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Lung function changes in relation to menstrual cycle in females with cystic fibrosis

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Oestrogen and progesterone have been shown to have impact on cystic fibrosis transmembrane conductance regulator (CFTR) gene expression, tone of smooth muscle in the airways, immune response, exhaled nitric oxide and cytology in the tracheobronchial epithelium. The aim of this investigation was to study the influence of menstrual cyclicity on airway symptoms among cystic fibrosis (CF) females.

Twelve CF women (mean age 30 years, mean Shwachman score 85) kept daily records during three menstrual cycles of lung function, sputum quality and need for intravenous antibiotics. Paired *t*-test was used as a statistical method to compare the airway symptoms between the time of ovulation (high levels of oestrogen and low levels of progesterone), the luteal phase (high levels of oestrogen and progesterone) and menstruation (low levels of oestrogens and progesterone).

Forced expiratory volume in 1 sec (FEV_1) was significantly higher during the luteal phase (66% of predicted) compared to during ovulation (63%) and menstruation (61%) ($P<0{\cdot}01$). Forced vital capacity (FVC) showed the same pattern, being significantly higher during the luteal phase compared with during menstruation (mean 75% *vs.* 70%, $P<0{\cdot}01$).

In conclusion, lung function changes were found during menstrual cycles in women with cystic fibrosis. These changes are probably related to changes in progesterone levels during the menstrual cycles. This result warrants further studies to understand the complexity of CF lung disease in women.

Key words: cystic fibrosis; females; lung function; menstrual cycle.

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Introduction

Cystic fibrosis (CF) is the most common autosomal recessive lethal disease among the Caucasian population. It is caused by mutations of the gene encoding for cystic fibrosis transmembrane conductance regulator (CFTR). CFTR is a cAMP-regulated chloride channel, ATP-transporter and a regulator of sodium channels. CF is characterized by abnormal thick mucus with symptoms mainly from the respiratory and gastrointestinal tract (1).

Previous studies have shown that sexual hormones have impact on CFTR mRNA expression, (2,3), the tone of smooth muscle in the airways (4), airway responsiveness (5) the immune response (6) and exhaled nitric oxide (NO) (7). The tracheobronchial epithelium also shows cytological changes during the menstrual cycle (8).

In our experience it is not unusual that female patients with CF have reported worsening of lung symptoms prior to menstruation. Therefore, we wanted to study whether the menstrual cyclicity of sexual hormones influences lung function and airway symptoms among these patients.

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Methods

Twelve CF women with regular menstruation, now using oral contraceptives, kept daily records during three menstrual cycles on lung function, sputum quality and need for intravenous antibiotics.

Clinical status was evaluated by Schwachman score (9) and pulmonary function by micro-spirometer (Micro Medical Ltd, Chatham, Kent, U.K.) in the morning before inhalation of bronchodilators and chest physiotherapy. Forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1) were compared with appropriate reference values and expressed as percentage of the reference values (10). The patients were asked to subjectively score the degree of tenacity of sputum on a scale from one to four. Intravenous antibiotic treatments were started when the patients presented one or several signs of low-grade infection (11).

Three time periods during menstruation were chosen from the daily records for comparison. (1) Ovulation, 24 h

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after luteinizing hormone (LH) peak, with high levels of oestrogen and low levels of progesterone (12). For determination of LH peak, morning urine samples were collected from cycle days 10–15, using a self-test (Ovu Qvick: Monoclonal Antibiotics Inc. Sunnyvale, CA, U.S.A.). (2) The luteal phase, 6–8 days prior to menstruation, characterized by high progesterone and oestrogen levels. (3) Second to fourth day of menstruation with low levels of oestrogen and progesterone (12).

