Use of estrogen supplementation is associated with higher quality of life scores in women with cystic fibrosis

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ABSTRACT

The association of estrogen supplementation use and quality of life in women with cystic fibrosis (CF) is not well characterized. In this cross-sectional study, women with CF completed quality of life questionnaires during a routine CF clinic visit. The use of estrogen supplementation was associated with higher quality of life scores in all domains of the CF questionnaire-revised (CFQ-R) and was significant in the role limitations and respiratory domains. Most participants who were not currently using estrogen supplementation had previously used estrogen supplementation. Most participants had used estrogen to regulate menses, prevent pregnancy and control symptoms around menses. Use of estrogen supplementation was not associated with differences in life-space mobility or screening for sexual dysfunction. This is the largest study to date investigating the association of estrogen supplementation and quality of life in women with CF. Prospective randomized studies are needed to clarify the association of estrogen supplementation and quality of life in women with CF.

Introduction

Cystic fibrosis (CF) is a multi-organ disease affecting over 30,000 people in the US [1] and more than 70,000 globally [2]. CF results from mutations of the CF transmembrane conductance regulator (CFTR) gene [3]. With rapid advancements in medical therapies to treat CF, the median predicted survival for individuals born with CF is now in the fifth decade [1]. These medical therapies still require daily time-intensive treatments and medications that may need to be performed or taken multiple times each day. As survival increases, so too does the prevalence of extra-pulmonary manifestations of CF such as CF-related diabetes and CF-related bone disease, which affect more adults with CF than children with CF [1].

In addition to extra-pulmonary complications of CF, an increasing number of people with CF self-report having anxiety (15%) or depression (16.7%) [1], which in turn is associated with decreases in quality of life and respiratory function [4]. In individuals without CF, many factors contribute to increased risk for having depression including having a chronic illness [4], stress, female sex and decreases in estrogen levels such as occurs during surgical menopause or perimenopause [5,6]. Women with CF have been shown to have low estrogen levels [7] and delayed puberty indicating hypogonadism compared to age-matched controls without CF [8]. The association of estrogen supplementation and quality of life was recently explored in 12 women with CF who were started on estrogen supplementation for two months by Holtrop and colleagues using the CF questionnaire-revised (CFQ-R) [9]. The CFQ-R is a CF-disease specific health-related quality of life instrument that assesses quality of life across 12 domains. The participants had improved CFQ-R respiratory, treatment burden and health perceptions domain scores compared to their baseline before initiating estrogen supplementation. However, it is not known if estrogen use is associated with changes in the other domains of the CFQ-R.

Abbreviations: CF, Cystic fibrosis; CFTR, CF transmembrane conductance regulator; CFQ-R, CF questionnaire-revised; FEV1, Forced expiratory volume in 1 second; BMI, Body mass index; FSFI-6, Female Sexual Function Index-6; LSA, Life Space Assessment; SD, Standard deviation; OCP, Oral contraceptive pill; MCID, Minimal clinical important difference; FDA, Food and Drug Administration.

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The purpose of this study was to investigate differences in quality of life in women with CF using estrogen supplementation compared to women with CF not using estrogen supplementation. Quality of life was assessed by the CFQ-R. In this cross-sectional study, women with CF seen in the CF clinic for routine care underwent detailed interviews regarding previous estrogen use and were administered questionnaires.

Methods

Study design

This was a single center, cross-sectional study to examine the association of estrogen supplementation in women with CF on quality of life. The study was approved by the Emory University Institutional Review Board. All participants provided informed consent for participation in this study. Participants were eligible if they were female, diagnosed with CF, between 16 and 50 years old and presenting to the CF clinic for routine care. Due to the COVID-19 pandemic, eligibility was modified to include participants who were presenting virtually to the CF clinic for a telemedicine appointment. Exclusion criteria included current use of systemic steroids, previous lung or liver transplant, or being too ill to participate. From October 4, 2019, to October 30, 2020, participants were recruited during a routine clinic visit at the Emory University Adult CF center in Atlanta, GA, to complete questionnaires and be interviewed about use of estrogen supplementation. Participants were interviewed about current and historical use of estrogen- and progesterone-containing medications, the reasons for use, the duration of use, the route and dose of the medication. The medical record was reviewed for historical prescriptions of estrogen-containing medications, and participants were asked prompted about these prescriptions to confirm if they had taken the prescriptions. Additional demographic and clinical information were extracted from their medical records including CFTR mutation, FEV1 (forced expiratory volume in 1 s), and body mass index (BMI).

