ORIGINAL ARTICLE

COMBINED ORAL CONTRACEPTIVE PILLS IMPROVE LUNG FUNCTION VARIABLES

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Background: The combined oral contraceptive pill is an extremely effective method of contraception that also confers health benefits beyond pregnancy prevention. Oral contraceptive users have been found to have significantly higher total lung capacities when compared with nonusers. **Methods:** This study was carried out in Family Planning Centres at social obstetrical unit Baqai Medical University and Reproductive and Health Sciences (RHS) Institute, a family planning unit, at Jinnah Postgraduate Medical Centre Karachi, from November 2010 to April 2011. Fifty healthy non smoking women were given combined oral contraceptive pills containing Ethinyloestradiol 0.03 mg, Levonorgesterel 0.15 mg, ferrous fumerate 75.0 mg for six months. **Results:** At 6 months, Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV_1), FEV_1/FVC% and Peak Expiratory Flow Rate (PEFR) increased significantly. **Conclusion:** Combined oral contraceptives have a measurable effect on lung function variables.

Keywords: Combined oral contraceptive pills, Spirometry, Ethinyloestradiol, Levonorgestrel, skeletal muscle, hormone replacement therapy, oestrogen receptor

INTRODUCTION

Birth control methods have been used around the world for many thousand years. Contraception also includes barrier methods such as condoms or diaphragm and injectable contraceptives.[1] Hormonal contraception can be both contraceptive and contragestive which includes intrauterine contraceptive devices (IUCD). The most common methods of hormonal contraception include the combined oral contraceptive pill and the minipill.

Contraception is one of the keys tones of reproductive health. The availability of effective contraception has helped to change dramatically the structure of the world's population during the last 50 years, through a demographic transition involving lower fertility rates and longer survival. Oral contraception is an extremely effective method of contraception that also confers health benefits beyond pregnancy prevention.[2] The oral contraceptives were first approved for contraceptive use in the United States in 1960. The leading method of contraception in the United States is the oral contraceptive pill used by 11.6 million women.

Oral contraceptives are being used by more than 100 million women worldwide which varies generally by country, age, education, and marital status. Knowledge of family planning is widespread in Pakistan. According to a survey familiarity of any contraceptive method was 88%. About 65% of females were practicing one or other method of contraception whereas 35% were not practicing any method of contraception.[3] Awareness of the various contraceptive methods were as follows; 72.7% were familiar with combined oral contraceptive pill (COCP), 60.7% were aware of IUCD's. 71.3% with injections, 24.3% with Sterilization and 18.3% with breastfeeding.[3]

All COCPs are not alike and brands differ in the amount of oestrogen or progesterone they contain. Many Oral Contraceptive combined brands now use Lower Oestrogen doses than previous brands and are proving to be safe and effective while providing a better quality of life than earlier Oral Contraceptives.[4]

The COCP is an extremely effective method of contraception that also confers health benefits beyond pregnancy prevention. The effects on the reproductive system are most convincing, especially those relating to the menstrual cycle. Almost immediate relief from troublesome symptoms associated with menstruation including heavy periods, dysmenorrhoea and irregular bleeding occurs,[5] which reduces the risk of iron deficiency anaemia by about 50%.[5] Combined oral contraceptives also offer several important health benefits unrelated to birth control, including a reduced risk of ovarian cyst, ovarian and endometrial cancer and benign breast disease. COCP have a measurable effect on pulmonary functions.[6] It has been found that women taking oral contraceptives have significantly higher total lung capacity when compared with nonusers.[7] Premenopausal women have been reported to experience drops in peak expiratory flow rate and worsening of asthma symptoms before and during menses, often experiencing relief after the onset of progesterone and/or oestrogen therapy.[8] Another study conducted on pregnant women, reported improvement in asthma symptoms during their pregnancy.[9] Oral contraceptive users have been found to have

significantly higher total lung capacities when compared with non-users during the follicular phase of the menstrual cycle.[10]

Therefore it was planned to determine whether administration of exogenous oestrogen in combined oral contraceptive pills affects lung function variables in our population.

