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Fertility and Reproductive Health Implications of Targeted Therapeutics for Cystic Fibrosis

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Abstract

Aim: To explore knowledge of fertility and knowledge of the impact of cystic fibrosis (CF) on reproduction and fertility among women of childbearing age with homozygous F508del mutation, and explore these women's perceptions on fertility changes secondary to lumacaftor/ivacaftor.

Methods: This pilot had a sample of 20 women. Ten women with CF, ages 19-35 with homozygous F508del mutation, stable lung function, and English proficient were included, as well as a non-CF comparison group. Three questionnaires were administered: demographics form, Knowledge of Fertility (KF), and Knowledge of Impact of CF on Reproduction and Fertility (KICFRF). A semi-structured interview was conducted with the CF group. Interview transcripts were coded and analyzed using thematic analysis.

Results: On the KF scale, participants in both groups reported a lot of knowledge about the effect of age on fertility. Seven participants in the CF group and eight in the non-CF group reported little knowledge about the infertility work up. On the KICFRF, seven reported a lot of knowledge on the role of cervical mucus viscosity on fertility. Only three reported a lot of knowledge on the role of cervical mucus pH. Half of the CF group correctly identified CF's genetic transmission. Three main themes emerged from the qualitative data: (1) "Positive, negative, and unknown effects of lumacaftor/ivacaftor"; (2) "Needing comprehensive reproductive and sexual health education and counseling by the CF care team"; and (3) "Wanting to have a child despite knowing or suspecting impaired fertility".

Discussion: Women with CF are knowledgeable about general fertility concepts. Areas of less knowledge (i.e., infertility work-up, genetic transmission, and role of cervical mucus pH) require future research. They desire comprehensive clinical care that includes discussions about fertility and reproductive health. They want to become mothers and are hopeful that targeted therapeutics will make their dream of motherhood a reality.

Keywords: Cystic fibrosis; Fertility; Reproductive health; Targeted therapeutics; Lumacaftor/ivacaftor

Introduction

Cystic fibrosis (CF) is the most common genetic disorder among Caucasians, with over 10 million people – or one out of every 31 Americans - carrying the defective gene [1]. This autosomal recessive disease, caused by a mutation on chromosome 7 that leads to an alteration in the function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, affects 30,000 people in the United States, with half of this population being age 18 or older [1]. The median predicted survival age for people with CF has steadily climbed since it was first described in the 1930s, rising from 31.3 to 41.1 years between 2002 and 2012 [2]. With significant advances in research, genetic testing, therapeutics, and comprehensive clinical care, people with CF are living well into adulthood and engaging in all developmental milestones including parenthood.

Women account for 48 percent of the CF population [2]. For women with CF, great strides have been made since 1960 when the first report of a "successful" pregnancy by a woman with CF tragically ended with maternal death from CF complications six weeks after delivery [3]. While exact data on CF female fertility rate is unknown, the CF Foundation Patient Registry indicates that the number of CF females who became pregnant has doubled in the last 20 years (116 pregnancies in 1992, and 249 pregnancies in 2012) [2,4].

As new CFTR-modulating drugs are developed and approved, the number of pregnancies will likely continue to increase. Two targeted therapeutics were recently approved by the United States Food and Drug Administration to treat the underlying cause of certain CF mutations. Ivacaftor is approved for G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R mutations [5]. The combination drug, lumacaftor/ivacaftor, is approved for those with homozygous F508del mutation, which affects approximately 50% of those with CF, representing a large portion of the CF population (CFF, n.d.). Both ivacaftor and lumacaftor/ivacaftor have shown to improve lung function, sweat chloride levels, and overall quality of life [6,7]. However, their impact on female fertility have not been previously examined.

Women with CF have normal reproductive structures, and except for those who are severely malnourished, they have normal or near normal menstrual cycles [8]. However, women with CF have decreased fertility primarily due to dehydrated, excessively thick cervical mucus

that blocks sperm transport, caused by a disturbance in the reproductive tract fluid microenvironment that is hostile to the sperm secondary to the defective CFTR protein that alters chloride and bicarbonate transport [9-12]. Cervical mucus and its properties are critical in a woman's fertility [13]. Cervical mucus is primarily composed of water (95-99 %), ions, enzymes, proteins, and mucins [13]. The function of cervical mucus is directly linked to a woman's stage in the menstrual cycle. Immediately prior to ovulation, increasing estrogen results in more abundant, watery-thin cervical mucus that facilitates sperm migration into the uterus [14]. After ovulation, progesterone is secreted and the cervical mucus becomes thicker and reduced in amount blocking sperm migration [15]. However, in women with CF, the alteration in CFTR function results in viscous cervical mucus, which is the primary underlying cause of impaired fertility [16].

