operative microscope and microsurgical training</li> </ul>

## Experiences, attitudes, and education surrounding sexual and reproductive health

The majority of males with CF are aware that CF impacts their fertility, however, the depth of their understanding varies. Across multiple surveys and qualitative studies in the United States, the United Kingdom, and Australia, 90–100% of adult males endorse knowledge about their own infertility [6,22,25–26]. However, fewer know of the prevalence of infertility or possible treatment options [6,22], and some confuse infertility with impotence [26]. Adults report they first learned of infertility at age 16, but state they would have preferred to learn earlier [25–26]. Males with CF prefer to hear about infertility from their CF team or their parents, as opposed to their primary care physician, other patients, friends, or educational materials; however, only half actually hear from their preferred source [6,26]. 90% of adults felt no distress upon first learning of infertility as adolescents, although some describe feelings of sadness – it is thought that the psychological impact of infertility as a diagnosis may develop over time [25].

As males with CF consider parenthood, many worry about passing CF on to their offspring and are interested in a preimplantation genetic diagnosis prior to pregnancy [22,27]. In addition, males with CF are concerned about the effect of CF on their ability to parent, specifically with regards to balancing their own healthcare with childcare responsibilities [22,28]. Males with CF often also weigh the physical and emotional toll that their morbidity and mortality would take on their families, as well as how to discuss these issues with their children [28].

Parents and providers have similar attitudes as males with CF toward disclosure of infertility. Nearly all parents of boys with CF are aware of their children's future infertility [29]. Parents feel that they share responsibility with the CF team to inform their sons about issues of infertility and most think this should take place during an outpatient clinic visit [29–30]. CF specialists report that they usually inform parents about male infertility soon after the diagnosis in infancy, but 20% defer disclosure until childhood or adolescence [31]. Providers feel the most appropriate age to discuss infertility is age 14, although they usually disclose later, at age 15 [31].

Gaps in patient-provider communication about sexual and reproductive health exist. Males with CF report a mean age at first intercourse of 18 years, similar to that in the general population [26]. Thus, they need information about fertility, but also about sexual performance, contraception, and sexually transmitted infection protection during early adolescence, and these latter subjects are not often addressed during clinical care [31–32]. CF providers cite insufficient time and training, as well as personal discomfort, as barriers to addressing sexual and reproductive health [31]. In response to this communication gap, authors Lyon and Bilton suggest seven key points that CF providers should review with male adolescents with CF, which provide a guide for sexual and reproductive health discussions: [33]

- The majority of CF males are infertile
- Infertility does not imply impotency, meaning sexual function is normal
- Spermatogenesis is likely normal
- Males with CF tend to have azoospermia due to the bilateral absence of the vas deferens
- Sperm aspiration and intra-cytoplasmic sperm injection can result in successful pregnancy
- Genetic counseling is available

## Conclusion

Going forward, it will be critical to better understand SRH attitudes, the prevalence of hypogonadism, and management of infertility in men with CF. A recent meeting of CF researchers across the country in varied disciplines identified male SRH and CF as a priority area [34]. CF providers should focus on improving their educational discussions with

their patients so that this also increases awareness about what men with CF should know about their SRH. HEMT is not currently expected to significantly impact the future of CF-related male infertility, however, its effects on hypogonadism remain to be seen.

## CRedit authorship contribution statement

**Farah Naz Khan:** Conceptualization, Methodology. **Kelly Mason:** Conceptualization, Methodology. **Andrea H. Roe:** Conceptualization, Methodology. **Vin Tangpricha:** Conceptualization, Methodology.

