

Research Priorities in the Health of Women with Cystic Fibrosis

June 2020

Areas of Research Focus:

- Gender gap in clinical outcomes
- Fertility
- Pregnancy
- Contraception
- Parenthood
- Urinary Incontinence
- Body image
- Menopause

Background

Continued advancements in therapy and health management have led to dramatic increases in the life expectancy of people with cystic fibrosis (CF).¹ This exciting progress has resulted in an increasingly older CF population with unique and emerging needs, including women with CF who are experiencing a variety of general and CF-specific women's health concerns.

To address these critical issues, the Cystic Fibrosis Foundation (CFF) recently formed a dedicated research working group to understand the unique interplay between having CF and being a woman. The early goals of the [Therapeutic Development Network \(TDN\) Women's Health Research Working Group \(WHR-WG\)](#) are to identify the gaps in knowledge around CF women's health issues, determine future research priorities, and begin to develop the infrastructure needed to efficiently move these research priorities forward.

Given that women's health issues are complex and multi-faceted, women with CF are included as key stakeholders in the WHR-WG. In addition to two women with CF being members of the WHR-WG, regular interactions with women in the CF community are occurring by using such CF Foundation programs as [Community Voice](#). The working group uses this forum to gather deeper as well as targeted insights and identify priorities, enabling the development of the most relevant research projects for women with CF.

The working group also recognizes that collaboration with other researchers who possess unique expertise is critical to advance our understanding of CF women's health. As research priorities are developed, input from specialty experts (e.g., fertility, obstetrics, gynecology, endocrinology) will be elicited and incorporated into related research protocols.

Women's Health Research Working Group Membership

Clinicians/Researchers

Jennifer L. Taylor-Cousar, MD, MSCS
Raksha Jain, MD, MSCI
Traci M. Kazmerski, MD, MS
Natalie E. West, MD, MHS
Moira L. Aitken, MD, FRCP
Alexandra W. M. Wilson, MS, RDN, CDE

CFF/TDN Foundation Staff

JP Clancy, MD
Dara Riva
Kelsie Pearson
Jill Van Daltsen
Anna Mead
Amalia Margaret, PhD
Nicole Hamblett, PhD

CF Community Members

Jackie Sjoberg
Madeline Poranski

How the Cystic Fibrosis Foundation Funds Research

Currently, researchers in academia can request funding through numerous CF Foundation funding channels. Reviewers include experts in CF research and some mechanisms also incorporate direct input of CF community members (people with CF and their families) into the review process. Applications are reviewed and funded based on the scientific merit of the proposal and the relevance to the CF Foundation's mission. The CF Foundation will receive applications for funding on a variety of topics related to women's health that will advance CF care, treatment, or research. However, applications addressing the priorities below are particularly encouraged.

The working group will continue to advise the CF Foundation, reviewing the portfolio bi-annually and updating recommendations for research priorities.

Current Priorities in the CF Women's Health Research Landscape and Examples of Existing Studies*

Below is a list of previously published prioritization projects. In the sections that follow, for each of the current women's health research focus areas, examples of ongoing studies and priority topics are described.

PRIORITIZATION PROJECTS

The Cystic Fibrosis Reproductive and Sexual Health Collaborative (CFReSHC) is a group of women with CF working with clinicians and researchers to develop patient-driven research projects. In 2016 and 2017, the group engaged a larger group of women with CF and CF providers and researchers to identify priority areas for CF sexual and reproductive health (SRH) research.² The priorities identified through this effort were:

1. Improved care coordination between CF centers and obstetrics/gynecology
2. Effective and satisfactory treatments for menopausal and peri-menopausal symptoms
3. Improved pregnancy planning
4. Improved care during motherhood
5. Evaluation of health risks and benefits of hormonal contraception
6. Improved management of mental health concerns surrounding body image and fertility issues

Dr. Kazmerski and her colleagues also conducted a concept mapping study of adolescent and young adult women with CF, their parents, and stakeholders in women's health and CF to identify the SRH topics and outcomes of importance to them.³ From the study, these key areas were identified:

1. Fertility and pregnancy (highest for adult women)
2. Deciding to have children
3. Birth control (highest for adolescent women)
4. Navigating life (e.g. mental health, substance abuse, transition readiness, quality of life)
5. Sex (sexually transmitted infections, sexual orientation and sexual functioning)
6. Gynecologic concerns (e.g. vulvovaginal candidiasis, urinary incontinence)

Thus, between women with CF and their families and CF providers and investigators there were several areas of overlap identified for priority areas of research in women's health. Finally, the WHR-WG has identified the survival (gender) gap between women and men with CF as another research priority.

