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INFLUENCE OF COMBINED ORAL CONTRACEPTIVES PILLS ON PULMONARY FUNCTIONS TESTS: A CROSS SECTIONAL ANALYTICAL STUDY AT A TERTIARY CARE CENTRE IN SOUTH INDIA

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Abstract: Recent research underscores the multifaceted impact of sex steroid hormones(SSH) on a wide range of physiological processes. For many years, estrogen and progesterone were responsible for classical reproductive development, but recent studies depict their role at a variety of tissues, including the lung airways**.** The objective of the study was to observe the effects of exogenously administered SSH in the form of combined oral contraceptive pills (COCP) on pulmonary function parameters in apparently healthy women receiving COCP for more than six months and compare it with that of non-users. A cross-sectional analytical study was conducted with sixty two randomly selected females of reproductive age group undergoing COCP therapy, visiting the family planning unit of a tertiary care hospital. Age and Body mass index matched other sixty-five non COCP user females were included in the study to compare the pulmonary function parameters. Pulmonary function variables recorded were Forced Expiratory volume in 1 second (FEV_1), Forced Vital Capacity (FVC),Timed vital capacity (FEV_1/FVC %), forced expiratory flow between 25-75% ($FEF_{25-75\%}$) and Peak Expiratory flow rate (PEFR). The mean age of the study population was 25±3.99 years. All the PFT variables

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were found to be higher for COCP users (study group) as compared to non-users (control group) and the difference was found to be statistically significant for FEV1/FVC and PEFR($p<0.05$). The difference was highly significant especially for FEV_1, FVC and $FEF_{25-75\%}$ values ($p<0.01$).Th conclusion drawn from the study is that the improvement of pulmonary functions in COCP users can be attributed to relatively higher concentration of estrogen and progesterone hormones in the form of COCP. These hormones work individually as well as synergistically in a non-genomic manner to reduce the calcium levels in the airway smooth muscles cells (ASM)and ultimately results in ASM relaxation and finally bronchodilation. The outcomes of this study hints towards possible role of both SSH supplementation in female patients of Chronic obstructive pulmonary disease, bronchial asthma and cystic fibrosis.

Keywords: pulmonary function test, Airway smooth muscle cells. Combined Oral contraceptive Pills, Estrogen, Progesterone.

Introduction: Sex steroid hormones (SSH) have long been recognized for their role in classical reproductive maturity, but recent studies have illuminated their critical involvement in maintaining a wide range of physiological processes, including homeostasis and aging.[1] Progesterone and estrogen, the primary SSHs in females, are typically produced endogenously but can also be additionally administered exogenously. Like other hormones, these hormones exert their effects through respective cognate receptors, leading to changes in gene expression. Recent research has depicted SSH receptors to be expressed in lung tissues, in addition to traditional sexual organs.[2] This discovery represents a significant departure from previous understandings, suggesting the potential involvement of SSH in pulmonary physiology and pathology, including the modulation of lung structure and function. Furthermore, studies by Luu

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et al. indicate that SSH can be locally produced in non-reproductive organs, including the lungs.[3] SSH can operate in two primary modes, either paracrine or endocrine to circulate and act on distant target tissues, with their effects varying from beneficial to detrimental. This variability in function depends on their relative local and circulatory concentrations, specific receptor expression, and interactions among different sex steroids.[4]

Natural physiological processes such as the menstrual cycle, pregnancy and menopause, along with externally administered oral contraceptive pills (OCP) and combined hormonal replacement therapy (HRT), cause fluctuations in SSH levels that can affect pulmonary outcomes.[5] Over a century back, Hasselbach reported pregnant females to have lower alveolar and arterial partial pressure of carbon-di-oxide levels.[6] Kadel et al. concluded that women taking OCP are at reduced risk and experience fewer episodes of bronchial asthma.[7] The observation of sex predilection in studies on sudden infant distress syndrome and obstructive sleep apnea further reinforce the significance of SSH in respiratory physiology. The crucial role of SSH in respiratory control is linked to either specific SSH or their receptor levels.[2]

Over one hundred million women worldwide are documented to use OCPs, with approximately 8.5% of these users residing in India, varying across different regions.[8,9] OCPs provide orally active synthetic estrogen and progestin in various compositions, which not only offer the benefit of reversible birth control but also regulate numerous critical pulmonary functions. Pulmonary function tests (PFT) rely in part on airway tone, which reflects the balance between bronchoconstriction and bronchodilation, modulated by the contractility and relaxation of airway smooth muscle (ASM).[10]

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Despite numerous studies attempting to assess the effects of exogenously administered SSH in the form of OCPs on PFT, the results have been inconclusive and conflicting.[11.12] In this context, our study was designed to explore the impact of combined OCP (COCP) on PFT and to compare PFT parameters among COCP users versus non-user females of reproductive age.