Sawyer et al. examined the knowledge, attitudes, and behaviors related to reproductive health among people with CF [17-24]. Their work primarily focused on male experiences and perspectives, and used questionnaires to demonstrate significant gaps in knowledge and behaviors [21]. Their most recent publication of a multi-site study showed that while men with CF were more aware of the extent and cause of their infertility than women, 28% did not know why CF affects male fertility, and only 41% had undergone a semen analysis, which is a clinical care standard [21]. The cause of male infertility, congenital absence of the vas deferens, is widely accepted and understood [25]. However, the same cannot be said for the cause(s) of reduced or impaired fertility in women with CF [26].

Korzeniewska et al. examined the sexual and reproductive health knowledge of women of childbearing age with CF. Out of the 64 women, aged 16-24, only 32.8% understood how CF affects fertility, and 84 % reported not using any form of contraception while sexually active [27]. Similarly, Siklosi et al. described the development, validation, and implementation of a questionnaire addressing general disease knowledge among adults with CF [28]. They showed that out of the 100 adult CF participants, only 66.7% of female participants were aware that CF can affect fertility. Furthermore, their knowledge of reproductive health and genetics scored lower than to their knowledge of CF-related lung and gastrointestinal complications [28].

With the emergence of targeted therapeutics and their potential impact on fertility and reproductive health, it is critical to examine the baseline knowledge of fertility concepts among childbearing women with homozygous F508del mutation, as well as explore their perceptions on any potential effects of lumacaftor/ivacaftor on fertility. This pilot study aimed to: (1) Explore knowledge of fertility and knowledge of the impact of CF on reproduction and fertility among women of childbearing age with homozygous F508del mutation; and (2) Explore these women's perceptions on fertility changes secondary to the drug.

Methods

This mixed methods, pilot study had a sample of 10 women with CF and 10 women without CF. Three questionnaires were administered: demographics form, Knowledge of Fertility (KF) scale, and Knowledge of Impact of Cystic Fibrosis on Reproduction and Fertility (KICFRF) questionnaire which was administered only to the CF group. A semi-structured, audiotaped interview was conducted with the CF group. Interview transcripts were reviewed, coded, and analyzed using thematic analysis. Quantitative data were analyzed using SPSS.

For the CF group, inclusion criteria included: (a) female; (b) age 19-35; (c) confirmed diagnosis of cystic fibrosis with homozygous F508del mutation; (d) forced expiratory volume in 1 second (FEV1) of at least 40%; and (e) ability to understand, write, and speak English. Exclusion criteria include: (a) male; and (b) CF mutations not specified in inclusion criteria. For the non-CF group, inclusion criteria included: (a) female; (b) age 19-35; and (c) ability to understand, write, and speak English. Exclusion criteria include: (a) male; and (b) CF disease.

After IRB approval, recruitment for the CF group took place at an Adult CF Center situated within a large academic medical center in the southeastern region of the United States. Study candidates were identified by the principal investigator (PI) by screening the clinic list shared by the clinical coordinator as approved by the Center Director. When study candidates were scheduled for their regular clinic appointments, the PI and/or her trained PhD student made every attempt to meet the study candidates in person to provide information about the study and invite them to participate. Snowball sampling was also used when potential or actual study participants referred other potential participants to the PI. Recruitment for the non-CF group took place by word-of-mouth and posting IRB-approved flyers in locations where women of childbearing age frequent (e.g., School of Nursing building, Student Recreation Center). Interested women contacted the PI at their convenience. The PI used the eligibility checklist for non-CF group to screen flyer responders and explained the purpose of the study and time commitment involved if the candidates chose to participate. For both groups, the PI sent the IRB-approved consent form either via postal mail or electronic mail with the address provided by the candidates for them to review at their leisure. The PI followed-up with a phone call to candidates within one week of receiving the consent form to answer any questions, and determine whether they would like to participate in the study. Interested participants were asked for their contact information, and a meeting date, time and location convenient to the participants was determined. At the meeting, the PI again explained the purpose of the study, answered any additional questions, and written informed consent was obtained. Participants were assigned a unique identification number to ensure confidentiality and privacy. All study information was stored in the PI's private and locked office's computer with password security. Participants were informed that their participation was voluntary and they could withdraw from the study at any time without fear of any repercussions.

After informed consent was obtained, the PI administered the demographics form, followed by the questionnaires. After the questionnaires were completed, the PI conducted taped, semi-structured interviews with the CF group using an interview guide with prompts. Open-ended questions about the participant's thoughts and feelings about the impact of CF on fertility as well as their perceptions on whether the new CFTR-modulating drugs will have an effect on fertility was explored. Prompts were used to elicit more elaboration if needed. Approximately 90 minutes were allotted for the completion of the informed consent, questionnaires, and interview. Interviews were transcribed and reviewed for accuracy, then loaded into a qualitative analysis program, Hyper RESEARCH [29]. The PI kept field notes and journal entries of personal observations and reflections. Participants were compensated for their time with $25 cash with receipt.