Questionnaires

CFQ-R [10]: The CFQ-R is a CF-specific health-related quality of life instrument with 12 domains scored from 0 to 100. Higher scores reflect better quality of life. The CFQ-R respiratory domain score is approved by the Food and Drug Administration (FDA) for use as a patient-reported outcome in clinical trials; the minimal clinical important difference (MCID) of the CFQ-R respiratory domain is four (4) [11]. Although a threshold of 4 is commonly used in CF quality of life research to represent the MCID in each of the CFQ-R domains, to our knowledge, MCID for the other 11 domains of the CFQ-R have not yet been established. Participants were administered the CFQ-R Teen/Adult version which is validated for participants with CF older than 14 years of age. The CFQ-R also collects demographic information including marital status, education level, employment status and racial background.

FSFI-6 [12]: The Female Sexual Function Index-6 (FSFI-6) is an abridged form of the Female Sexual Function Index which is a diagnostic test for female sexual dysfunction validated for use in women who were sexually active in the previous four weeks. The responses to the six questions form a composite FSFI-6 score; scores less than or equal to 19 are concerning for female sexual dysfunction. The maximum score is 30; higher scores reflect better quality of life. The FSFI-6 was only administered to participants who responded that they had been sexually active in the previous four weeks. This questionnaire has been used in adolescent and young adult women with CF [13].

LSA [14]: The Life Space Assessment (LSA) is a measure of a person’s mobility through five areas of their environment: from their bedroom to beyond their town. The maximum score is 120; higher scores reflect improved mobility. LSA score ≤ 60 reflect that a community-dwelling adult is “restricted”. This questionnaire was designed for the geriatric population, but the LSA has previously been used in people with CF [15,16].

Statistical methods

Descriptive statistics were compiled. Continuous variables were visually inspected to assess normality. Baseline demographics that were continuous variables and the LSA scores are reported as mean (standard deviation) and were compared between estrogen supplemented and non-supplemented groups by T test. Categorical variables are reported as count (percentage) and were compared between estrogen supplemented and non-supplemented groups by Chi square test or Fishers exact test if rare. CFQ-R domain scores and FSFI-6 scores were non-parametrically distributed and are reported as median (interquartile range). CFQ-R domain scores were compared between estrogen supplemented and non-supplemented groups by Kruskal Wallis test, with a Bonferroni correction for multiple comparisons. The CFQ-R domain scores overall were compared by Wilcoxon rank sum between estrogen supplemented and non-supplemented groups. The FSFI-6 scores and FSFI-6 composite scores are reported as median (interquartile range) and were compared between estrogen supplemented and non-supplemented groups by Kruskal Wallis test. Analysis was done with SAS version 9.4 (Cary, NC). Significance was set to 0.05.

Results

Study participants

A total of 26 participants consented to participation in this study. Eleven participants were taking estrogen supplementation, and fifteen participants were not. The participants taking estrogen and the participants not taking estrogen had similar baseline characteristics (Table 1).

Estrogen status

The participants currently taking estrogen supplementation were all using an oral contraceptive pill containing ethinyl estradiol and progesterone. The mean ethinyl estradiol dose was 22.9 mcg (SD 9.0 mcg), with a range of 10–40 mcg/day. They had been using estrogen supplementation for at least six months prior to participation. Only four (36%) participants reported they were currently using estrogen supplementation as contraception. Other reasons for using estrogen supplementation included control of symptoms around menses (64%), regulation of menses (36%), treatment of acne (27%) and prevention of recurrence of ovarian cysts (9%) (Table 2).

History and indications for estrogen

In addition to the eleven participants currently taking estrogen supplementation, ten (67%) of the non-supplemented participants had previously taken estrogen supplementation. Four participants had stopped less than 1 year prior to participation, stopping at least 3 months prior to participation; the other six participants had stopped more than 2 years prior to participation. Participants had used estrogen-containing medications for 2 months to 4 years. Most participants reported having used estrogen supplementation for regulation of menses that were irregular, heavy, frequent, or prolonged (52%), for contraception (43%), to control symptoms around menses (33%), or to treat acne (29%) (Table 2). Additional reasons to use estrogen supplementation included treatment of catamenial hemoptysis (5%), prevention of ovarian cysts (5%), pain due to endometriosis (5%), polycystic ovarian syndrome (5%), and for in vitro fertilization treatment (5%). The 21 participants who had used estrogen supplementation had all used a combined oral ethinyl estradiol and progesterone product. One participant had also previously used transdermal ethinyl estradiol combined with progesterone, and another participant had also used transvaginal ethinyl estradiol combined with progesterone. One participant had additionally
Impact of estrogen on quality of life