MATERIAL AND METHODS

Two hundred and thirty women were attended in the hospital, presenting for regular gynaecologic check-ups. Sixty-two met the inclusion criteria, out of which only 50 were followed for six months. Six of them were dropped from the study due to change of contraceptive method, four due to improper use of combined oral contraceptive pills (COCPs) like missing one or more pills and two of them got pregnant. All participants signed informed consent.

Twenty eight women had never used COCPs before. The remaining women had previously used oral contraceptives but discontinued treatment at least 2 years before enrolment in our study. Participants were considered healthy on the basis of medical history, physical examination and vital signs.

All participants went Spirometric evaluation with Electronic portable spirometer, Vitalograph®, before, 1, 3, and 6 months after starting combined oral contraceptive pills, containing Ethinyloestradiol: 0.03 mg, Levonorgestrel: 0.15 mg. Usually three or four participants were evaluated successfully between 9 AM and 12 PM. The investigation was completed in seven months.

Forced expiratory tests were performed according to American Thoracic Society (ATS) recommendations. The diagnostic spirometer is capable of measuring volumes up to 9.99 litres at normal body temperature, ambient pressure, with an accuracy of at least ±3% of reading at an operating temperature of 15–37 °C. The spirometer is capable of accumulating volume for at least 30 seconds. Spirometric standards are according to the ATS 2005 Guidelines. A daily calibration of the spirometer was not required with the model used in this study.

The appropriate technique was clearly demonstrated to the patient before initiating the test. Initial couple of manoeuvres was disregarded before patient was able to perform test satisfactorily.

Every patient made three attempts and the best values for each parameter were selected. Patients were given adequate rest of two to three min in between the tests.

Patients were made to sit upright and nose clips were not used. Barrier filter with high filtration efficiency rate, low resistance, and small dead space were used for each subject. They were asked to take in a deep breath then to blow out in the mouthpiece of spirometer as hard and as long as possible.

Comparison of FVC, FEV_1, PEFR and FEV_1/FVC%, was done before and after the treatment by finding the means, calculating the standard deviation and standard error of mean. Student's *t*-test was applied to spirometric values. Correlation between FVC, FEV_1, PEFR and FEV_1/FVC%, platelet count and BMI was found by applying regression analysis.

RESULTS

Simultaneous evaluation of spirometric values included FVC, FEV_1, Percentage ratio and PEFR. In controls the mean value of FVC was found to be 2.48±0.04. In comparison no significant change was observed during the 1 month regimen. At 3 months, in category 2 significant correlation was observed ($p<0.05$) on comparison with control. After 6 months in category 3, highly significant correlation was observed ($p<0.001$) when compared with control. It was due to 8% rise in mean FVC, 2.68±0.04 as shown in Table-1.

Table-1: Comparison of FVC between Control and various Categories (n-50)

Categories	FVC (Mean±SEM)	*p*-value
Control (0 month)	2.48±0.04	
Predicted	3.29±0.03	<0.001 **
Category 1 (1 month)	2.54±0.04	>0.05 $^{\Delta}$
Category 2 (3 month)	2.6±0.04	<0.05 *
Category 3 (6 month)	2.68±0.04	<0.001**

Note: Lung function values are in litres
*Significant, **Highly significant, $^{\Delta}$Non significant

Table-2: Comparison of FEV_1 between Control and various Categories (n-50)

Categories	FEV_1 (Mean±SEM)	*p*-value
Control (0 month)	2.1±0.03	
Predicted	2.87±0.03	<0.001**
Category 1 (1 month)	2.14±0.03	>0.05$^{\Delta}$
Category 2 (3 month)	2.17±0.03	>0.05$^{\Delta}$
Category 3 (6 month)	2.2±0.03	>0.05$^{\Delta}$

Note: Lung function values are in litres
*Significant, **Highly significant, $^{\Delta}$Non significant

The mean FEV_1 of control was 2.1±0.03. The highest levels were observed in the Category 3 with mean FEV_1 of 2.2±0.03 as these subjects received COCPs for the longest of the duration. Although there was an increase in mean FEV_1 but the results observed are not so high to give significant correlation ($p>0.05$).