In terms of study measures, the CF group completed: demographics form, Knowledge of Fertility Scale, Knowledge of Impact of Cystic Fibrosis on Fertility, and taped interview. The non-CF group completed: demographics form and Knowledge of Fertility Scale. The

Demographics Form (administration time ≈5 minutes) was used to collect demographic, treatment-related variables and information about fertility status. The tool consisted of 19 items (e.g., age, ethnicity, education level, marital status, work status, fertility status) completed by both the CF- and non-CF groups, and an additional 10 items (e.g., age at diagnosis, CF complications) to be completed only by the CF-Group. Knowledge of Fertility Scale (administration time ≈ 3 minutes) was used to assess the participants' general knowledge of female fertility. This is a 13-item questionnaire with fixed responses for the participant's self-assessed knowledge (A Little, Some, A Lot). This questionnaire was adapted from previous studies by Meneses et al. on female cancer patient's knowledge of fertility, where the instrument had a high internal consistency (Cronbach alpha=0.89), based on literature and expert review [30]. Permission to use was obtained. Pretesting for readability and relevance was conducted on a small group of CF and non-CF women prior to implementation of instrument. Knowledge of Impact of Cystic Fibrosis on Reproduction and Fertility (administration time ≈3 minutes) was adapted with permission from the previous work of Siklosi et al. on CF patient's knowledge of reproductive health [28]. The first section tested the participant's specific knowledge on CF-related reproductive health while the second section was a 13-item questionnaire with fixed responses for self-assessed knowledge (A Little, Some, A Lot). This questionnaire was developed based upon expert review and an exhaustive literature review of CF-related fertility complications [28]. Pretesting for readability and relevance was conducted on a small group of CF and non-CF women prior to implementation of instrument. Interview Guide with prompts (Table 1) were used to elicit the CF group's perceptions on the potential impact of the new CFTR-modulating drugs on fertility. Changes to their sexual practices and behaviors as a result of potentially improved fertility was explored, and when applicable, questions about pregnancy or fertility diagnostics and treatment were also addressed.

Have you been pregnant?	
a. If Yes: Describe your pregnancy experience.	i. Was it a planned or unplanned pregnancy?
	ii. If planned, did your CF Care Team support your decision to get pregnant?
	iii. Did you have an easy or difficult time getting pregnant?
	iv. Did you have to get help from a fertility specialist?
	v. How was your overall pregnancy experience?
	vi. What were the positive and negative aspects of being pregnant with CF?
	vii. Did you get sick or get hospitalized more often while pregnant?
	viii. Who were your sources of support when you were pregnant?
b. If No: Do you want to become pregnant someday?	i. Do you have any fears related to getting pregnant? What are they?
	ii. Do you have any fears related to being a mom with CF? What are they?
2. Do you think or feel that CF affects your fertility?	a. If Yes: Describe how CF affects your fertility
3. How did you learn about your possible challenges in getting pregnant? Describe the circumstances around that first discussion.	
4. How did you feel when you learned about your possible challenges in fertility?	
5. Do you think or feel that the new drugs (ivacaftor and lumacaftor/ivacaftor) have any effect on women's fertility?	a. If Yes: Describe how the new drugs could have an effect on women's fertility
Is there anything else that I should have asked you to about your fertility and thoughts on the new drugs as they relate to women's fertility?	
PROMPTS:	1. Tell more more about
	2. Can you explain that a little bit more?
	3. Can you clarify what you mean by

Table 1: Sample of questions from interview guide.

The PI conducted the ten interviews with the CF group after participant demographic information and survey responses were collected. Interviews ranged from 26-67 minutes, with an average of 45 minutes per participant. Thematic saturation was reached after the 8th interview [31]. Two interviews were conducted in person, and the remaining eight interviews were conducted via telephone. All interviews were audiotaped and transcribed verbatim. Transcripts were reviewed for accuracy before data analysis commenced. Braun and Clarke's approach to thematic analysis was used to identify the major themes that emerged from the data [32]. The steps to thematic analysis

are the following: (a) Interview transcripts were read repeatedly to search for meanings and patterns, and the extracted data about the participants' perceptions and implications of improved fertility were coded with descriptive tags; (b) Codes were sorted and grouped into potential themes; and (c) Themes were further reviewed, collapsed, and refined before arriving at the final schema. A PhD student, trained in qualitative data analysis and who worked closely with the PI as part of her research immersion experience in the doctoral program, independently analyzed and coded three transcripts. Her coding revealed approximately 90% agreement with the PI's coding scheme, thus, demonstrating strong inter-rater reliability between the two coders. Analysis and coding were conducted in an iterative process until no new codes emerged. Initial codes were clustered and collapsed into higher order themes. Emerging themes were shared with three participants who volunteered to provide validation of the findings. All three agreed with the major themes extracted from the qualitative data. Figure 1 for flow-chart of mixed methods approach used in this study.