Compared to women not taking estrogen supplementation, women taking estrogen supplementation had higher CFQ-R domain scores in physical functioning, vitality, treatment burden, role limitations, weight, respiratory symptom scale and digestion symptom scale (Table 3). However, when correcting for multiple comparisons, this only remained statistically significant in the role limitations domain ($p = 0.02$). The difference in the median of each CFQ-R domain between the groups was greater than 4 for each CFQ-R domain pair. The women taking estrogen supplementation had consistently higher CFQ-R domain scores than women not taking estrogen supplement ($p = 0.0005$, Wilcoxon rank sum test).

**Impact of estrogen on sexual function**

A total of 14 participants had been sexually active in the previous 4 weeks: four participants taking estrogen and ten participants not taking estrogen supplementation. The estrogen supplemented and non-supplemented groups had similar FSFI-6 composite scores (Table 4). Two participants in each group had scores $\leq 19$ signaling female sexual dysfunction.

**Impact of estrogen on mobility**

The mean LSA score of all participants was 88 (SD 19). LSA scores were similar between the estrogen supplemented and non-supplemented groups ($p = 0.4$). Estrogen supplemented participants had a mean LSA score of 85.3 (SD 15.9) and non-supplemented participants had a mean LSA score of 90.5 (SD 20.6). Only one participant in each group had restricted Life-Space mobility with a LSA score less than 60.

**Discussion**

In this cross-sectional study, current use of estrogen supplementation by women with CF was associated with improved quality of life as assessed by the CFQ-R pairwise in all CFQ-R domains and overall. When comparing pairwise by each CFQ-R domain and adjusting for multiple comparisons, this remained statistically significant in the role limitations domain ($p = 0.02$). The difference between estrogen supplemented and not supplemented groups was greater than the minimal clinical important difference in the respiratory domain ($p = 0.06$). There were
CF highlights that women with CF are using estrogen supplementation products that are not used for contraception. Our sample of women with CF includes 26 participants—14 taking estrogen and 11 not taking estrogen. Few studies of women with CF have examined estrogen-containing products and have not necessarily distinguished different formulations.

In a recent prospective study by Holtrop and colleagues, 23 women with CF were assessed repeatedly during their regular ovulatory cycle and then 12 women continued in a sub-study during which they initiated 2 months of oral contraceptive pill (OCP) containing 30 mcg ethinyl estradiol and progesterone [9]. While on OCP, the participants had statistically significantly decreased sputum markers of inflammation: neutrophil free elastase, IL-8 and TNF-alpha relative to ovulation when not taking OCP. While on OCP, participants had increased CFQ-R respiratory, treatment burden and health perceptions domain scores, compared to when they had been menstruating or ovulating. Our results affirm Holtrop and colleagues’ recent findings that estrogen supplementation is associated with higher CFQ-R domain scores [9]. Unlike Holtrop and colleagues, we found that estrogen supplementation was associated with higher CFQ-R domain scores in all domains with a difference greater than 4 in each domain. Our findings may relate to a longer duration of estrogen supplementation amongst our estrogen-supplement participants and comparing intra-patient vs inter-patient differences in CFQ-R domain scores.

Our results support previous findings in women without CF that estrogen supplementation improves quality of life in postmenopausal women. Postmenopausal women with intact uteri randomized in the Women’s Health Initiative to conjugated equine estrogens with progesterone or placebo had small but statistically significant improvements in some domains of the RAND-36, a general health-related quality of life measure.

no significant differences by FSFI-6, a tool to assess female sexual dysfunction, between the estrogen supplemented and not supplemented groups. Four participants (15.4%) had low FSFI-6 scores, concerning for female sexual dysfunction [12], which was similar to adolescent and young adult females with CF from five CF centers in the US (16%) [13]. The most common reasons for ever using estrogen supplementation were controlling menses, contraception and reducing premenstrual symptoms.