The estimation of % Ratio in all the categories was found to decrease in comparison to control with mean levels of 84.78±0.24. The mean value in category 2 was 83.32±0.19 and category 3, 81.96±0.21 both showing highly significant

correlation with control (p<0.001).

Table-3: Comparison of FEV_1/FVC% between Control and various Categories

Categories	% Ratio (Mean±SEM)	*p*-values
Control (0 month)	84.78±0.24	<0.001
Predicted	83.5±0.09	<0.001**
Category 1 (1 month)	84.32±0.22	>0.05 $^{\Delta}$
Category 2 (3 month)	83.32±0.19	<0.001**
Category 3 (6 month)	81.96±0.21	<0.001**

Note: Lung function values are in litres
*Significant, **Highly significant, $^{\Delta}$Non significant

Table-4: Comparison of PEFR between control and different Categories (n-50)

Categories	PEFR (Mean±SEM)	*p*-values
Control (0 month)	297.52±4.81	
Predicted	396.58±2.19	<0.001**
Category 1 (1 month)	305±4.95	>0.05 $^{\Delta}$
Category 2 (3 month)	308.38±4.95	>0.05 $^{\Delta}$
Category 3 (6 month)	312.2±5.1	<0.05 *

Note: Lung function values are in litres
*Significant, **Highly significant, $^{\Delta}$Non significant

In control the mean value of PEFR was 297.52±4.81. Category 1 and category 2 both showed non-significant correlation (p>0.05) with control. While comparing Control with category 3, significant correlation was observed (p<0.05) which was due to rise in mean PEFR to 312.2±5.1.

DISCUSSION

Oral contraceptives offer several important health benefits unrelated to birth control, including a reduced risk of ovarian cyst, ovarian and endometrial cancer, and benign breast disease. We found that an oral contraceptive containing a low oestrogen dose improved lung mechanics after 6 months of use. The increase in lung flow and volume were not great (8%–15%) but significantly consistent. The observed improvements in lung mechanics were due to oestrogen rather than progesterone content of the contraceptive.

However, we adjusted for many factors e.g., effect of oestrogen on skeletal muscle strength, alveolar maintaining effect of ovarian hormone, and progesterone causing hyperventilatoy changes, which could have influenced our results.

Oestrogen receptors have been shown to be expressed and are localised in skeletal muscles,[11,12] supporting the notion that sex hormones have regulatory role concerning protein turnover within these tissues, influencing protein mass and biomechanical strength of the tissues.

Oestrogens primarily bind to the oestrogen receptors (α and β) in the nucleus, but have recently also been shown to have binding site in the plasma membrane.[11,13] After oestrogen binding to nuclear oestrogen receptors they disassociates and form dimmers followed by an interaction with specific DNA sequences initiated either through an oestrogen receptor element (ERE) or indirectly through other transcription factors that bind DNA in the regulatory region of target gene promoters.[13]

In the skeletal muscle, both oestrogen receptor types are expressed, but only oestrogen receptor-β protein has been shown to be present in human vastus muscle.[11]

There are a number of studies in support of our findings. Strinic[6] in 2003 demonstrated that after 6 months, all forced expiratory flow and volumes (FVC, FEV_1, PEFR) were increased significantly (6.5%–15%), and concluded that Combined oral contraceptives had a measurable effect on lung mechanics. This could be due to the effects of oestrogen and progesterone that play a role in strengthening respiratory muscle.[14] It may also be the effect of oestrogen and progesterone to reduce contractility and increase relaxation of bronchial muscle *in vitro*.[15]