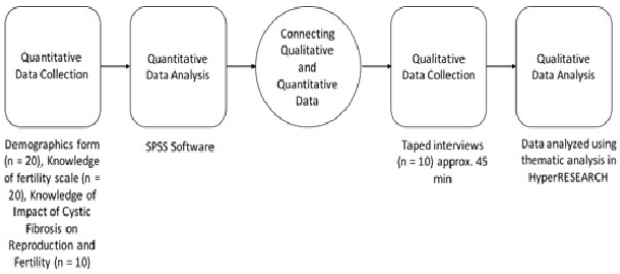

Figure 1: Flow-chart of mixed methods approach.

Results

Table 2 shows the demographic information for all participants. The participants were between the ages of 25 and 34 years with a mean age of 29. Fifteen participants were Caucasian, five were African American, and 18 were college graduates. Twelve participants were married, and 7 were single. Seventy percent (n=14) of the participants (2 with CF) indicated that they were pregnant at least once, and 30% (n=6) indicated that they were never pregnant.

Variables	CF (N=10)		Non-CF (N=10)	
	N	%	N	%
Age				
Range	25-34		26-33	
Mean	29		29	
Race/Ethnicity				
White	10	10%	5	50%
Black/African American	0	0%	5	50%
Educational Level				
High school graduate	1	10%	0	0%
Some college or Technical School	1	10%	1	10%
Four-year college degree	3	30%	4	40%
Masters or doctoral degree	5	50%	5	50%
Marital Status				
Single	1	10%	6	60%
Married	8	80%	4	40%
Separated	1	10%	0	0%
Ever been pregnant				
Yes	2	20%	4	40%
No	8	80%	6	60%

Table 2: Demographics of CF and non-CF groups.

Quantitative findings

On the KF scale (Table 3), participants in both the CF (N=7) and non-CF group (N=8) reported a lot of knowledge about the impact of age on fertility. Approximately half of the participants in both groups reported only some knowledge about the effect of smoking on fertility. Similarly, around half reported a lot of knowledge about the impact of weight on fertility. Seven participants in the CF group and eight in the non-CF group reported little knowledge about the infertility work up.

Variables	CF	(N = 10)	Non-CF	(N = 10)
	N	%	N	%
Age				
Some	2	20	3	30
A lot	8	80	7	70
Smoking				
A little	1	10	1	10
Some	5	50	4	40
A lot	4	40	5	50
Weight				
A little	1	10	2	20
Some	3	30	3	30
A lot	6	60	5	50
Infertility work-up				
A little	7	70	8	80
Some	0	0	2	20
A lot	3	30	0	0
Reproductive cycle				
Some	2	20	3	30
A lot	8	80	7	70

Table 3: Knowledge of fertility (CF, N=10; non-CF, N=10).

On the KICFRF questionnaire (Table 4), all ten CF participants reported that they knew CF could affect fertility; however, half of the CF group did not correctly identify the genetic transmission of CF. Nine participants agreed that most males with CF are infertile and all participants understand that contraception is necessary for females with CF who do not wish to have children. Seventy percent (n=7) of the participants perceived that a CF carrier always passes the CF gene mutation on to all their children. Similarly, 70% (n=7) reported having a lot of knowledge regarding the impact of CF on cervical mucus thickness. However, only 30% (n=3) reported a lot of knowledge on how CF impacts cervical mucus pH and fertility. Additionally, 70% (n=7) of participants reported some knowledge of the impact of weight on fertility. Similarly, 70% (n=7) participants indicated a lot of knowledge on pregnancy complications with CF. Only 20% (n=2) of respondents indicated that they had little knowledge on genetic counseling before pregnancy. Only 10% (n=1) of the CF participants reported a lot of knowledge about the option of surrogacy and gestational carriers. In addition, none of the participants reported a lot of knowledge on the adoption option to achieve motherhood.

Variables	CF	(N = 10)
	N	%
Cervical mucus thickness on fertility		
	1	10%
	2	20%
A lot	7	70%
Medications on fertility		
A little	1	10%
Some	9	90%
A lot	0	0%
Weight on fertility		
A little	0	0%
Some	7	70%
A lot	3	30%
Pregnancy on health		
A little	0	0%
Some	3	30%
A lot	7	70%
Pregnancy complications with CF		
A little	1	10%
Some	2	20%
A lot	7	70%
Cervical mucus p		
A little	5	50%
Some	2	20%
A lot	3	30%
Genetic counseling before pregnancy		
A little	2	20%
Some	2	20%
A lot	6	60%
Genetic counseling before delivery		
A little	4	40%
Some	5	50%
A lot	1	10%
Surrogacy and gestational carriers		
5	5	50%
Some	4	40%
A lot	1	10%
Being a mother with CF		
A little	3	30%
Some	2	20%
A lot	5	50%
Adoption		
A little	7	70%
Some	3	30%
A lot	0	0%
Child-free living		
A little	2	20%
Some	2	20%
A lot	6	60%
Psychosocial concerns		
A little	6	60%
Some	2	20%
A lot	2	20%

Table 4: Self-reported knowledge on the impact of CF on reproduction and fertility scale.