Previous studies of the role of estrogen supplementation for women with CF have focused on outcomes of inflammation [17–19], pulmonary function [18,19], nutrition [19], and bone mineral density [20,21]. Oral contraceptive use by women with CF has been associated with decreased frequency of acute pulmonary exacerbations, decreased bone mineral density, similar declines in FEV1 and similar BMI compared to women with CF not using oral contraception [17–21]. Most previous studies in women with CF have analyzed the use of contraceptive products and have not necessarily distinguished different formulations and routes of estrogen or combination estrogen and progesterone from progesterone only; previous studies on participants using contraception may have included progesterone-only contraception users in the analysis. Few studies of women with CF have examined estrogen-containing products that are not used for contraception. Our sample of women with CF highlights that women with CF are using estrogen supplementation for more reasons than just contraception.

### Table 3
CFQ-R Results.

| CFQ-R Domain                  | All participants (N = 26) | Taking estrogen (N = 11) | Not taking estrogen (N = 15) | P value | Difference in median scores |
|-------------------------------|---------------------------|--------------------------|-----------------------------|---------|-----------------------------|
| Physical Functioning          | 85.4 (37.5, 100)         | 100 (83.3, 100)          | 70.8 (29.2, 95.8)           | 0.19*   | 29.2                        |
| Vitality                      | 58.3 (41.7, 66.7)        | 66.7 (50, 83.3)          | 50 (25, 58.3)               | 0.24*   | 16.7                        |
| Emotional State               | 76.7 (66.7, 86.7)        | 80 (66.7, 93.3)          | 66.7 (50, 80)               | 1.03*   | 13.3                        |
| Eating disturbances           | 100 (77.8, 100)          | 100 (77.8, 100)          | 88.9 (66.7, 100)            | 2.36*   | 11.1                        |
| Treatment burden              | 66.7 (44.4, 77.8)        | 66.7 (55.6, 88.9)        | 55.6 (33.3, 66.7)           | 0.39*   | 11.1                        |
| Health perceptions            | 66.7 (44.4, 88.9)        | 77.8 (55.6, 100)         | 66.7 (44.4, 88.9)           | 0.99*   | 11.1                        |
| Social                        | 72.2 (55.6, 83.3)        | 77.8 (55.6, 94.4)        | 72.2 (50, 83.3)             | 2.70*   | 5.6                         |
| Body image                    | 77.8 (66.7, 100)         | 88.9 (66.7, 100)         | 77.8 (55.6, 100)            | 1.72*   | 11.1                        |
| Role/School                   | 79.2 (58.3, 91.7)        | 91.7 (83.3, 100)         | 58.3 (41.7, 83.3)           | 0.015*  | 33.3                        |
| Weight (symptom scale)        | 100 (66.7, 100)          | 100 (100, 100)           | 66.7 (33.3, 100)            | 0.11*   | 33.3                        |
| Respiratory (symptom scale)   | 69.4 (44.4, 83.3)        | 83.3 (72.2, 94.4)        | 44.4 (38.9, 72.2)           | 0.06*   | 38.9                        |
| Digestion (symptom scale)     | 83.3 (66.7, 100)         | 100 (77.8, 100)          | 77.8 (66.7, 100)            | 0.38*   | 22.2                        |

*Bonferroni correction of Kruskal Wallis test, †Wilcoxon Rank Sum Test.

CFQ-R domain scores by estrogen supplementation status. The minimal clinical important difference for the CFQ-R is 4. The median CFQ-R domain score for estrogen supplemented participants was consistently higher than the median CFQ-R domain score of non-supplemented participants (p = 0.0005, Wilcoxon rank sum test); this difference was more than 4 points in each domain. Reported P value comparing each domain is the Bonferroni correction of Kruskal Wallis test.

### Table 4
Female Sexual Function Index-6 Results.

|                     | All participants (N = 14) | Taking estrogen (N = 4) | Not taking estrogen (N = 10) | P value |
|---------------------|---------------------------|-------------------------|-----------------------------|---------|
| Libido              | 4.0 (3, 4)                | 3.0 (2.45)              | 4.0 (3, 4)                  | 0.46*   |
| Arousal             | 4.0 (3, 5)                | 3.0 (2.5, 4)            | 4.0 (4, 5)                  | 0.24*   |
| Lubrication         | 4.0 (3, 5)                | 2.5 (1.5, 4)            | 4.5 (4, 5)                  | 0.14*   |
| Orgasm              | 3.5 (2.5)                 | 3.0 (2.45)              | 3.5 (2, 5)                  | 0.83*   |
| Satisfaction        | 5.0 (3, 5)                | 2.0 (1.5)               | 5.0 (4, 5)                  | 0.15*   |
| Dyspareunia         | 4.5 (3, 5)                | 4.5 (3, 5)              | 4.5 (3, 5)                  | 0.94*   |
| Composite score     | 22.0 (18, 28)             | 17.5 (12.5, 24.5)       | 24.0 (2, 28)                | 0.32*   |
| Female sexual dysfunction | 4.0 (15.4%)          | 2 (50.0%)               | 2 (20.0%)                   | 0.52*   |

The FSFI-6 is validated for use in women who were sexually active in the previous 4 weeks. A composite score from summing the results from the six questions less than 19 is concerning for female sexual dysfunction. The median and interquartile range or count and percentage are reported for continuous and categorical variables respectively.