STATISTICS

Mean values for the three menstrual cycles were used in the analysis. Comparisons between mean FEV_1 and FVC during the three different time periods were made using ANOVA (repeated measurements) and paired *t*-test. FEV_1 and FVC was log-transformed in order to achieve a normal distribution. Comparisons between use of antibiotics and sputum quality between the three time periods were made with the Kruskal–Wallis test. The intra-individual correlation coefficient was calculated when comparing FEV_1 and FVC from the three menstrual cycles within in each subject. A *P*-value $< 0{\cdot}05$ was considered significant. The results are presented as mean $\pm$ SD.

Results

Patient characteristics are presented in Table 1. All but one of the patient were colonized with *Pseudomonas aeruginosa*. FEV_1 was significantly higher during the luteal phase $66 \pm 20\%$ compared to during ovulation $63 \pm 20\%$ and menstruation 61 ± 20 ($P < 0{\cdot}01$; Fig. 1). FVC showed the same pattern, being significantly higher during the luteal phase compared to during menstruation ($75 \pm 17\%$ *vs.* 70 ± 17, $P < 0{\cdot}01$; Fig. 2). Mean FVC during ovulation was lower ($72 \pm 18\%$) than during the luteal phase, but this difference was not statistically significant ($P = 0{\cdot}051$). The total number of courses of intravenous antibiotics was 28 during the 3-months study period. Nine of the courses were started during ovulation, eight during the luteal phase and 11 during menstruation (non-significant). No statistical difference in sputum quality was found when comparing the three time periods.

There were no significant differences in mean FEV_1 and FVC in the three menstrual cycles. The intra-individual correlation in FEV_1 and FVC in the three cycles varied between 0·95 and 0·99.

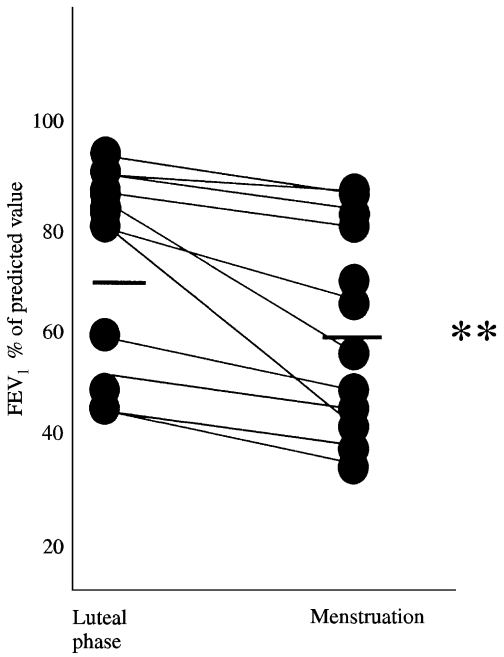

FIG. 1. Forced expiratory volume in 1 sec (FEV_1) during the menstrual cycle (individual changes and mean,** = $P < 0{\cdot}01$).

TABLE 1. Patient characteristics

Patient	Genotype*	Age	Age at diagnosis	Shwachman score	FEV_1† (% pred)	FVC† (% pred)
1	+/−	39	18	80	59	72
2	+/+	31	At birth	75	46	57
3	+/+	30	2	75	46	55
4	+/−	39	34	90	92	93
5	+/+	33	4	80	37	59
6	+/−	31	2	95	95	99
7	+/+	30	At birth	90	90	93
8	+/−	27	4	80	47	51
9	+/+	24	At birth	85	78	86
10	+/+	23	At birth	80	68	81
11	+/−	32	1	85	77	91
12	+/−	18	4	90	59	61

*+/+homozygous for delta F508, +/−heterozygous for delta F508.
†One week prior to menstruation.