Qualitative findings

The qualitative data supported and enriched the quantitative findings. The initial 84 codes were collapsed into three clusters that resulted in the final thematic schema (Table 5). The three main themes that emerged from the interviews with the CF group were: (1) "Positive, negative, and unknown effects of lumacaftor/ivacaftor"; (2) "Needing comprehensive reproductive and sexual health (RSH) education and counseling by the CF care team"; and (3) "Wanting to have a child despite knowing or suspecting impaired fertility". Each theme will be discussed below and illustrated by verbatim quotations from participants.

Main Theme #1: Positive, negative, and unknown effects of lumacaftor/ivacaftor (12 codes)	**Total Participants (participant number)**
Lumacaftor/ivacaftor can help improve quality of life and plan for future	6 (1, 5, 6, 7, 8, 10)
Lumacaftor/ivacaftor positive effect - lung clearance and energy	5 (1, 6, 7, 8, 10)
Lumacaftor/ivacaftor is reversing my disease	2 (7, 10)
Lumacaftor/ivacaftor helped to achieve pregnancy	1 (8)
Lumacaftor/ivacaftor may affect fertility	6 (1, 4, 5, 6, 7, 9)
Lumacaftor/ivacaftor side effect - reproductive health	6 (1, 2, 3, 4, 6, 10)
Unsure about how Lumacaftor/ivacaftor works to affect reproductive health	5 (2, 4, 5, 6, 9)
Lumacaftor/ivacaftor's potential fetal effects	7 (2, 3, 4, 5, 6, 7, 10)
Staying on Lumacaftor/ivacaftor during pregnancy despite being dissuaded by CF care team	4 (6, 7, 8, 10)
Using double protection to avoid pregnancy while on Lumacaftor/ivacaftor	4 (1, 5, 6, 7)
Need to continue studying Lumacaftor/ivacaftor	2 (4, 5)
Deciding to wait to start Lumacaftor/ivacaftor	3 (2, 3, 5)
Main Theme #2: Needing comprehensive RSH education and counseling by the CF care team (17 codes)	
Need for comprehensive RSH education and counseling	3 (4, 7, 8)
Getting clearance and support from CF care team before fertility tx is important	5 (1, 3, 5, 8, 10)
Unprepared to learn about sex and reproduction from CF care team	2 (1, 4)
Need better collaboration with CF care team	3 (6, 8, 9)
Having a good CF care team is key to staying healthy	4 (4, 5, 8, 10)
Feeling emotional and uncertain about fertility tx	2 (1, 8)
CF care team discouraged plans for pregnancy	1 (8)
Disappointed that CF care team did not support wishes to get pregnant	1 (8)
Feeling conflicted about staying on lumacaftor/ivacaftor when pregnant	2 (7, 10)
Fears during pregnancy – keeping body healthy	6 (2, 3, 4, 5, 6, 10)
Learning about sex and reproduction from CF care team	3 (1, 4, 5)
Learning about sex and reproduction from mother or family member	4 (2, 5, 6, 8)
Learning about CF fertility via personal research	3 (1, 3, 4)
Learning about CF fertility from PCP	1 (7)
Unsure of how CF affects pregnancy or fertility	1 (4)
Choosing to get partner tested for CF	7 (2, 3, 4, 5 6, 7, 10)
Choosing NOT to get partner tested for CF	3 (1, 8, 9)
Main Theme #3: Wanting to have a child despite knowing or suspecting impaired fertility (8 codes)	
Wanting to have child despite potential risks	10 (1-10)
Exploring all options to achieve motherhood	8 (2, 3, 4, 5, 6, 8, 9, 10)
Seeking help from fertility specialists	4 (1, 3, 5, 6)
Using fertility treatments	4 (1, 2, 5, 6)
Trying to get pregnant without fertility treatments	4 (1, 3, 5, 6)
Not waiting to have child later due to CF uncertainty	6 (3, 4, 5, 6, 7, 10)
Knowing that I may have impaired fertility	10 (1-10)
Impaired fertility – cervix or fallopian tube blocked with mucus	7 (1, 2, 5, 6, 8, 9, 10)

Table 5: Clustering and collapsing of initial codes into three main themes.

Positive effects of lumacaftor/ivacaftor

Half of the participants with CF were on lumacaftor/ivacaftor and described positive effects from the drug (e.g., improved lung function and clearance, increased energy, improved quality of life, and improved fertility).

