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 (FEV1) was significantly higher during the luteal phase (66% of predicted) compared to during ovulation (63%) and menstruation (61%) (P<0.01). Forced vital capacity (FVC) showed the same pattern, being significantly higher during the luteal phase compared with during menstruation (mean 75% vs. 70%, P<0.01).

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.

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.

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 (FEV1) 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
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 Quick: 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 FEV₁ and FVC during the three different time periods were made using ANOVA (repeated measurements) and paired t-test. FEV₁ 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 FEV₁ and FVC from the three menstrual cycles within in each subject. A P-value < 0.05 was considered significant. The results are presented as mean ± sd.

Results

Patient characteristics are presented in Table 1. All but one of the patient were colonized with Pseudomonas aeruginosa. FEV₁ was significantly higher during the luteal phase 66±20% compared to during ovulation 63±20% and menstruation 61±20 (P<0.01; Fig. 1). FVC showed the same pattern, being significantly higher during the luteal phase compared to during menstruation (75±17% vs. 70±17, P<0.01; Fig. 2). Mean FVC during ovulation was lower (72±18%) than during the luteal phase, but this difference was not statistically significant (P=0.051). 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 FEV₁ and FVC in the three menstrual cycles. The intra-individual correlation in FEV₁ and FVC in the three cycles varied between 0.95 and 0.99.

TABLE 1. Patient characteristics

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<th>Age</th>
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<th>FVC (%) pred</th>
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</table>

*+/+ homozygous for delta F508, +/- heterozygous for delta F508.

†One week prior to menstruation.
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 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 cycle. This results warrants further studies to understand the complexity of CF lung disease in women.

Acknowledgements

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