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 χ² 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 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)6; 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,7 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
infections with *Pseudomonas aeruginosa*, was higher.\(^9\) These 
results led to the suspicion of a negative effect of physio-
logical 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 popu-
lation, 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, fol-
lowed at the CF clinic of a large university hospital center 
between 1989 and 2007, were included in the study. Pa-
tients 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 contra-
ception 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 last visit at CF clinic, 
before 19 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 contracep-
tive use. Exacerbation of pulmonary condition was defined 
as the need to hospitalize the patient because of complica-
tions 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 \(\chi^2\) test. Quantitative data were expressed as mean 
(\(\pm SD\)). The significance level was \(P \lt 0.05\).

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, psy-
chosocial 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 (\(\pm 1.11\)) vs 0.18 (\(\pm 11.12\)) ; \(Z\) score, not sig-
nificant (NS); FEV1, 77.47% (\(\pm 19.2\)) vs 76.37% (\(\pm 20.09\) ; NS); 
number of hospitalizations for exacerbation of pulmonary 
condition, 3.06 (\(\pm 3.47\)) vs 2.54 (\(\pm 3.71\) ; NS).

\(\text{Fig. 1. Flow chart of patient selection for HC and non-HC groups. COC, combined oral contraception; MDPA inj, medroxyprogesterone acetate injection.}\)
Table 1
Comparison Between Patients With and Without Contraception (HC Group vs Non-HC Group) at 13-Year-Old Baseline According to Sociofamilial Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All</th>
<th>HC Group</th>
<th>Non-HC Group</th>
<th>Statistic (df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family environment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Both parents</td>
<td>14 (11.02%)</td>
<td>19 (14.66%)</td>
<td>5 (7.64%)</td>
<td>-.2 (4) = 2.75; P = .601</td>
</tr>
<tr>
<td>B: Reconstituted</td>
<td>17 (13.39%)</td>
<td>14 (10.94%)</td>
<td>5 (7.94%)</td>
<td></td>
</tr>
<tr>
<td>C: Single-parent</td>
<td>7 (5.51%)</td>
<td>2 (3.33%)</td>
<td>5 (7.94%)</td>
<td></td>
</tr>
<tr>
<td>D: Foster care</td>
<td>12 (9.45%)</td>
<td>10 (7.94%)</td>
<td>5 (7.94%)</td>
<td></td>
</tr>
<tr>
<td>E: Shared custody</td>
<td>7 (5.51%)</td>
<td>10 (7.94%)</td>
<td>5 (7.94%)</td>
<td></td>
</tr>
<tr>
<td>Family problems</td>
<td>NA: 7 (5.51%)</td>
<td>NA: 2 (3.33%)</td>
<td>NA: 5 (7.94%)</td>
<td></td>
</tr>
<tr>
<td>Behaviour, adaptation or psycho-social disorders</td>
<td>Yes: 96 (75.59%)</td>
<td>Yes: 47 (74.44%)</td>
<td>Yes: 7 (77.88%)</td>
<td>+.2 = 0.324; P = .620</td>
</tr>
<tr>
<td>Mental disorder</td>
<td>No: 26 (20.47%)</td>
<td>No: 15 (23.44%)</td>
<td>No: 11 (17.46%)</td>
<td></td>
</tr>
<tr>
<td>School attendance</td>
<td>Yes: 78.7 (85.0)</td>
<td>Yes: 55 (87.5)</td>
<td>No: 11 (17.46%)</td>
<td></td>
</tr>
<tr>
<td>School level</td>
<td>Yes: 44 (34.65%)</td>
<td>Yes: 25 (39.06%)</td>
<td>Yes: 19 (30.16%)</td>
<td>+.2 (1) = 0.546; P = .460</td>
</tr>
</tbody>
</table>

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 $\lambda_1 = 1.11$; $P = .101$. 

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 ($\pm$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% ($\pm$19.58) to 70.42% ($\pm$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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-HC Group (n = 63)</th>
<th>HC Group (n = 64)</th>
<th>HC $&gt; 3$ years (n = 12)</th>
<th>Statistic (df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean FEV1 (SD), range</td>
<td>71.05% (22.16), 19-116</td>
<td>69.80% (21.31), 23-112</td>
<td>85.17% (19.56), 57-109</td>
<td>t (125) = 0.324*; P = .746</td>
</tr>
<tr>
<td>Mean hospitalizations for worsening of pulmonary condition, n (SD), range</td>
<td>2.57 (3.96), 0-18</td>
<td>4.27 (5.23), 0-25</td>
<td>3.58 (4.78), 0-25</td>
<td>t (73) = 2.06; P = .043</td>
</tr>
<tr>
<td>Atb Neb</td>
<td>78.7</td>
<td>85.0</td>
<td>80.0</td>
<td>$\chi^2$ (1) = 1.79*; P = .189</td>
</tr>
</tbody>
</table>

Atb Neb: percentage receiving nebulized antibiotics; FEV1, forced expiratory volume in 1 second; HC, hormonal contraception. Bold indicates significant P value (<.05).
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, unlike progesterone for which we have no data. More recently, lung function changes were found during menstrual cycles in women with CF: 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 and modulate CFTR. Taken together, these data support a detrimental effect on airway epithelial cell ion channel regulation.

Decrease of FEV1 is known to be hastened in young patients. 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., 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, 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. Estradiol was also found to induce mucoid conversion of P. aeruginosa, more resistant to antibiotics. 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. However, in their recent literature review, Chotirmall et al., 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 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.

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

### Table 3

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

<table>
<thead>
<tr>
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<th>B</th>
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<th>Z</th>
<th>P</th>
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<td>All</td>
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<tr>
<td>Intercept</td>
<td>-3.80</td>
<td>1.33</td>
<td>-2.86</td>
<td>.004</td>
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<tr>
<td>HC</td>
<td>0.692</td>
<td>0.124</td>
<td>5.59</td>
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<tr>
<td>Tobacco</td>
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HC, hormonal contraception.
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.

References