Improved lung function and clearance: Five participants reported a significant improvement in their lung function and lung clearance. One participant described her experience: "My baseline [lung function] before starting on lumacaftor/ivacaftor was around 50; 55 at best. This week I blew a 75". She added: "I feel different. Just little things. Going up and down the stairs, whenever I exercise, I just feel like I can take deeper breaths. I don't get out of breath as quickly as I used…We live in a hilly neighborhood. It's not difficult for me to go up and down the hills like it would have been a couple years ago. Definitely feel… different".

Another participant shared: "The second week I was on it, I dried up immediately. My mucus dried up. I could tell a difference… My cough has not been productive at all. I don't really cough stuff up. My parents have also said that they notice a change in my voice, that it's less raspy, or gravely, or nasal. I've had absolutely no sinus problems".

Increased energy: Several participants remarked that being on lumacaftor/ivacaftor provided them with more energy to tackle their daily activities. One participant described, "My energy level is so much better... and my ease with just everyday stuff, like if I wake up and don't to the vest right away, I feel okay". Another participant echoed these same sentiments: "I went through a period where I'd wake up in the morning and I actually would forget to do my first treatment right away because I wasn't feeling that urgent need to do it right away".

Improved quality of life: Six participants reported an overall improvement on their quality of life secondary to the drug. One participant reported that being on lumacaftor/ivacaftor has allowed her to not focus all of her energy on CF care maintenance: "Now I feel like I can go about my day, and then think about CF when I'm ready. Like if I go away for 48 hours, I don't freak out about not having the vest. I will go on a run, or take a flutter or something, and just not freak out".

Another participant reported significant changes in her health: "I've had nothing but positive response from the second I started taking it... My lung function's done nothing but go up. I've gained ten pounds... I just feel really great". Another participant stated that she believes the drug is "reversing" her disease. Another participant shared that being on the drug opened up the future for her and her family: "It's just now you can make plans, and before… we really couldn't". Another participant reported a similar positive outlook toward the future, a future that includes being a mother: "I think being on this drug has changed my understanding of my vulnerability, but also my future. I don't know that I got serious about thinking about having kids 'til I knew that I was gonna be on lumacaftor/ivacaftor within a year".

Improved fertility: All of the participants believe that the drug has the potential to affect fertility by making the cervical mucus less viscous, thus, allowing for easier sperm transport. One participant theorized that, "on some basic level, since it has the ability to decrease the thickness of secretions in the digestive tract and in the lungs, that it should also, in theory, make basic reproductive function a bit more smooth". Another participant directly linked her pregnancy to the drug after taking it for two weeks. She reported that after trying to conceive for over two years, she became pregnant shortly after taking lumacaftor/ivacaftor. She attributed her ease of conception to a change in her cervical mucus: "When I started lumacaftor/ivacaftor…I was coughing up less mucus…and I think because of lumacaftor/ivacaftor…taking away some of the mucus in my body, it also freed up the amount of cervical mucus I had. That allowed the sperm to get through the cervix".

Other positive effects: Several participants described their ability to rebound quickly from an acute illness, and improvement in gastrointestinal and diabetes symptoms. One participant noted that while on lumacaftor/ivacaftor, "any time that I've gotten really sick in the past eight months, it hasn't been as bad as it used to be". Another participant reported, "For the first time in years, my hemoglobin A1C has spontaneously gone down. It's been around 6.1 for a very long time, and now it's 5.8, so that was a huge shock and exciting".

Negative effects of lumacaftor/ivacaftor

A few participants identified negative effects of the drug. One participant described her experience: "I started taking it, and I was doing all right until it was getting hard to breath… I couldn't cough anything up… It [chest] was just tight. I had to stop taking it". She took the drug for two weeks without any appreciable positive effects so her CF care team decided to discontinue the medication. Another participant who was taking the drug at the time of the interview described side effects related to her menstruation and gastrointestinal system: "I've had more bowel movements… five times a day, that's a lot. Then I was supposed to start my menstrual cycle yesterday [and] I haven't yet". Another participant reported that the drug "can make you bleed more; it can make you miss periods". Lastly, several described how the lumacaftor/ivacaftor can "decrease the effectiveness of the birth control pill" and had to switch to another form of contraception while on the drug.

Unknown effects of lumacaftor/ivacaftor

Several participants described that the drug, as new as it is, may have unknown effects, especially on their reproductive system. Some were waiting to start the drug at the recommendation of their CF care team because they were actively trying to conceive. The majority of the participants shared their concerns about the unknown effects of the drug on a developing fetus, and reported that the drug needs to be studied further to investigate its safety in pregnant women and fetus. One participant described how the drug "might harm the baby", and another participant described her concern and frustration with the lack of definitive advice given by her CF care team on this issue: "I'm definitely concerned [about teratogenic effects]…I haven't found anyone that's willing to have that conversation with me. Neither my CF team nor the fertility team is willing to go beyond basic speculation… I need to know more, and to the point where I think that I will try and get in touch with someone at Vertex [drug maker]".