*Kruskal Wallis test, †Chi-Square Test, ‡Fisher’s Exact Test.

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Our results support previous findings in women without CF that estrogen supplementation improves quality of life in postmenopausal women. Postmenopausal women with intact uteri randomized in the Women’s Health Initiative to conjugated equine estrogens with progesterone or placebo had small but statistically significant improvements in some domains of the RAND-36, a general health-related quality of life measure.
of life survey [22]. There is less data regarding estrogen supplementation for quality of life of premenopausal women. In an industry-sponsored study of premenopausal women initiating a specific OCP containing 30 mcg ethinyl estradiol and progesterone, participants had improved mental component summary scales of the SF-12, another general health-related quality of life instrument, after two months of using this OCP compared to their baseline scores before initiating this OCP, in addition to reduction of premenstrual symptoms [23]. A cross-sectional study of university students in Spain using the SEC-QOL, a Spanish contraception-specific quality of life instrument, found that women using contraception had higher SEC-QOL scores and that women using hormonal contraception had higher SEC-QOL scores than women using non-hormonal contraception [24].

Estrogen has similarly been shown to improve depressed mood in women. Women with acute decreases in estrogen levels, i.e. surgically post-menopausal women, perimenopausal and recently post-menopausal and post-partum women, are at an increased risk for depression. In a double-blinded placebo-controlled randomized control trial of 100 mcg transdermal 17-beta estradiol for 12 weeks, more perimenopausal women with depression or dysthymic mood disorder randomized to estradiol had remission of their depression than women randomized to placebo [25]. Similarly, postpartum women with newly diagnosed major depressive disorder randomized to estradiol supplementation more rapidly had resolution of their depressed symptoms than the women randomized to placebo [26].

The association of estrogen with higher quality of life scores in women with CF may relate to the physiologic suppression of ovulatory estradiol surges affecting respiratory pathophysiology and inflammation or relate to the demographic and clinical reasons for which participants had chosen to use estrogen supplementation. Additionally, women with depression have larger amplitudes of fluctuation of estradiol levels within a menstrual cycle [27]; these fluctuations in estrogen level would be suppressed with the use of estrogen supplementation. The use of estrogen in contraception by premenopausal women has also ameliorated premenstrual symptoms, which may further improve quality of life scores in women taking contraception. In addition to suppressing estradiol fluctuations, estrogen receptors are widely distributed in the brain, and estrogen is involved in multiple neurochemical pathways. Synthetic estrogens, including ethinyl estradiol, bind to the estrogen receptors. Furthermore, it is possible that a person who can focus on aspects of their health not directly related to their chronic disease and thus chooses to start estrogen supplementation may experience better quality of life than a person who is only focused on treatment of their CF.

Our study is limited by its small sample size and cross-sectional study design. Due to the small size of our study, analysis of subgroups of participants such as by lung function or employment status was not done. To our knowledge, with 26 participants, this is the largest study of the association of estrogen supplementation and quality of life in women with CF. Our study is strengthened by the detailed interview with participants regarding current and previous estrogen use, instead of relying on prescription or pharmacy data; however, it is limited by recall bias of events that may have occurred more than a decade earlier. Unfortunately, few participants recalled the details of previous estrogen doses; however, they did recall if they used combination OCP or progesterone-only OCP products and the reasons for using estrogen-containing products. Participants were not interviewed about their quality of life beyond the questionnaires administered. Participants’ study visit overlapped with their routine clinical visit and was not scheduled with respect to their menstrual cycle or timing of placebo contraceptives. Participants who had previously used estrogen containing products but were not currently taking estrogen products were included in the analysis as not currently taking estrogen products which further limits our conclusions.

In conclusion, current use of estrogen supplementation was associated with higher quality of life scores in women with CF in this cross-sectional study. These are promising findings as women with CF may be considering using estrogen supplementation for contraception or other purposes. Larger, prospective randomized studies and qualitative studies are needed to clarify the association of estrogen supplementation and quality of life for women with CF.

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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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