## References

- [1] Foundation. CF. Patient Registry 2019 Annual Report. Bethesda; 2019.
- [2] de Souza DAS, Fauz FR, Pereira-Ferrari L, Sotomaior VS, Raskin S. Congenital bilateral absence of the vas deferens as an atypical form of cystic fibrosis: reproductive implications and genetic counseling. *Andrology* 2018;6(1):127–35. <https://doi.org/10.1111/andr.12450>.
- [3] Chen Y, Li X, Liao H, et al. CFTR mutation compromises spermatogenesis by enhancing miR-15b maturation and suppressing its regulatory target CDC25A $\beta$ . *Biol Reprod* 2019;101:50–62. <https://doi.org/10.1093/biolre/iox062>.
- [4] Leifke E, Friemert M, Heilmann M, et al. Sex steroids and body composition in men with cystic fibrosis. *Eur J Endocrinol* 2003;148(5):551–7. <https://doi.org/10.1530/eje.0.1480551>.
- [5] Elkin S. Hypogonadism in adult males with cystic fibrosis. In: Burgess J, editor. *Thorax*; 2000.
- [6] Sawyer SM, Farrant B, Wilson J, Ryan G, O'Carroll M, Bye P, et al. Sexual and reproductive health in men with cystic fibrosis: consistent preferences, inconsistent practices. *J Cyst Fibros*. 2009;8(4):264–9. <https://doi.org/10.1016/j.jcf.2009.05.005>.
- [7] Ahmad A, Ahmed A, Patrizio P. Cystic fibrosis and fertility. *Curr Opin Obstet Gynecol*. Jun 2013;25(3):167–72. <https://doi.org/10.1097/GCO.0b013e32835f1745>.
- [8] Dreyfus DH, Bethel R, Gelfand EW. Cystic fibrosis 3849+10kb C > T mutation associated with severe pulmonary disease and male fertility. *Am J Respir Crit Care Med* Feb 1996;153(2):858–60. <https://doi.org/10.1164/ajrccm.153.2.8564145>.
- [9] Stuhmann M, Dörk T. CFTR gene mutations and male infertility. *Andrologia* Mar 2000;32(2):71–83. <https://doi.org/10.1046/j.1439-0272.2000.00327.x>.
- [10] Duguéroux I, De Braekeleer M. The CFTR 3849+10kbC->T and 2789+5G->A alleles are associated with a mild CF phenotype. *Eur Respir J*. Mar 2005;25(3):468–73. <https://doi.org/10.1183/09031936.05.10100004>.
- [11] Kaplan E, Shwachman H, Perlmutter AD, Rule A, Khaw KT, Holsclaw DS. Reproductive failure in males with cystic fibrosis. *N Engl J Med* Jul 1968;279(2):65–9. <https://doi.org/10.1056/NEJM196807112790203>.
- [12] Landing BH, Wells TR, Wang CI. Abnormality of the epididymis and vas deferens in cystic fibrosis. *Arch Pathol Dec 1969;88(6):569–80*.
- [13] Denning CR, Sommers SC, Quigley HJ. Infertility in male patients with cystic fibrosis. *Pediatrics* Jan 1968;41(1):7–17.
- [14] Cuppens H, Cassiman J-J. CFTR mutations and polymorphisms in male infertility. *Int J Androl*. 2004;27(5):251–6. <https://doi.org/10.1111/ija.2004.27.issue-150.1111/j.1365-2605.2004.00485.x>.
- [15] Yoon JC, Casella JL, Litvin M, Dobs AS. Male reproductive health in cystic fibrosis. *J Cyst Fibros* 2019;10(Suppl 2):S105–10. <https://doi.org/10.1016/j.jcf.2019.08.007>.
- [16] Abdulwahed SR, Mohamed EE, Taha EA, Saleh MA, Abdelsalam YM, ElGanainy EO. Sensitivity and specificity of ultrasonography in predicting etiology of azoospermia. *Urology*. May 2013;81(5):967–71. <https://doi.org/10.1016/j.urology.2013.01.001>.
- [17] Hubert D, Patrat C, Guibert J, et al. Results of assisted reproductive technique in men with cystic fibrosis. *Hum Reprod* 2006;21(5):1232–6. <https://doi.org/10.1093/humrep/dei453>.
- [18] McCallum TJ, Milunsky JM, Cunningham DL, Harris DH, Maher TA, Oates RD. Fertility in men with cystic fibrosis: an update on current surgical practices and outcomes. *Chest* Oct 2000;118(4):1059–62. <https://doi.org/10.1378/chest.118.4.1059>.
- [19] Van Peperstraten A, Proctor ML, Johnson NP, Philipson G. Techniques for surgical retrieval of sperm prior to intra-cytoplasmic sperm injection (ICSI) for azoospermia. *Cochrane Database Syst Rev* 2008;2. <https://doi.org/10.1002/14651858.CD002807.pub3>. CD002807.
- [20] Akerman JP, Hayon S, Coward RM. Sperm Extraction in Obstructive Azoospermia: What's Next? *Urol Clin North Am* May 2020;47(2):147–55. <https://doi.org/10.1016/j.ucl.2019.12.003>.
- [21] Boyd JM, Mehta A, Murphy DJ. Fertility and pregnancy outcomes in men and women with cystic fibrosis in the United Kingdom. *Hum Reprod*. Oct 2004;19(10):2238–43. <https://doi.org/10.1093/humrep/deh405>.
- [22] Popli K, Stewart J. Infertility and its management in men with cystic fibrosis: review of literature and clinical practices in the UK. *Hum Fertil (Camb)*. Dec 2007;10(4):217–21. <https://doi.org/10.1080/14647270701510033>.
- [23] Sergeev V, Chou FY, Lam GY, Hamilton CM, Wilcox PG, Quon BS. The Extrapulmonary Effects of Cystic Fibrosis Transmembrane Conductance Regulator Modulators in Cystic Fibrosis. *Ann Am Thorac Soc* 2020;17(2):147–54. <https://doi.org/10.1513/AnnalsATS.201909-671CME>.