The one participant who became pregnant while on lumacaftor/ivacaftor was initially concerned about possible teratogenic effects, but after consulting with her obstetrician, CF care team and Vertex, she decided to stay on the drug for the duration of her pregnancy, and reported, "I'm not concerned about it at all anymore because the baby is actually measuring ahead of time, and he's already measuring above what he should be".

Needing comprehensive RSH education and counseling by the CF care team

All of the participants described how they learned about their potential fertility challenges from various sources, with two of the participants hearing it from the CF care team at an earlier age than they would have liked. Other participants described how they received guidance and education from their primary care physicians, gynecologists, parents, and personal research using online CF resources. One participant shared that her parents were instrumental in normalizing her life and future, "My parents said, 'It doesn't matter what the doctor says. You can…do it [get pregnant]… and we'll figure it out".

There was no uniformity in how RSH information was disseminated, and participants reported a desire for more collaboration with their CF care team when discussing pregnancy plans. Several described how their CF care team dissuaded them from becoming pregnant, or did not provide information on other ways (e.g., assisted reproductive technology, gestational carrier, adoption) to achieve motherhood. One participant reported: "We had decided on our own to actively try, and with or without their [CF care team] blessing, we were going to do it. However, we did tell them that we were trying, and of course they tried to talk me out of it, and said, 'You should do it a different way and it's not safe'. Me and my husband, we decided that we weren't gonna listen to them. We were gonna do it our way... They really didn't give any options. They just kinda said, 'You shouldn't do it.' Their idea was, 'Do it our way or we're not gonna really support; we'll watch you and we'll guide you, but we're not gonna support you trying [to get pregnant]". She summed up her frustration with the lack of comprehensive care she received from her CF care team: "Their approach is just to keep me as healthy as they can for as long as they can, and their approach is just towards my CF, not my body as a whole".

One participant who believed she became pregnant due to lumacaftor/ivacaftor experienced strong resistance from her CF care team after she decided that she wanted to stay on the drug throughout her pregnancy. She described that, "it was kind of an argument... because they wanted me to stop it, but I had felt so good for the first three weeks [of taking the drug], and I didn't want to NOT be on it, specifically during my pregnancy, because my lungs obviously were doing better on it". She shared that her obstetrician and CF care team

consulted with the makers of the drug to make sure it was safe to use during pregnancy. She reported that she did not have any negative effects during her pregnancy.

Wanting to have a child despite knowing or suspecting impaired fertility

All of the participants wished to have at least one child despite knowing or suspecting that they may have problems conceiving secondary to CF. All of the participants also shared that they know they may have impaired fertility, and seven theorized that thick mucus blocking the cervix and/or fallopian tube may be the culprit. One participant voiced that, "Going to the gynecologist before, she always said [I had] a vast amount of cervical mucus". Another participant who was actively trying to conceive reported, "I know that it would be more difficult for me because of the mucus. I knew it would be more difficult in the long run". Another participant described how a hysterosalpingogram cleared the mucus blocking her fallopian tubes: "During that procedure, my tubes were blocked. They asked permission to go ahead and push the dye through to see if it would unblock. It did. Two weeks later, [my daughter] was conceived".

The majority of the women were exploring all options to become mothers. This includes the use of egg donors, gestational surrogacy, assisted reproductive technology, and adoption. A participant described her experience, "There were many years of my life when I was not on birth control and in long-term relationships and I never got pregnant. We didn't use condoms. That's when I knew… I'm gonna have to seek other assistance". She was the same woman who became pregnant after the hysterosalpingogram, years before lumacaftor/ivacaftor was approved for use.

Several sought assistance from fertility specialists, had their partners tested for the CF gene prior to starting treatment, and reported that they did not want to wait until later in life to have children due to their inevitable declining health. A participant reported, "Life's already short enough that I [want to] be able to maximize my time with my child". Another participant who was undergoing *in vitro* fertilization (IVF) at the time of the interview shared that she was acutely aware that the younger she was and the better her lung function, the better her chances of conceiving a child. She added, "Another part of the decision-making process of why we wanted to do this [IVF] now, as opposed to six or eight years from now is that I have a lot of healthy years ahead of me, and I wanna be able to share that with my children as much as possible."

Several participants shared that being on lumacaftor/ivacaftor made it possible for them to make plans for the future, which includes being mothers. One woman shared, "The future is definitely bright… We're ready to have kids…It's possible for me".

Discussion

This study illustrated that women with homozygous F508del mutation are generally knowledgeable about certain fertility concepts, and self-reported knowledge were comparable between those with CF and those without CF. The educational levels for both the CF and non-CF groups were comparable. Both groups were highly educated, and their self-reported knowledge on fertility concepts reflected their education and experience. Areas of less knowledge (i.e., infertility work-up, genetic transmission of CF, and role of cervical mucus pH) require additional research to inform educational interventions.

