Hormonal Contraception Effects on Pulmonary Function in Adolescents with Cystic Fibrosis

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A B S T R A C T

Study Objective: Estrogens are suspected to have a negative effect on pulmonary function in women with cystic fibrosis (CF). The aim of our study was to investigate, in a CF adolescent population, the effect of hormonal contraception (HC) on lung function by assessing the forced expiratory volume in 1 second (FEV1), the number of exacerbations of pulmonary condition, and antibiotic use.
Design, Setting, Participants, Interventions, and Main Outcome Measures: We conducted a cohort retrospective chart review of girls from age 13 to 18 years old who were followed in the CF clinic of a university hospital center. Wilcoxon rank sum test with continuity correction, 2-sample *t* test, conditional test of Poisson rates, and χ^2 test were conducted to identify differences in results between adolescents with or without use of HC for the following outcomes: FEV1, use of antibiotics by nebulizer, and hospital admission for exacerbations of pulmonary condition.
Results: Among 127 adolescents, 64/127 (50.4%) took HC; 12/127 (9%) continuously had been taking HC over 3 years. For girls taking HC for more than 3 years, FEV1 at 18 years old was significantly higher than for girls who had never taken HC (85.17% vs 71.05%; $P = .043$). However, there was no difference in the number of hospital admissions for exacerbation of pulmonary condition between these 2 groups ($P = .057$). There was no difference between HC vs non-HC users in the percent of patients taking antibiotics by nebulizer over the 6 years of follow-up.
Conclusion: Our study suggests that in adolescents with CF, HC has no deleterious effects on the FEV1. Further prospective studies could be done to confirm these results.
Key Words: Cystic fibrosis, Hormonal contraception, Pulmonary function

Introduction

Cystic fibrosis (CF) is a lethal genetic disease, most common in populations of northern European descent, among whom the disease occurs in approximately 1 in 3000 births.[1] In recent years, life expectancy has increased in CF patients, the median age of survival being 37 years old, which is in the range of reproductive age.[2] Thus, more and more women with CF use hormonal contraception (HC), some starting early during adolescence.

Few studies address sexuality and contraception in adult women with CF and even fewer in adolescent women with CF. However, a 1995 study showed comparable rates of sexual activity in CF patients compared with the general population, but as found in other patients with chronic diseases, CF patients used less effective methods of contraception, resulting in unwanted or unplanned pregnancies.[3] In 2015, Rousset Jablonski et al reported that in 120 CF women of childbearing age (18-48 years old), only 64% were using contraception.[4] Among them, 65% were taking oral contraceptives (estrogen and progestin or progestin-only pill), 18% used condoms, 10% had an intrauterine hormonal or copper device, 3% the vaginal hormonal ring, and 4% used tubal ligation. In 2016, Roe et al interviewed 53 CF women (17-42 years old): 83% were sexually active but only 49% used contraception compared with 65% in a general population of Caucasian women.[5,6] The oral contraceptive pill and condoms were the most commonly reported methods of contraception in the CF group. More recently, in a study by Kazmerski et al of 188 women with a mean age of 19.7 (±2.7) years old, 54% reported having had vaginal sex with a male partner vs 66% in the general US population for the same age ($P = .55$)[7]; women with CF were less likely to have ever used contraception (55% vs 74%; $P = .0001$).

Female steroid hormones, especially estrogen, have an influence on the CF transmembrane conductance regulator (*CFTR*) gene, which is responsible for CF. This influence is known and proven since the 1990s,[8] when researchers described for the first time the hormonal upregulation of *CFTR* in vivo, implying estrogen as a physiological regulator of *CFTR* in the female reproductive tract. A study conducted with 32,766 patients showed that life expectancy for CF women was shorter than that of men (36.0 years vs 38.7 years; $P < .001$) and morbidity, especially lung