- [24] 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):1715–44. <https://doi.org/10.1210/jc.2018-00229>.
- [25] Sawyer SM, Tully M-A, Dovey ME, Colin AA. Reproductive health in males with cystic fibrosis: knowledge, attitudes, and experiences of patients and parents. *Pediatr Pulmonol*. 1998;25(4):226–30. [https://doi.org/10.1002/\(ISSN\)1099-049610.1002/\(SICI\)1099-0496\(199804\)25:4<>1.0.CO;2-F10.1002/\(SICI\)1099-0496\(199804\)25:4<226::AID-PPUL2>3.0.CO;2-I](https://doi.org/10.1002/(ISSN)1099-049610.1002/(SICI)1099-0496(199804)25:4<>1.0.CO;2-F10.1002/(SICI)1099-0496(199804)25:4<226::AID-PPUL2>3.0.CO;2-I).
- [26] 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* Apr 2005;60(4):326–30. <https://doi.org/10.1136/thx.2004.027599>.
- [27] Janssens S, Chokoshvilli D, Binst C, Mahieu I, Henneman L, De Paepe A, et al. Attitudes of cystic fibrosis patients and parents toward carrier screening and related reproductive issues. *Eur J Hum Genet*. 2016;24(4):506–12. <https://doi.org/10.1038/ejhg.2015.160>.
- [28] Hailey CE, Tan JW, Dellon EP, Park EM. Pursuing parenthood with cystic fibrosis: Reproductive health and parenting concerns in individuals with cystic fibrosis. *Pediatr Pulmonol* 2019;54(8):1225–33. <https://doi.org/10.1002/ppul.24344>.
- [29] Frayman KB, Cerritelli B, Wilson J, Sawyer SM. Reproductive and sexual health in boys with cystic fibrosis: what do parents know and say? *Pediatr Pulmonol*. Nov 2008;43(11):1107–16. <https://doi.org/10.1002/ppul.20911>.
- [30] Madge SL, Carr SB. Reproductive health in males with cystic fibrosis: knowledge, attitudes, and experience of patients and parents. *Pediatr Pulmonol*. 1999;27(4):293. [https://doi.org/10.1002/\(SICI\)1099-0496\(199904\)27:4<293::AID-PPUL13>3.0.CO;2-3](https://doi.org/10.1002/(SICI)1099-0496(199904)27:4<293::AID-PPUL13>3.0.CO;2-3).
- [31] 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*. Jan 2001;28(1):36–40. [https://doi.org/10.1016/s1054-139x\(00\)00172-5](https://doi.org/10.1016/s1054-139x(00)00172-5).
- [32] Lonabaugh KP, O'Neal KS, McIntosh H, Condren M. Cystic fibrosis-related education: Are we meeting patient and caregiver expectations? *Patient Educ Couns* 2018;101(10):1865–70. <https://doi.org/10.1016/j.pec.2018.06.004>.
- [33] Lyon A, Bilton D. Fertility issues in cystic fibrosis. *Paediatr Respir Rev*. Sep 2002;3(3):236–40. [https://doi.org/10.1016/s1526-0542\(02\)00184-7](https://doi.org/10.1016/s1526-0542(02)00184-7).
- [34] Khan FN, Tangpricha V, Hughan KS, et al. Men's health in the modern era of cystic fibrosis. *J Cyst Fibros*. Dec 2020. <https://doi.org/10.1016/j.jcf.2020.12.013>.