Our findings are supported by many studies which show a positive correlation between skeletal muscular strength and oestrogen levels as the one that demonstrated effects on the quadriceps,[16] hand muscles[17] and adductor pollicis muscle.[18] Therefore, this result did suggests the possibility of ovarian hormone effects on the contractile component and respiratory motor control, as previously reportedby,[19] since diaphragm and intercostals muscles work together in producing inspiratory and expiratory force.[20] Since inspiratory and expiratory strength is performed by a skeletal muscle component, represented by the intercostals and abdominal muscles that work together with the diaphragm,[21] it could be expected that sexual hormones affect respiratory muscle strength. Our results reinforce the idea that, despite progesterone being primarily involved in increased ventilation during the luteal phase,[19] oestradiol could be intensifying the effect of progesterone in humans.[21]

In our study there was an increase in mean FEV_1 but the results observed were not so high to give significant correlation (p>0.05). These findings are supported by Catherine[14] who demonstrated that all women and subgroups of women without asthma, and non-smokers on HRT (Hormone Replacement Therapy) were more likely to have higher FEV_1 and FVC than women who were not using HRT. This finding is in agreement with Köksal[22], who evaluated the effects of HRT on the pulmonary functions. There were no statistically significant differences found between the groups considering FVC, FEV_1 and FEV_1/FVC in initial months. But PEFR levels of the

HRT group were significantly different than the initial values three months after the treatment. The increase in PEFR may be due to the use of synthetic form of progesterone (progestins) present in combined oral contraceptive pills which causes hyperventilatory changes. These hypervetilatory changes result in opening up of dormant alveoli causing increase in PEFR.[23]

As it is observed that combined oral contraceptive pills have a measurable effect on lung mechanics with changes in spirometry. This can be explained by the alveolar maintaining effect of ovarian hormones. The loss of alveoli in mice after ovariectomy and their regeneration during oestradiol replacement suggest that oestrogen is the ovarian hormone responsible for maintaining alveolar structural stability.[24] Thus evidence is growing to indicate oestrogen may delay the loss of, and also improve, those lung functions that reflect maintenance of alveolar structure.[6,21]

The administration of oestrogen plus progesterone,[22] oestrogen alone, or an oestrogen-like compound to postmenopausal women increases their FVC and FEV_1. Even in women aged 24–35 year, use of an oral contraceptive containing oestradiol and a progestin increases forced expiratory flow rates, especially flow rates at low lung volumes.[6] Diffusing capacity is an indicator of alveolar surface area.[25] In non-smoker females, the rate of decline accelerates after menopause.[26] This menopause-related accelerated decline of diffusing capacity is due to a fall in the concentration of oestrogen and is supported by alveolar regeneration after oestrogen replacement.[24]

Another explanation of our findings is based on more recent work with women on the effect of oestrogen on forced time expiratory flow rates. The evidence about the oestrogen-preserving effect on alveolar architectural stability and its alveolar-regenerating effect is evolutionarily. Hence, these findings in women point to the alveolar-maintaining effect, and perhaps alveolar-regenerating ability, of ovarian hormones. The loss of alveoli in mice after ovariectomy and their regeneration during oestradiol replacement suggest oestrogen is the ovarian hormone responsible for maintaining alveolar structural stability, and for inducing alveolar regeneration, in women.[24] Oestrogen and progesterone use have been associated with improved pulmonary function in pre-menopausal women. In the same study elderly women receiving hormone replacement (oestrogen plus progesterone) exhibited a higher FEV_1 than similar-age women not receiving hormone replacement.[14] In postmenopausal women, oestrogen maintains[14] and improves lung function.

Some controversial data with regard to our data has also been reported. A study by El-Heneidy[27] has documented the short and long term effect of COCP on the pulmonary functions. The study was carried out on 106 women receiving the pills for periods ranging from 6 months to 8 years and the results were compared with those of 30 normal women who never received these pills. No statistically significant difference was found between users and nonusers of the pills. He suggested that effects of combined pills on pulmonary functions were fairly benign.

Another study by Juniper,[28] demonstrated that, changes in symptoms occurring during the menstrual cycle, both in women with natural cycles and those using contraceptives, are not related to serum progesterone levels or airway responsiveness. The results remained significant and clinically detectable, and are supported by *in vitro* models.

CONCLUSION

Combined oral contraceptive pills measurably affect lung function variables.

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