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EFFECT OF ORAL CONTRACEPTIVES ON RESPIRATORY FUNCTION

RESMI S. S., ELIZABETH SAMUEL, C. KESAVACHANDRAN AND SHANKAR SHASHIDHAR*

School of Biosciences,
Mahatma Gandhi University,
Kottayam – 686 560

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Abstract : The present study was carried out to assess the lung functions in oral contraceptive administered women. Lung function tests were carried out with Spirometer (Vitallograph Compact II). A significant increase in vital capacity (VC) was observed in these women as compared to normal control. There was also a significant decrease in forced expiratory volume in 1 sec./vital capacity (FEV_1/VC%) and forced expiratory volume in 1 sec./forced vital capacity (FEV_1/FVC%) among oral contraceptive administered women as compared to controls. Further, a significant increase in peak expiratory flow rate (PEF), reduction in forced expiratory flow rate ($FEF_{75-85\%}$) and $FEF_{75\%}$ were observed among oral contraceptive administered women as compared to controls. The increase in VC and PEF might be due to the synthetic form of progesterone (progestins) present in oral contraceptive pills which causes hyperventilatory changes. Synthetic progesterone during luteal phase of menstrual cycle might increase the static and dynamic volumes of lung i.e. VC and PEF. But $FEF_{75\%}$ showed a decrease which might be due to the lower neuromuscular coordination during breathing.

Key words : lung volumes flow rate oral contraceptives

INTRODUCTION

Contraception in one form or another, has been practised by humans for thousands of years. Birth control pills, also called oral contraceptives protect against pregnancy when taken exactly as prescribed. Oral contraceptives are now being widely used all over the world in different compositions and dosages; by millions of women for over 30 years. They are available in several forms and more than 20 different formulations. Most common of them are the "combination" pills, which contain synthetic version of the two major female hormone; estrogen and progestogen. Oral contraception is effective, convenient, reversible and for most of the woman it is remarkably safe (1).

Estrogens and progestins affect many systems of the body, not just the reproductive tract. The most serious complications linked to the pills are cardiovascular diseases, including thrombophlebitis and blood clots. The formation of blood clots in the vein,

*Corresponding Author

particularly in the legs, is perhaps the most important cardiovascular effects, although it does not occur very often. The danger of such clots is that it can break off, get stuck somewhere in the blood stream, and block the blood supply to an important organ like the heart, brain, lungs and eye. Oral contraceptive pills can cause hyperventilatory changes in normal women and progestin play a pivotal role (2). Large number of women have ingested synthetic progestins and estrogens chronically for contraceptive purposes yet the ventilatory effects of these synthetic steroids have received little attention. The present study was undertaken to assess the pulmonary functions of oral contraceptives used by women of Kerala. In addition to this, the Body Mass Index, waist-hip ratio and other anthropometric measurements were taken to assess the fat index and excess body weight of these subjects.

METHODS

The study consisted of 22 subjects belonging to the age group 23–36 years. Subjects were selected from different primary health centres of Kottayam district. The oral contraceptive pills used by the subjects were Mala N containing etinyl estradiol (30 μg) and norgestrel (30 μg). Age, height, weight, body surface area (BSA), body mass index (BMI), waist-hip ratio were measured in addition to the lung function tests carried out with Vitallograph Compact II Spirometer. Forteen age and height matched, healthy subjects who were not an oral contraceptives were selected as normal controls.

RESULTS

Mean physical characteristics of oral contraceptive administered women were 30.14 years of age, 1.54 m of height, 52.8 kg of weight, 22.48 of BMI, 80.27 cm of waist, 89.43 cm of hip, 83.9 cm of chest, 0.89 of waist-hip ratio and 1.49 of BSA (Table I).

TABLE I: Anthropometric measurements of oral contraceptive administered women.

Parameters	*Mean ± S.D.*
Age (yrs)	30.14±3.89
Height (m)	1.54±0.05
Weight (kg)	52.8±8.52
BMI (kg/m^2)	22.48±3.95
Waist measurement (cm)	80.27±9.24
Hip measurement (cm)	89.43±8.27
Chest measurement (cm)	83.9±8.02
Waist-Hip ratio	0.89±0.05
BSA	1.49±0.10

A significant increase ($P<0.001$) in VC was observed in oral contraceptive group as compared to control. There was a significant decrease in $FEV_1/VC\%$ ($P<0.05$) and $FEV_1/FVC\%$ ($P<0.001$) among oral contraceptive users as compared to controls (Table II).

There was a significant increase ($P<0.05$) in PEF among oral contraceptive users compared to controls. A significant reduction in $FEF_{75-85\%}$ ($P<0.05$) was observed among oral contraceptive users as compared to controls. Forced expiratory flow rate $FEF_{75\%}$ ($P<0.05$) showed a remarkable reduction among oral contraceptive administered women than normal controls (Table III).

