Use of Oral Contraceptives in Women with Cystic Fibrosis

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Oral contraceptive pills (OCP) represent the most common contraceptive method among teenagers and young adults. Because many women with cystic fibrosis (CF) are now surviving into childbearing age and are at risk for the complications of pregnancy in CF, oral contraceptive use may be indicated. However, it has been suggested that OCP use by CF patients may be associated with deterioration in pulmonary function. Ten adolescent and young adult women with CF and moderate-to-severe obstructive lung disease were studied while taking a combination oral contraceptive pill (Ovral 28). No significant deterioration was found in clinical status or pulmonary function. Careful follow-up should nevertheless be continued to monitor for other adverse effects of oral contraceptive use in CF, such as cholelithiasis.

Many women with cystic fibrosis (CF) are now surviving to childbearing age.  With this improved outcome, issues related to sexuality and reproduction are pertinent to physicians caring for CF patients. Although there are no published data concerning fertility rates in women with CF, it has been estimated that fertility is less than 20 percent of that observed in a comparable group of unaffected women, probably due to thick, tenacious cervical mucus with a decrease in water content. Nevertheless, pregnancy is not uncommon in women with CF, and it may represent a significant risk to both mother and offspring unless the mother's clinical status is excellent.

In 1980, Cohen et al reported the results of a survey of 129 pregnancies which occurred in 100 patients with CF. Although the mortality of pregnant women with CF was not higher than the mortality of nonpregnant women with CF, a higher than expected rate of preterm births and perinatal deaths and an increased incidence of maternal complications were observed in CF patients. Because of these risks of pregnancy, the effectiveness and risks of various contraceptive methods are of major concern in this group of patients.

Although combined oral contraceptive pills (OCP) represent the most common contraceptive method among teenagers and young adults, little information is available on their use in patients with CF. Polypoid cervicitis and Candida vaginitis have been reported in association with OCP use in CF patients. It has also been suggested that OCP use by CF patients may be associated with marked deterioration in pulmonary status.

This previous report did not include pulmonary function studies, and therefore, a prospective study was undertaken to examine the effect of OCP use on the clinical status and pulmonary function of women with CF.

**Methods**

**Patient Selection**

All menstruating females, 13 to 30 years of age who attended the Cystic Fibrosis Centers at the Johns Hopkins Hospital and the National Institutes of Health, and who requested oral contraceptive therapy for dysmenorrhea or family planning were invited to participate in the study. Excluded from the study were patients who had been menstruating for less than one year, and those with a history of hypertension, thromboembolism, an abnormal Pap smear, or clinical evidence of cirrhosis or cholelithiasis. The study was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions and informed consent was obtained from all participants.

**Patient Profiles**

The study sample consisted of ten patients ranging in age from 15 to 24 years (mean of 19.7 years). Nine were white, and one was black. The mean age at diagnosis was 6.5 years (range one to 16 years). These patients had relatively mild clinical disease as evidenced by a Shwachman-Kulczycki mean score of 81.2 (range 70 to 94), based on activity, physical examination, nutritional status, and chest roentgenogram findings. A clinical score of 86 to 100 is considered excellent; 71 to 85, good; 56 to 70, mild; 41 to 55, moderate; and 40 and below, severe. Two patients smoked tobacco (one pack a day for four years). Two patients had diabetes mellitus requiring daily insulin therapy. One patient had a history of a cholecystectomy for cholelithiasis. All ten patients had normal liver function tests (transaminases and alkaline phosphatase). Nine of the women requested birth control pills for family planning; in one patient, oral contracep-
tive therapy was used to treat dysmenorrhea (after other medications had failed).

The mean age of menarche was 14.2 years (range 12 to 15 years). Stages for secondary sex development were normal as evidenced by a mean Tanner stage of 4.5. Among the ten patients, there had been one previous pregnancy which terminated in a spontaneous abortion. Three patients had a history of Candida or Trichomonas vaginitis, and one had a history of pelvic inflammatory disease. Prior to the onset of the study, contraceptive methods included foam/condoms (three) and diaphragm (one). Of the six remaining patients, five used no method of birth control, and one patient had not been sexually active.