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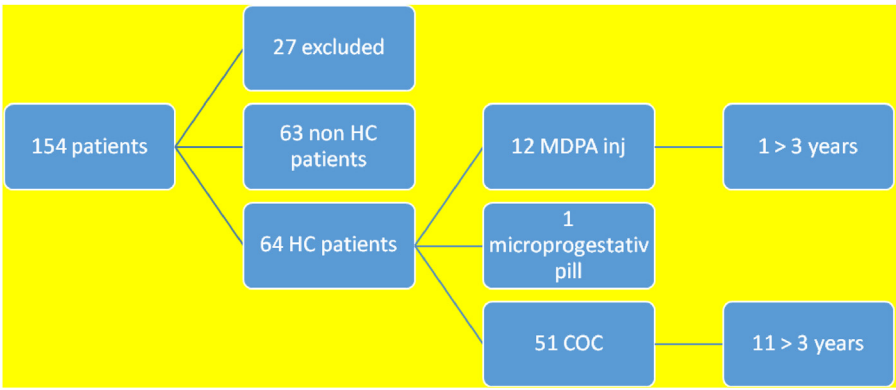

Fig. 1. Flow chart of patient selection for HC and non-HC groups. COC, combined oral contraception; MDPA inj, medroxyprogesterone acetate injection.

infections with *Pseudomonas aeruginosa*, was higher.[9] These results led to the suspicion of a negative effect of physiological hormonal cycles in women with CF. In addition to its action on the gene, estrogens could play a negative role in infection, inflammation, and mucociliary clearance. It is thus important to determine if HC use is safe for these patients.

Despite the small amount of data in the adult CF population, HC seems to be effective and not harmful, and might even have lung benefits as shown in some studies.[10–13] To our knowledge, no data have been published in the adolescent population.

The aim of our study was to investigate, in adolescents with CF, the effect of HCs on lung function by assessing the forced expiratory volume in 1 second (FEV1), the number of exacerbations of pulmonary condition, and antibiotic use.

Materials and Methods

The study was a retrospective cohort study with chart review.

All girls between 13 and 18 years old inclusively, followed at the CF clinic of a large university hospital center between 1989 and 2007, were included in the study. Patients were excluded from the study if they had fewer than 5 measures of FEV1 in the time frame of the study.

The HC group was defined by girls who took at least 6 months of any type of HC from the age of introduction until the end of the follow-up (younger than 19 years old). The non-HC group was defined by girls who were not taking contraception during the 6 years of follow-up from 13 years old.

In the clinic, all adolescents with CF were followed every 3 months. At each appointment, many questions were asked systematically as well as a medical examination and tests performed. The medical records seem to have been completed very well. Especially for the use of HC, even if not prescribed by the team, questions were asked and regular use assessed.

Data were collected from the medical records by only 1 investigator using a standardized grid. For all girls, baseline data were collected: date of birth, age at diagnosis, age at menarche, and comorbidity. From 13 years old, data were collected every 3 months until the final visit at CF clinic, before19 years old, and data on every hospitalization were recorded.

Data on the following items were collected: weight, height, body mass index, FEV1 (expressed in percentage), nebulized or oral antibiotics, hospitalizations for worsening of the pulmonary condition, contraception (type and age of introduction, continuity of use), adherence to various treatments, smoking, and drug use. To compare the groups HC and non-HC, we collected some family and personal data to avoid biases of social problems on hormonal contraceptive use. Exacerbation of pulmonary condition was defined as the need to hospitalize the patient because of complications or worsening of the pulmonary disease.

Tests were conducted to identify differences between adolescents who use HC or not (HC group and non-HC group) using Wilcoxon rank sum test with continuity correction, 2-sample *t* test, conditional test of Poisson rates, and χ^2 test. Quantitative data were expressed as mean (±SD). The significance level was $P < .05$.

The project was approved by the ethics review board of the center (2966). Informed consent was obtained from all individual participants included in the study.

Results

Population

One hundred fifty-four adolescent girls were followed in the clinic from 1989 to 2007. Only 127 patients fulfilled the inclusion criteria of more than 5 FEV1 measures. The mean age at diagnosis was 27.3 months and at menarche was 13.5 years old. No more than 1.09% of data were missing.

Among the 127 patients, 64/127 (50.4%) took HC at least 6 months continuously (HC group) during the study period (Fig. 1), starting contraception between 14 and 18 years old. Two patients died during the follow-up period and they were in the non-HC group.