TABLE II : Comparison of lung volumes between oral contraceptive (OC) administered women and controls.

Parameters	*Control*[14] *Mean ± S.D.*	*O.C. administered women*[22] *Mean ± S.D.*	*P value* (<)
VC (L)	1.68±0.40	2.37±0.57	0.001
FVC (L)	2.34±1.30	2.40±0.46	NS
$FEV_{0.5}$ (L)	1.65±0.92	1.52±0.32	NS
FEV_1 (L)	2.17±1.22	2.03±0.40	NS
$FEV_{0.5}$/FVC (%)	69.71±10.36	63.36±10.72	NS
FEV_1/VC (%)	139.86±104.00	86.32±6.90	0.05
FEV_1/FVC (%)	93.14±3.86	84.36±5.64	0.001
MVV_{ind}	81.43±45.64	74.91±15.28	NS

Superscription denotes the number of observations.

TABLE III : Comparison of flow rates between oral contraceptive (OC) administered women and controls.

Parameters	*Control*[14] *Mean ± S.D.*	*O.C. administered women*[22] *Mean ± S.D.*	*P value* (<)
PEF (L/min)	211.86±90.53	222.41±79.27	0.05
$FEF_{0.2-1.2}$ (L/sec)	2.96±1.41	3.27±1.31	NS
$FEF_{25-75\%}$ (L/sec)	2.44±0.78	2.37±0.69	NS
FMFT (sec)	0.49±0.25	0.53±0.157	NS
$FEF_{75-85\%}$ (L/sec)	1.61±1.36	0.85±0.32	0.05
$FEF_{25\%}$ (L/sec)	3.18±1.40	3.48±1.37	NS
$FEF_{50\%}$ (L/sec)	2.92±1.16	2.83±0.69	NS
$FEF_{75\%}$ (L/sec)	1.89±1.37	1.19±0.39	0.05
PIF (L/sec)	2.65±0.67	2.58±1.07	NS
$FIF_{75\%}$ (L/sec)	2.37±0.67	2.16±0.97	NS
$FIF_{50\%}$ (L/sec)	2.14±1.02	2.34±1.08	NS
$FIF_{25\%}$ (L/sec)	2.12±0.95	2.20±0.97	NS

Superscription denotes the number of observations.

DISCUSSION

The ventilatory changes brought about by contraceptive pills are generally similar, qualitatively and quantitatively to those observed in the luteal phase of the menstrual cycle. An important difference is that the mean slope of the CO_2 response lines of the non-pill taking subjects do not increase significantly as do the mean slope of the pill-taking group. The slope of the CO_2 response is apparently quite variable among subjects and whether or not changes occur during the menstrual cycle are controversial (3). Orally administered norethindrone doses found in current oral contraceptives was found to be a moderate ventilation stimulator in normal subjects. Most of the studies implicate progestins as the source of the ventilatory response.

In the present study anthropometric measurements of oral contraceptive administered women were taken. BMI of oral contraceptive administered women were 22.48, that lies within the normal range (Table I). The waist-hip ratio a measure of upper body adiposity was above the permissible limit in the present study (Table I). Increase in waist-hip ratio may be a good indicator for obesity. Oral contraceptive pills are found to be very well associated with

obesity. The progestin in the pill can cause an increase in appetite and consequent slight weight gain but it is seldom more than 2 to 4 pounds (4). Commonly occurring side effects with oral contraceptives are frequent occurrence of moderate obesity apart from nausea and vomitting during first few days (5).

In the present study the VC is increased among oral contraceptive administered women than control (Table II). The reason for the increase in VC may be due to the action of progesterone. Studies conducted by Tarun (6) showed that hyperventilation and increase in oxygen consumption occur during the luteal phase of menstrual cycle and that if pregnancy occurs, the respiratory stimulation continues throughout gestation. Probably progesterone plays a key role in this phenomenon. It is also reported that the tendency for central apnea and hypopnea is reduced during pregnancy and that could be due to increased progesterone levels. This hyperventilation could be attributed to progesterone, as it was observed only during the luteal phase of menstrual cycle. It has been shown that the resting $PaCO_2$ decreases with increasing serum progesterone levels (7–9). The inverse changes in hypoxic sensitivity and resting $PaCO_2$ have been associated with changes in serum progesterone level, i.e., the higher serum progesterone level, the greater hypoxic sensitivity with the lower resting $PaCO_2$.

Central alkalosis and or hypocapnia occur during the luteal phase (7) and the administration of medroxy progesterone acetate (10) may play a role in central amplification of neural input from the peripheral chemoreceptors. A major part of the increase in hypoxic sensitivity is governed in the central nervous centre or peripheral chemoreceptors, or a combination of both. There may be a threshold for P_{CO_2} and hence an increase in peripheral chemoreceptor sensitivity. The central chemoreceptor stimulation has an important influence on cholinergic outflow of the airways. It may cause reflex increase in ventilation and hypocarbia with hypoxic broncho constriction (11).