**Oral Contraceptive Selection**

The oral contraceptive used in the study was a combination pill containing norgestrel 0.5 mg and ethinyl estradiol 0.05 mg (Ovral 28). It was selected for the following reasons: (a) the recommended maximum estrogen dose for adolescents is 0.05 mg; (b) using this estrogen dose would minimize the possibility of breakthrough bleeding; (c) ethinyl estradiol does not require hepatic hydroxylation and conjugation for activity; and (d) norgestrel is the most potent form of progesterone available in combination oral contraceptives, and it has little androgenic or estrogenic effect.

**Study Protocol**

The ten women were evaluated over a six-month period while receiving OCP therapy. Prior to initiation of oral contraceptive therapy, each patient had the following: counselling for family planning and/or dysmenorrhea; a physical and gynecologic examination including Pap smear, cervical swab slide examination for Trichomonas, cultures for Candida and gonococcal infection; respiratory questionnaire regarding current health status; and arterial blood gas (axillary site) and pulmonary function testing (PFTs). A physical examination was not performed unless the respiratory symptom questionnaire revealed one of the following: change in sputum production or cough frequency, fever, decrease in appetite, change in exercise tolerance, or recent pulmonary infections.

After beginning oral contraceptive therapy, patients were reevaluated with a respiratory symptom questionnaire (to identify patients with acute pulmonary exacerbations), arterial blood gas levels, and PFTs at two weeks, and two, four, and six months. Pulmonary function tests were performed at the same time of day and at the same midmenstrual cycle point for each patient. Pulmonary function testing consisted of spirometry (FVC, FEV₁, FEV₁/FVC x 100) using a 9-L water filled spirometer; lung volumes (total lung capacity [TLC], functional residual capacity [FRC], and residual volume [RV]) measured in a variable pressure body plethysmograph; diffusing capacity for carbon monoxide (D.CO) by the single breath method; and total minute ventilation (VT) and alveolar ventilation (VA) by timed collection of expired gases at rest. Gynecologic examination with a Pap smear and vaginal culture was repeated only at the six-month visit unless the patient was symptomatic for vaginitis or pelvic inflammatory disease.

An acute pulmonary exacerbation was defined as a change in clinical status, ie, cough, sputum production, exercise tolerance, auscultatory or chest x-ray findings, significant enough to warrant a change in therapy.

At the end of the six-month study period, data were tabulated and pulmonary function test results analyzed by the paired Student's t-test.

**RESULTS**

Baseline pulmonary function studies in the ten subjects are summarized in the Table. In general, despite their good clinical scores, these patients had significant lung disease with moderate-to-severe airways obstruction (mean FEV₁ of 56 ± 20 [SD] percent predicted, range 29 percent to 81 percent), air trapping (mean residual volume 217.8 ± 58.1 [SD] percent predicted, and RV/TLC ratio of 49.2 ± 10.0 percent), and mild-to-moderate hypoxemia (mean PaO₂ 71.8 ± 12 [SD] mm Hg, range 62 to 99). None was hypercapnic.

Pulmonary function test results were compared at baseline, two weeks, and two, four, and six month intervals to determine the effect of OCP on pulmonary function. During the study period, no significant changes between time periods were observed in spirometric values, lung volumes, diffusing capacity, and total minute or alveolar ventilation (p > 0.05). There was a slight fall in PaCO₂ at two weeks compared to baseline values (p < 0.05), but the PaCO₂ was not significantly different from values at any other time interval. Results of serial measurements of FEV₁, lung volumes, PaO₂, and PaCO₂ for the patients are shown in Figures 1 through 3.

During the study period, four patients developed acute pulmonary exacerbations treated with oral antibiotics, and one patient required hospitalization for intravenous antibiotic therapy. No difference was ob-

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*Expressed as percent predicted, except as noted.
episodes of Trichomomas vaginitis were seen; both occurred in patients with a prior history of Trichomomas infection. One patient developed a recurrence of pelvic inflammatory disease. Cervical cultures were negative, and the patient improved after a ten-day course of tetracycline. Throughout the six month study period, no cervical polyp was noted, and no abnormality was seen on Pap smears. Four patients were reevaluated one year after the start of the study; all had normal Pap smears, and none had evidence of polypoid cervicitis. Lastly, as evidenced by baseline and six- or 12-month liver function studies, physical examinations and histories, there was no evidence of cholelithiasis or liver disease related to OCP use.