At baseline (13 years old), none of the patients were taking HC or reporting sexual activities. Also, the 2 groups (HC and non-HC) did not differ significantly on sociofamilial characteristics (family environment, family problems, psychosocial disorders, mental disorders, school attendance, school grade) or tobacco use (Table 1). Between groups, clinical data were also comparable: body mass index was respectively 0.02 (±1.11) vs 0.18 (±1.12); Z score, not significant (NS); FEV1, 77.47% (±19.2) vs 76.37% (±20.09; NS); number of hospitalizations for exacerbation of pulmonary condition, 3.06 (±3.47) vs 2.54 (±3.71; NS).

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Table 1
Comparison Between Patients With and Without Contraception (HC Group vs Non-HC Group) at 13-Year-Old Baseline According to Sociofamilial Characteristics

Characteristic	All	HC Group	Non-HC Group	Statistic (*df*)
Family environment	A: 73 (57.48%)	A: 34 (53.13%)	A: 39 (61.90%)	$\div^2$ (4) = 2.75; *P* = .601*
A: Both parents	B: 14 (11.02%)	B: 9 (14.06%)	B: 5 (7.64%)	
B: Reconstituted	C: 17 (13.39%)	C: 9 (14.06%)	C: 8 (12.70%)	
C: Single-parent	D: 4 (3.15%)	D: 3 (4.69%)	D: 1 (1.59%)	
D: Foster care	E: 12 (9.45%)	E: 7 (10.94%)	E: 5 (7.94%)	
E: Shared custody	NA: 7 (5.51%)	NA: 2 (3.13%)	NA: 5 (7.94%)	
Family problems	Yes: 96 (75.59%)	Yes: 47 (73.44%)	Yes: 49 (77.78%)	$\div^2$ = 0.324; *P* = .620†
	No: 26 (20.47%)	No: 15 (23.44%)	No: 11 (17.46%)	
	NA: 5 (3.94%)	NA: 2 (3.13%)	NA: 3 (4.76%)	
Behaviour, adaptation or psycho-social disorders‡	Yes: 44 (34.65%)	Yes: 25 (39.06%)	Yes: 19 (30.16%)	$\div^2$ (1) = 0.546; *P* = .460*
	No: 81 (63.78%)	No: 39 (60.94%)	No: 42 (66.67%)	
	NA: 2 (1.57%)	NA: 0 (0%)	NA: 2 (3.17%)	
Mental disorder§	Yes: 26 (20.47%)	Yes: 15 (23.44%)	Yes: 11 (17.46%)	$\div^2$ (1) = 0.274; *P* = .601*
	No: 99 (77.95%)	No: 49 (76.56%)	No: 50 (79.37%)	
	NA: 2 (1.57%)	NA: 0 (0%)	NA: 2 (3.17%)	
School attendance	Yes:118 (92.91%)	Yes: 61 (95.31%)	Yes: 57 (90.48%)	$\div^2$ = 1.40; *P* = .122†
	Yes, with absenteeism: 3 (2.36%)	Yes, with absenteeism: 0 (0%)	Yes, with absenteeism: 3 (4.76%)	
	NA: 6 (4.72%)	NA: 3 (4.69%)	NA: 3 (4.76%)	
School level	A: 10 (7.87%)	A: 5 (7.81%)	A: 5 (7.94%)	$\div^2$ = 0.000; *P* = 1.00†
A: Appropriate	B: 111 (87.40%)	B: 56 (87.50%)	B: 55 (87.30%)	
B: Fall behind	NA: 6 (4.72%)	NA: 3 (4.69%)	NA: 3 (4.76%)	

NA, non available.
* χ^2 Test.
† χ^2 Test with simulated *P* value on the basis of 2000 replicates for variables with expected frequency less than 5 in at least 1 cell.
‡ Adjustment disorder, anxiety disorder, compliance disorder, eating disorders, somatization disorder.
§ Depression, adjustment disorder, phobias, attention-deficit/hyperactivity disorder.

The number of follow-up visits did not differ between the 2 groups. The HC group had a median of 9.000 follow-ups and the non-HC group had 8.136 follow-ups, for λ2/λ1 = 1.11; *P* = .101.

Contraception in the HC Group

The 64 adolescents who had been taking HC at least 6 months started at a mean age of 16 years and 5 months (±14 months; Fig. 1); the youngest was 14 years and 2 months, the oldest, 18 years and 4 months. Only 12 patients (9%) had used HC over 3 years continuously (HC > 3 years subgroup), having started at a mean age of 15 years and 3 months.