The lung volumes ratios are reduced in oral contraceptive administered women as compared to normals (Table II). It might be due to the poor mechanical properties of the lung. The determination of ventilatory tests in different groups revealed that all lung function variables attained maximum peak at the age of 21–25 years and thereafter steadily decreases. Since all the dynamic ventilatory functions depend upon the compliance of the thoracic-lung system, airway resistance and muscular strength rather than the absolute anatomical lung volumes. The deterioration in the lung function with advancing age, is mainly caused by change in these factors. The age-related loss in pulmonary function is due to decrease in lung compliance, increase in airway resistance and reduction in the strength of respiratory muscles associated with changes in the elastic recoil of the lung and increase in the stiffness of thoracic cage (12).

In the present study the PEF is increased among oral contraceptive administered women than controls (Table III). This increase is associated with the role of progesterone. The contraceptive pills contain synthetic form of progesterone (progestins) which are highly reactive than

progesterone. Contraceptive pills containing norethindrone and mestranol or ethinyl estradiol can cause hyperventilatory changes in normal women (2). However Tyler (13) detected no ventilatory changes in response to norethindrone administration which could be due to the fact that Tyler (13) only studied one patient with the course of 2 drugs. Further, it is possible that the norethindrone may not have been administered for long period to produce any ventilatory effects. The progestational and ventilatory effects of progestins are mediated by different portions of the progestin molecule. The chief differences between progesterone and the two synthetic progestins (Norethindrone, Medroxy progesterone acetate) involve the constituents at the 6, 17, 19, 20 and 21 positions. Specifically, norethindrone lacks a methyl group at position 19, and has a 17α-ethinyl group substituted for the 17α-hydrogen and a hydroxyl group in lieu of constituents at the 20 and 21 positions. Medroxy progesterone acetate is identical to progesterone except for the 17α-acetate group, and the additional methyl group at position 6. Skatrud et al. (10) observed a relatively small ventilatory effects as a result of Medroxy progesterone acetate administration which demonstrates that a 17α-ethinyl group is not required to reduce the ventilation-stimulating ability of progestin, as MPA does not have an ethinyl group. However, substitutions at one of the other positions listed, or a combination of these may also be important to the inhibition of the ventilatory effects.

Another important observation in the present study was the reduction of $FEF_{75\%}$ among oral contraceptive administered women than normal control. These reductions may be associated with reduced effort of inspiratory and expiratory muscles. It also indicates higher airway resistance and lower lung compliance. The FVC, FEV_1 and $FEF_{25-75\%}$ during each phase reflect the unchanged mechanical properties of lungs during the menstrual cycle (6). FEV_1 in fact is a measure of flow rate during the first second of forced expiratory spirography. It includes sufficient flows at lower lung volumes to reflect the small airway patency in addition to large airway changes. Thus increase in inspiratory flow during luteal phase without any alteration in pulmonary mechanics, mainly indicates an augmented central ventilatory drive, although the role of peripheral chemoreceptor cannot be ruled out. However, evidences suggest that both luteal phase of menstrual cycle and pregnancy are associated with central ventilatory drive as indicated by increase in mouth occlusion pressure (14). Tarun (6) showed the effective time ratio or duty cycle T_I/T_{tot} which was essentially unchanged. This indicates the inspiratory muscle activity probably did not alter during the menstrual cycle.

The observation of reduced $FEF_{75\%}$ in the present study supports earlier findings of Chen and Tang (15). The terminal portion of FVC curve ($FEF_{75-85\%}$) is relatively variable due to factors like maintenance and co-ordination of efforts which are to some extent dependent on neuromuscular factors (16). Normally, steroids easily traverse the blood-brain barrier and activate the central chemoreceptors of central nervous system to raise the ventilation. If progestin had influenced the central chemoreceptor, then $FEF_{75\%}$ should have higher in oral contraceptive administered women due to better neuromuscular coordination. But in

the present study $FEF_{75\%}$ showed a decline in oral contraceptive administered woman. This shows that progestin may not have influenced the central chemoreceptor activity. So it should be assumed that there is a reduced neuromuscular co-ordination which resulted in reduced FEF.

Conclusion

The increase in VC and PEF may be due to the synthetic form of progesterone (progestins) present in oral contraceptive pills which causes hyperventilatory changes. Synthetic form of progesterone during luteal phase of menstrual cycle increases the volume of lung functions especially static volumes (VC) and dynamic volumes (PEF). But $FEF_{75\%}$ showed a decrease in oral contraceptive administered women. This may be due to the lower neuromuscular coordination during breathing.

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