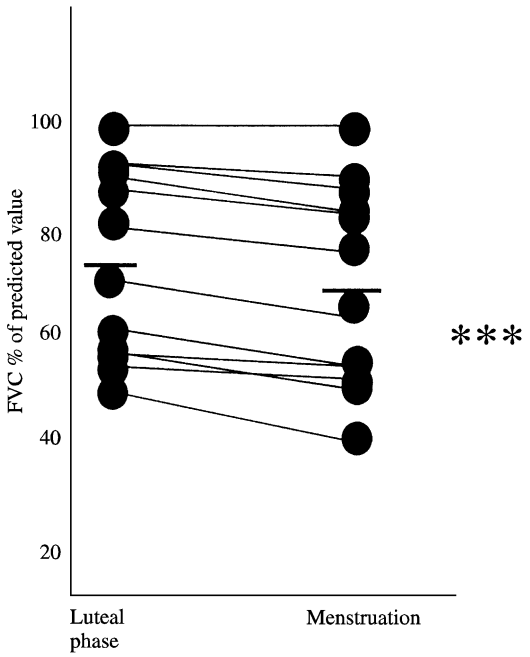

FIG. 2. Forced vital capacity (FVC) during the menstrual cycle (individual changes and mean,** = $P<0{\cdot}01$).

Discussion

In our study we found lung function changes during menstrual cycles in women with cystic fibrosis. This is in contrast to a previous, less extensive, study (13). This discrepancy might be related to the fact that we studied different time periods during the menstrual cycle and thereby different levels of sexual hormones (12).

Cystic fibrosis and asthma share common features such as bronchial responsiveness (14) and increased eosinophilic activation (15). There are reports of increased frequency of exacerbation of asthma during menstruation when progesterone and oestrogen levels are low (16). Increased bronchial responsiveness and decreased peak flow have also been found in women with asthma during the menstrual phase (5,17). The mechanism behind these menstrual cycle related changes are not known but previous studies have shown that progesterone may relax the tone of the smooth muscle in the airways (4). Leukotrienes seem to be partly involved in the pathogenesis of premenstrual exacerbations of asthma and leukotriene antagonists may prevent airflow obstruction in these patients (18). Changes in airway concentration of nitric oxide during the menstrual cycle with the lowest NO levels during menstruation have been observed (7). Although NO is a mediator of bronchodilation the physiological significance of this finding is still not known and inhaled NO at physiological levels present in the airways of normal individuals does not seem to change lung function in patients with cystic fibrosis (19).

The mean change in FEV_1 and FVC between the luteal phase and menstruation was 153 ml and 173 ml, respectively. This magnitude of change was relatively low and probably not clinically detectable in most patients. Only one patient had a mean decrease in FEV_1 above 10% of predicted during ovulation and menstruation compared to the luteal phase. The changes in FEV_1 and FVC were, however, consistent with higher lung function level during the luteal in nearly all patients. The luteal phase is characterized by high levels of both progesterone and oestrogen compared to ovulation when progesterone levels are low but oestrogen is high, and during menstruation when the levels of both sex hormones are low (12). This indicates that the changes in lung function in the present study were related to changes in progesterone levels. Our data is in accordance with the data on asthma exacerbations in women, where the lowest prevalence of exacerbations was found in the luteal phase (16).

We were unable to detect any statistical differences in sputum quality using a subjective scoring system or in the use of intravenous antibiotics during the menstrual cycle.

In conclusion lung function changes were found during menstrual cycles in women with cystic fibrosis. It is probably related to changes in progesterone levels during the menstrual cycles. This results warrants further studies to understand the complexity of CF lung disease in women.