Pulmonary Function (FEV1)

During the follow up period, FEV1 decreased significantly in all adolescents with CF, from 76.92% (±19.58) to 70.42% (±21.66); *P* < .001.

No significant difference between HC and non-HC groups was shown in FEV1 at the last visit before 19 years old (Table 2). However, participants who had taken HC for more than 3 years had significantly higher scores of FEV1 than the participants who had never taken HC (85.17% vs 71.05%; *P* = .043).

At baseline, no patients reported tobacco use. At age 18, the 2 groups were not significantly different with 13% of patients smoking tobacco.

Hospitalization for Exacerbation of Pulmonary Condition

At 13 years old, 47/127 (37%) of patients had been hospitalized more than 2 times, 42/127 (33%), 1 or 2 times, and 38/127 (30%) had never been hospitalized. At the end of the follow-up, before 19 years old, we observed that there were more hospitalizations in the HC group for worsening of pulmonary condition. For this analysis, we removed a patient from the HC group hospitalized 25 times. However, when we compared the subgroup HC > 3 years vs non-HC group, no significant difference was observed between the 2 groups with regard to number of hospitalizations (*P* = .057; Table 2). Also, within the HC group (n = 64), there was no significant difference in the number of hospitalizations before the introduction of HC and after (2.31 vs 2.28; *P* = .95).

Table 2
Pulmonary Health in HC, Non-HC, and HC > 3 Years Groups at 18 Years Old

Variable	Non-HC Group (n = 63)	HC Group (n = 64)	HC > 3 years (n = 12)	Statistic (*df*)
Mean FEV1 (SD), range	71.05% (22.16), 19-116	69.80% (21.31), 23-112	85.17% (19.56), 57-109	*t* (125) = 0.324*; *P* = .746†
				t (73) = 2.06‡; *P* = **.043**†
Mean hospitalizations for worsening of pulmonary condition, n (SD), range	2.57 (3.96), 0-18	4.27 (5.23), 0-25	3.58 (4.78), 0-25	λ_2/λ_1 = 1.79*; *P* < .001§
				λ_2/λ_1 = 1.39‡; *P* = .057§
Atb Neb	78.7	85.0	80.0	χ^2 (1) = 0.810*; *P* = .368‖
				χ^2 = 0.009‡; *P* = 1.000‖

Atb Neb: percentage receiving nebulized antibiotics; FEV1, forced expiratory volume in 1 second; HC, hormonal contraception. Bold indicates significant *P* value (<.05).
* Result of the comparison between the non-HC and HC groups.
† *t* Test.
‡ HC > 3 years vs non-HC group.
§ Conditional test of Poisson rates.
‖ χ^2 Test with simulated *P* value on the basis of 2000 replicates for variables with expected frequency less than 5 in at least 1 cell.

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Table 3
Poisson Regression Model of HC, Tobacco Consumption, Age at Last Follow-up, and Follow-up Count Over Hospitalizations for Decompensation

Variable	B	Standard Error	Z	*P*
All				
Intercept	−3.80	1.33	−2.86	.004
HC	0.692	0.124	5.59	< .001
Tobacco	0.260	0.140	1.864	.062
Age at last follow-up	0.027	0.007	3.677	< .001
Follow-up count	−0.107	0.039	−2.75	.006
Outlier excluded				
Intercept	−2.52	1.55	−1.627	.104
HC	0.780	0.145	5.393	< .001
Tobacco	0.517	0.146	3.544	< .001
Age at last follow-up	0.018	0.008	2.242	.025
Follow-up count	−0.112	0.047	−2.410	.016

HC, hormonal contraception.

A Poisson regression model was computed using HC group, age at the last follow-up, tobacco consumption, and follow-up count over hospitalization for worsening of pulmonary condition (Table 3). All variables were significant to predict hospitalization and the HC group showed the greatest B at 0.692; $P < .001$.