Several quantitative findings from our study were consistent with those of Korzeniewska et al. in which 80% of that sample (vs. 100% in our study) reported knowing the need for contraception in women who have CF to prevent unplanned pregnancy [27]. Additionally, consistent with a similar study done on the reproductive and sexual health of men with CF, most of the women in our study reported wanting to have children but lacked the knowledge on assisted reproductive technologies and the process related to infertility diagnostics and treatment [23]. In fact, in the study by Korzeniewsk et al. none of the participants knew about assisted reproductive technologies [27]. Both the quantitative and qualitative results from our study validate the knowledge gap that exists in women with CF in terms of their full reproductive options, including alternative paths such as surrogacy and adoption.

Our study also demonstrates there continues to be a general lack of knowledge related to the genetic transmission of CF. In a 1995 study, Sawyer et al. reported that while over 50% of women who had CF reported that it is important to know the genetic risks involved with having a child, only 15% were able to accurately explain their chances of having a child who has CF. While our small pilot showed that 50% understood the inheritance pattern of CF, this increase in knowledge since 1995, most likely due to the ease of obtaining information over the internet, shows that a dire need for education on genetic transmission still remains [22].

Additionally, women with CF included in our study also reported a lack in knowledge on how cervical mucus pH impacts reproduction and fertility. While 70% of women who had CF reported a lot of knowledge on the effects of cervical mucus thickness on fertility, only 30% reported a lot of knowledge on the impact of cervical mucus pH on fertility. Cervical mucus viscosity has been widely accepted as the root cause of infertility in women with CF, however, it has only been recently that attention is given to the critical role of cervical mucus pH in the reproductive tract's fluid microenvironment [11]. To our knowledge, there is no large study found in the literature that reported on CF women's knowledge of cervical mucus pH as it relates to fertility and reproductive health. Herein lies the potentially unique contribution of our pilot study, and one that could lead to a large scale study in the future.

Our study also reveals that women with CF want to become mothers even with potentially impaired fertility. While there is currently no clear evidence that show lumacaftor/ivacaftor improves fertility, these women are hopeful that targeted therapeutics will make their dream of motherhood a reality. They are also aware of the drug's effects and concerned about its unknown effects on the fetus.

Findings from our study demonstrate that women with CF need comprehensive clinical care, and this includes sensitive and timely discussions on reproductive health and family planning. The narratives that emerged from our study are consistent with those from a recent study by Kazmerski et al. in which women with CF reported that their disease is a major factor in pregnancy decision making, and yet they were disappointed in the lack of support and comprehensive care they received from their CF care team when the topic of reproductive health was broached [33]. In fact, a participant in the study, echoed the same sentiments about the lack of comprehensive care she received from her CF care team, "I don't think [CF providers] think about vaginas. I think they just think about lungs [33]". The discouragement and disapproval that the participants received from their CF care team when pregnancy plans are shared illustrates the need for improved communication and sensitive counseling. Another study by Kazmerski

et al. reported that both patient and provider discomfort in initiating sexual and reproductive health (SRH) discussions poses a significant barrier in the provision of comprehensive care [34]. The study also highlighted the need for SRH educational resources and provider training to improve SRH care, as well as standardization around SRH care in the current CF care model [35].

The qualitative findings from our study support the notion that has been suggested in previous studies that targeted therapeutics like lumacaftor/ivacaftor, which systematically alter the basic defect in the CF protein, may, in fact, lead to positive changes in women's fertility by changing the properties of their cervical mucus as seen in other systems (e.g., pulmonary and gastrointestinal) [6,36,37]. A case report of a woman's unanticipated pregnancy after using ivacaftor for five months appears to mirror what the one participant in the current study experienced when she described becoming pregnant after being on lumacaftor/ivacaftor for two weeks [38].

Additional research needs to be done to determine whether targeted therapeutics for CF affects women's fertility and reproductive health. One such study could investigate whether lumacaftor/ivacaftor affects the viscoelasticity of the woman's cervical mucus by comparing the mucus properties of those who are on the drug versus those who are not on the drug versus healthy controls. Another study could investigate whether lumacaftor/ivacaftor affects reproductive endocrinological function, and to test the hypothesis that the drug can alter the women's hormonal profile to improve their fertility.

Limitations

The high level of educational achievement in both the CF and non-CF groups may have potentially biased the overall results and affect the overall generalizability of the study findings to the larger population. Additionally, the small sample size of this pilot study requires caution in extrapolating findings to the general population of women with CF. However, despite the limited generalizability, the survey responses and narratives shared by the group of women with CF provide a critical first step in understanding the complexity of female fertility in this era of personalized medicine so that healthcare providers can adequately meet their unique needs.

Conclusion

This pilot study with its mixed methods research approach opens up new frontiers in the care of young women with cystic fibrosis. Findings from this study, specifically the gaps in knowledge evident from the survey responses and the unique perspectives offered by this group of women during the interviews can be used to design the next steps in clinical education, care provision and research.

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