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References

1. Davis PB, Drumm M., Konstan MW. Cystic fibrosis. *Am J Respir Crit Care Med* 1996; **154:** 1229–1256.
2. Rochwerger L, Buchwald M. Stimulation of the cystic fibrosis transmembrane regulator expression by estrogen *in vivo*. *Endocrinology* 1993; **133:** 921–930.
3. Mularoni A, Beck L, Sadir R, Adessi GL, Nicollier M. Down-regulation by progesterone of CFTR expression in endometrial epithelial cells: a study by competitive RT-PCR. *Biochem Biophys Res Comm* 1995; **217:** 1105–1111.
4. Foster PS, Goldie RG, Paterson JW, Effect of steroids on B-adrenoreceptor-mediated relaxation of pig bronchus. *Br J Pharmacol* 1983; **78:** 441–445.
5. Tan KS, McFarlane LC, Lipworth BJ. Modulation of airway reactivity and peak flow variability in asthmatics receiving the oral contraceptive pill. *Am J Resp Crit Care Med* 1997; **155:** 1273–1277.
6. Athreya BH, Pletcher J, Zulian F, Weiner DB, Williams WV. Subset-specific effects of sex hormones and pituitary gonadotropins on human lymphocyte proliferation *in vitro*. *Clin Immun Immunpath* 1993; **66:** 201–211.
7. Kharitonov SA, Logan-Sinclair RB, Busset CM, Shinebourne EA. Peak expiratory nitric oxide

differences in men and women: relation to the menstrual cycle. *Br Heart J* 1994; **72:** 243–245.
8. Chalon J, Loew DA, Orkin LR. Tracheobronchial cytologic changes during the menstrual cycle. *JAMA* 1971; **218:** 1928–1931.
9. Shwachman H, Kulczycki L. Long-term study on one hundred five patients with Cystic Fibrosis. *AMA J Dis Child* 1958; **96:** 6–15.
10. Quanjer, PhH. Standardized lung function testing. Report from Working Party 'Standardisation of lung function tests'. European Community for Coal and Steel. *Bull Europ Physiopath Resp* 1983; **19** (Suppl. 5): 45–51.
11. Strandvik B, Hjelte L, Malmborg A-S. Cystic fibrosis pulmonary infections: the Swedish experience. In: Bauernfeind A, Marks MI, Strandvik B, eds. *Cystic Fibrosis Pulmonary Infections: Lessons from Around the World*. Basel: Birkhäuser Verlag, 1996; 293–302.
12. Speroff L, Glass RH, Kase NG. Regulation of the menstrual cycle. In: Speroff L, Glass RH, Kase NG, eds. *Clinical Gynecological Endocrinology and Infertility*. 5th edn. Baltimore: Williams & Wilkins, 1994; 91–119.
13. Brascia TS, Thomas S, McGinley C, Diaz RP. Behaviour and pulmonary function changes during luteal phase in females with cystic fibrosis (abstract). *Ped Pulm* 1995; **8** (Suppl. 12): 256.
14. Sanchez I, Powell RE, Pasterkamp H. Wheezing and airflow obstruction during methacholine challenge in children with cystic fibrosis and in normal children. *Am Rev Respir Dis* 1993; **147:** 705–759.
15. Koller DY, Nething I, Otto J, Urbanek R, Eichler I. Cytokine concentrations in sputum from patients with cystic fibrosis and their relation to eosinophil activity. *Am J Respir Crit Care Med* 1997; **155:** 1050–1054.
16. Skobeloff EM, Spivey Wh, Silverman R, Eskin BA, Harchelroad F, Alessi TV. The effect of the menstrual cycle on asthma presentations in the emergency department. *Arch Int Med* 1996; **156:** 1837–1840.
17. Chandler MH, Schuldheisz S, Philips BA, Muse KN. Premenstrual asthma: the effect of estrogen on symptoms, pulmonary function and beta-2-receptors. *Pharmacotherapy* 1997; **17:** 224–2234.
18. Nakasato H, Ohrui T, Sekizawa K, Matsui T, Yamaya M, Tamaura G, Sasaki H. Prevention of severe premenstrual asthma attacks by leukotriene receptor antagonist. *J Allergy Clin Immunol* 1999; **104:** 585–588.
19. Ratjen F, Gartig S, Wiesemann HG, Grasemann H. Effect of inhaled nitric oxide on pulmonary function in cystic fibrosis. *Respir Med* 1999; **93:** 579–583.