Throughout the study period, no other adverse effects of oral contraceptive therapy were noted, and there were no pregnancies.

**DISCUSSION**

Although there are several alternative methods, combination birth control pills represent the most successful and frequently used contraceptive method among teenagers and young adults. No previous data are available on the physiologic effects of OCP use in CF, but concerns have been raised over their use in these patients. Dooley et al reported clinical deterio-
oration in two of four women with CF within a few months after starting various combination oral contraceptives. It was speculated that progesterone in OCP could stimulate airway mucus production and lead to impaired lung function. In contrast to these anecdotal observations regarding OCP, we did not find any evidence of significant deterioration in lung function or an increase in acute pulmonary exacerbations in ten CF patients followed carefully for six months.

Healthy women show a variety of cardiopulmonary changes while receiving OCP, including vasodilation, increased blood volume, and increased pulmonary capillary blood volume. The separate components of combination pills have also been shown to have physiologic effects at higher doses. Progesterone can increase minute ventilation, reduce alveolar CO₂ tension, and enhance ventilatory responses to hyperventilation or hypoxemia. Administration of estrogen decreases the carbon monoxide diffusing capacity. Thus, physiologic changes might occur in CF patients receiving oral contraceptives due to these effects and could result in altered gas exchange or ventilatory studies. This present study excluded any major deterioration in lung function associated with oral contraceptive use, but intrasubject variability of pulmonary function studies reduces the sensitivity of these tests in detecting small changes. Therefore, large differences in pulmonary function variables, such as diffusion capacity, would have to occur before being accepted as significant. A slight fall was observed in PaCO₂ at two weeks on OCP which is consistent with an increase in ventilation secondary to progesterone effect. However, there was no significant increase in measured ventilation, and in doing multiple paired Student's t-tests, it is possible that a significant difference might be found by chance alone. Further specific studies of control of ventilation with OCP use in CF are necessary to confirm this preliminary observation.

In addition to possible pulmonary effects, there are a number of other complications associated with OCP use for which CF patients may be at increased risk. Normal women receiving oral contraceptives have twice the risk of cholelithiasis, presumably due to alteration in the composition of bile with an increased concentration of cholesterol. Patients with CF also have an increased risk of cholelithiasis and other abnormalities of the gallbladder. None of our patients developed clinical evidence of cholelithiasis, although one had a history of prior cholecystectomy. Longitudinal liver function studies and possibly ultrasonography of the gallbladder should be monitored in women with CF while on OCP.

Atypical polypoid endocervical hyperplasia has been observed in normal women receiving oral contraceptives. On biopsy examination, there is microglandular hyperplasia along with inflammatory cell infiltrates, squamous epithelial cell dysplasia, and increased mucus production. Although the etiology of these changes is unknown, among patients showing these changes and in whom the duration of OCP use was known, all had been receiving oral contraceptives for longer than six months, and the majority for over 12 months. Dooley et al. reported similar polypoid cervicitis changes in three of four CF patients who were using OCP. Changes were noted two, five, and 12 months following initiation of OCP use. In this present study, polypoid cervicitis was not observed over a six-month period (ten patients) or a 12-month period (four patients) of OCP use. However, it is important to continue gynecologic examinations and periodic Pap smears in all CF patients who are using OCP.

Five episodes of Candida vaginitis were observed, four of which occurred following antibiotic therapy, and two episodes of Trichomonas vaginitis. This is consistent with the observation that both antibiotic therapy and OCP use increase the risk for Candida vaginitis. There are no data concerning the baseline incidence of Candida or Trichomonas vaginitis in CF patients who are not on OCP.

Intrauterine devices (IUD), condoms, vaginal foams, rhythm, withdrawal, and douching are all associated with higher contraceptive failure rates than oral contraceptives. Since pregnancy can represent a life-threatening risk in patients with CF, contraceptive methods with high failure rates should be avoided. Intrauterine devices have a twofold higher failure rate when compared to OCP and are associated with several significant complications, including pelvic infections, dysmenorrhea, and uterine perforation. Although the diaphragm is an effective contraceptive in well-motivated women, failure rates are high in adolescents. Thus, use of the diaphragm should probably be avoided in young teenagers and older women who are not well motivated. However, it is otherwise a safe and acceptable alternative to OCP for women with CF.

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