Antibiotic Use

At 13 years old, 50/127 (39%) of the patients were using nebulized antibiotics, 108/127 (85%) were taking oral antibiotics, and 2/127 (1.6%) azithromycin. All of these percentages increased at the end of the follow-up. There was no significant difference in the percent of patients taking nebulized antibiotics over the 6 years of the study between the HC group and non-HC group (Table 2). It was the same for the subgroup HC > 3 years vs the non-HC group. There was no significant difference in the HC group before and after introduction of HC regarding the use of oral antibiotics (88.9% vs 79.4%; $P = .14$) or azithromycin (1.6% vs 6.6%; $P = .17$).

Discussion

This study is the first to our knowledge to be conducted with only an adolescent population with CF, aged 13-18 years old, with a retrospective observation of the evolution of the disease with regard to HC use.

Estrogens have been shown in the past to have an effect on *CFTR* gene expression,[8] unlike progesterone for which we have no data. More recently, lung function changes were found during menstrual cycles in women with CF[14]: FEV1 was significantly higher during the luteal phase (66% of predicted) compared with during the ovulation phase (63%) and menstruations (61%; $P < .01$). Estrogens would regulate specifically calcium-mediated chloride channels[10] and modulate *CFTR*. Taken together, these data support a detrimental effect on airway epithelial cell ion channel regulation.[15]

Decrease of FEV1 is known to be hastened in young patients.[11] As expected, we found an important decrease of FEV1 in our patients between 13 and 19 years old. However, in our study, taking HC did not alter the progression of the disease in terms of FEV1 values. In our subgroup of patients who took HC for more than 3 years, we found not only that HC does not decrease FEV1, but that HC could minimize that decrease of FEV1. Despite a small number of patients who took HC for more than 3 years (12 patients), we found a statistically significant difference compared with those who had not used HC, suggesting a beneficial effect on lung function after several years of HC, certainly due to inhibition of ovulation.

In comparison, Kernan et al,[11] in a retrospective cohort study, reported data from an annual review of CF female patients aged 16-45 years for at least 4 years, compared women who never used HC with HC users. They reported no significant differences between those exposed and those not exposed to HC in median annual change in FEV1.

Contrary to what has been shown in adults,[12] we observed more hospitalizations for exacerbation of pulmonary condition in the HC group vs non-HC group at the end of the follow-up, but it does not seem to be related to the HC because we found no difference between those not taking HC and those taking HC more than 3 years, even if the *P* value was close to significant. However, there was no difference in number of hospitalizations before the introduction of HC and after. We have no explanation for this result. A broader study should be able to improve our knowledge on this topic.

No significant difference was found between HC and HC > 3 years groups vs the non-HC group regarding the use of antibiotics oral or nebulized, nor was there any difference before and after the introduction of contraception. However, the negative effect of natural estrogens on *P aeruginosa* pulmonary infections has already been shown in vitro and in vivo; in vitro, estrogen can modulate the formation of *P aeruginosa* biofilms through suppression of activated protein kinase, lactoferrin.[16] Estradiol was also found to induce mucoid conversion of *P aeruginosa*, more resistant to antibiotics.[12] In an adult population, a study of 77 women with CF suggested that estradiol (natural estrogen secreted mainly by the ovaries during the follicular phase and ovulation) increases the number of exacerbations of pulmonary condition, by causing a greater number of infections and worsening of pulmonary condition during the first phase of the cycle.[12] However, in their recent literature review, Chotirmall et al[6,12] concluded that HC might reduce pulmonary exacerbation rates and decrease the need for antibiotics. Our result could be because younger CF patients use antibiotics more often[11] and the length of HC use was too short to observe a difference. Moreover, the subgroup of HC > 3 years was small, thus preventing statistical power. Because the number of progestin-only users was small, it was not possible to compare subtypes of hormonal contraceptives.

Moreover, in the future, adoption of new therapies that alter the *CFTR* defect, such as ivacaftor and lumacaftor/ivacaftor, might limit the use of hormonal contraceptives because they decrease their efficacy.[17]

This study has some limitations. CF is a rare disease; the sample was limited to 127 patients. Because it was a study with adolescents, we have only 6 years of follow-up and the number of patients who took the contraception more than 3 years in this sample was low (9%). The adherence to hormonal contraceptive was assessed only by questioning

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adolescents, which is not always accurate. However, none were pregnant.

In conclusion, our study suggests that in adolescents as in adults with CF, HC has no deleterious effects on the evolution of FEV1. Further prospective studies could be done to confirm these results.

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