*Listed examples do not represent a comprehensive list of all research that is currently being funded in women's health.

GENDER GAP

Definition

In the general population the average life expectancy is 78.6 years; however, it is 76.1 years for males and 81.1 years for females.⁴ However, amongst people with CF, women have decreased survival compared to men.⁵ The

biological and sociocultural contributors to the existence of the gap in survival between men and women with CF remain poorly understood.

Examples of existing research efforts

Investigators are examining the impact of sex on the occurrence and outcomes of pulmonary exacerbation.⁶ Furthermore, work is being done to examine the association between sex hormone levels and respiratory outcomes in women with CF. Additionally, based on *in vitro* data demonstrating an impact of estrogen on the mucoidy of *Pseudomonas aeruginosa*, and differences in pulmonary exacerbation occurrence between women on or off hormonal contraception⁷, investigators are studying the impact of estrogen on inflammation and ion transport.⁸ Investigators recently reported differences in outcomes between women with CF and men with CF who took ivacaftor.⁹

Research Priorities

- Understand the biological basis of difference in survival between women with CF versus men with CF
- Confirm previously reported survival differences in post-menopausal women in a modern cohort
- Describe the epidemiology and treatment of catamenial hemoptysis in women with CF
- Determine whether there are consistent sex differences in clinical response to cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy and the biological etiology of those differences if they exist (e.g. interaction with estrogen, weight-based pharmacokinetics)

FERTILITY

Definition

Women with CF generally have reproductive anatomy that is similar to that of women without CF. Factors that can affect fertility in women with CF include thick, dehydrated, pH imbalanced cervical mucus, delayed puberty and ovulation and suboptimal nutritional status.¹⁰ Most women with CF can become pregnant, yet ~25-49% of pregnancies in women with CF are unplanned.^{11,12} However, Shteinberg et al reported 35% decreased rate (pancreatic insufficiency and older age at first attempt were associated with decreased fertility.)¹³ Case reports and case series suggest that highly effective CFTR modulators, may increase fertility in women with CF.^{14,15}

Examples of existing research efforts

Investigators are studying the properties of cervical mucus in women with CF and whether the properties are altered before and after administration of CFTR modulators.

Research Priorities

- Describe the rates of infertility for women with CF in a modern cohort/in the era of highly effective CFTR modulator therapy (HEMT) for most women with CF
- Determine the biological etiology of risk factors for infertility for those women who experience it

PREGNANCY

Definition

Based on data from the Cystic Fibrosis Foundation Patient Registry (CFFPR) over the last 20 years, the number of women with CF who became pregnant has doubled (from 140 in 2008 to 280 in 2018).¹ Survey data suggests that almost 80% of young women hope to have a child in the future.¹⁶ To date, the majority of studies examining

pregnancy outcomes for women with CF have been retrospective single site or registry studies.¹⁷⁻²⁴ Although data from some studies suggested negative impact of pregnancy on lung function and survival for some women²⁵⁻²⁸, large retrospective cohort studies did not show worse survival or accelerated disease progression.^{29,30} There has never been a large, multicenter prospective study of pregnancy outcomes in women with CF. Furthermore, the safety of CFTR modulators in pregnancy and lactation is relatively unknown/based on case studies, case series and one multicenter/multinational retrospective survey study.³¹⁻³⁶

Examples of existing research efforts

A large, multicenter retrospective study is currently being conducted to evaluate pregnancy outcomes in a modern cohort of women with CF. A prospective Multicenter Study of Pregnancy and Infant Outcomes in the Era of CFTR Modulators (MAYFLOWERS) evaluating pregnancy-related outcomes in women on and off modulators will begin in 2020.

Research Priorities

- Women with CF· Understand the pharmacokinetics of systemic CF therapy (e.g. CFTR modulators, antibiotics, vitamin replacement) use during pregnancy and lactation
- Women with CF· Describe the nutritional deficiencies during pregnancy that are unique to women with CF and devise an appropriate intervention to address the deficiencies

CONTRACEPTION

Definition

Up to half of pregnancies in women with CF are unplanned.^{11,12} Historically, women with CF have relied on their CF care providers for discussion and prescription of contraception.³⁷ Over time, likely influenced by CFTR modulator trials³⁷, the use of long acting reversible contraception has increased.^{12,38} However, it is unclear which contraceptive method is most safe and effective for women with CF

Examples of existing research efforts

Using a retrospective cohort study survey of women with CF from 10 U.S. CF Centers, investigators plan to determine whether pulmonary exacerbation rates vary significantly between hormonal contraceptive users and non-hormonal users.

Research Priorities

- Determine the safety and effectiveness of contraceptives for women with CF
- Evaluate the impact of varying form of contraception on bone health in women with CF

PARENTHOOD

Definition

For those women with CF who experience decline in their physical and mental health in the year(s) following pregnancy³⁰, it is unclear whether pregnancy is the cause, or if being a parent contributes. At this point in time, there is no registry that captures whether adults with CF have chosen to become parents naturally, through in vitro fertilization or through adoption or surrogacy.

Examples of existing research efforts

Investigators will conduct a qualitative study of women and men with CF who have chosen to become parents. The goal of the study is to identify critical outcomes for a multicenter study.

Research Priorities

- Determine whether parenthood adversely impacts mental or physical health in parents with CF
- Determine if there is are sex and/or gender-based differential impact of parenthood on omen with CF versus men with CF
- Determine what aspects of parenthood are most likely to influence the health of the parent with CF (e.g. daycare versus home care, biological child versus adopted child)

URINARY INCONTINENCE

Definition

A systematic review of the prevalence and impact of urinary incontinence (UI) in CF found the prevalence to range from 30%-76% with older age of the participants impacting prevalence.³⁹ UI commonly impacted the use of airway clearance/exercise and lead to worry and embarrassment for many participants.

Examples of existing research efforts

There is an on-going multisite survey of 500 women with CF age ≥ 25 years, partners of adult women with CF and female peers of adult women with CF that will identify SRH concerns and preferences of adult women with CF.

Research Priorities

- Assess the etiology/mechanisms of incontinence in women with CF
- Identify effective treatment strategies for prevention, identification and treatment of incontinence in women with CF

BODY IMAGE

Definition

As there are societal rewards for thin stature, adherence to CFTR modulators and to nutrition, diabetes management and physical activity recommendations may be adversely impacted.

Examples of existing research efforts

There is a pilot study being conducted that is using the CFQ-R to measure body image and weight in addition to individual interviews to explore body image and weight concerns among both men and women with CF.

Research Priorities

- Describe the epidemiology/prevalence/effective intervention of the impact of body image on adherence

MENOPAUSE

Definition

While women with CF have shorter survival compared to men with CF⁵, for the subgroup of Women with CF who live past the age of menopause, their survival exceeds that of men with CF.⁴⁰ Although it is hypothesized that estrogen may play a role in this reversal in survival trends amongst those with CF⁴¹, this issue has not been thoroughly investigated.

Examples of existing research efforts

There is an on-going multisite survey of women with CF age ≥ 25 years, partners of adult women with CF, and female peers of adult women with CF that will identify SRH concerns and preferences of adult women with CF.

Research Priorities

- Determine how the experience of menopause is similar or dissimilar between women with and without CF
- Evaluate safety of symptomatic treatment options for menopause in Women with CF
- Evaluate safety of medications to prevent or treat osteoporosis in Women with CF

Men's Health

While the focus of the WHR-WG is women's health, there are on-going efforts to establish expertise and research efforts in men's health. Please consider submitting projects addressing issues specific to men's health (e.g. SRH knowledge, hypogonadism, infertility, fertility preservation, body image).

For More Information

We are committed to transparency regarding our research efforts for women's health. For more information regarding the TDN Women's Health Research Working Group, go to:

<https://www.cff.org/Research/Researcher-Resources/Therapeutics-Development-Network/TDN-Womens-Health-Research-Working-Group/>, or to discuss research ideas, please contact Jennifer Taylor-Cousar at TaylorCousarJ@NJHealth.org.

Please contact Dara Riva (driva@cff.org) for more information on funding opportunities.

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