MATERIAL & METHODOLOGY:

Type & setting: This cross-sectional analytical study was conducted at the Department of Physiology in association with Department of Obstetrics & Gynaecology, at a tertiary care teaching hospital, South India from October to December 2021. The study was initiated after obtaining approval from the Institutional Ethics Committee (KBNIMS/Phy/IEC/B0115/02/21). The participants who fulfilled the inclusion criteria were asked to fill an informed written consent form, maintaining complete anonymity after explaining the risk and implications of the study.

Exclusion criteria: Females who had history of acute or chronic respiratory illness, known occupational exposure to respiratory hazards, amenorrhoea, bleeding disorders, on regular medication for any other disease and substance abuse were excluded. Patients with known metabolic, endocrine, neuromuscular or cardiovascular abnormality which could hinder the procedure of PFT recordings were also excluded from the study.

Sample size: To attain adequate statistical power to test the hypothesis and avoid Type I errors, sample size was calculated on the basis of Cochran's formula, where Z=1.96, P=8.5%, Q=1-0.085, d=sampling error of 5%, accounting for a sample size of 119.[13] Taking into consideration 10% of non-responders, the total number of participants was raised to 130.

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Participants: A total of one hundred and thirty apparently healthy females, aged between 18-36 yrs. attending the family planning unit of the hospital were included into the study. Study group comprised of sixty five randomly selected females using the COCP for more than six months. The constituents of COCP (Mala-N, supplied freely by Government of India) per tablet used was levonorgestrel I.P. 0.15 mg and ethinylestradiol I.P. 0.03 mg.[14] One tablet of COCP each day preferably in the night was taken continuously for twenty one days, to be started from the 1st day of menstrual cycle (MC). In addition, the strip contained seven brown tablets containing ferrous fumarate I.P. 60 mg equivalent to ferrous iron 19.5 mg, one tablet each day to be taken for next seven days. After (21+7) twenty eight days, a gap was given during which no medication was provided and the female underwent withdrawal bleeding and subsequently the cycle was repeated again. Another sixty-five age and BMI matched COCP non-user (naturally occurring MC) females in luteal phase of MC, were randomly selected as control group for comparison.

Procedure: The anthropometric measurement of all the participants was recorded and Body Mass Index (BMI) in Kg/m^2 and Body Surface Area (BSA) in m^2 was calculated based on Quetelet Index and Du Bois Formula respectively. The PFT of all the participants was performed using Vitalography Compact II computerised spirometry. The PFT recordings were conducted between 10 AM and 2 PM according to the American Thoracic Society/ European Respiratory Society (ATS/ERS) guidelines in a quiet room in a comfortably sitting position. All the participants were first given a demonstration of the manoeuvre, following which a practise session was held. The participants were told to replicate the procedure using a disposable mouth piece. According to ATS/ERS guidelines for performing PFT, three recordings were taken at an interval of fifteen minutes and the best of the three was considered.[15] The parameters tested were forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), forced expiratory flow

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between 25-75% ($FEF_{25-75\%}$) in litres and peak expiratory flow rate (PEFR) in litres/sec. For all pulmonary function parameters, the percentage predicted values for respective age, height and weight were also taken into consideration.

Statistical Analysis: Data was collated and expressed in the form of frequency, percentages and mean- standard deviation. Statistical difference was calculated using students' unpaired t-test between COCP users and non-users assuming equal variance using IBM-SPSS statistics for Windows, Version 22.0, and a p-value of <0.05 was considered as statistically significant.

RESULTS: Out of one hundred and thirty females contacted, a total of one hundred and twenty seven agreed to participate in the study, with sixty two females in the study group (COCP users) while sixty five as controls (naturally cycling females, NCF). The mean age, height, weight, BMI and BSA of the study group and controls is depicted in Table 1. There was no significant difference between the study and control group for anthropometric variables.

Table 1: Anthropometric profile of the control & study group

Sl. No.	Anthropometric Profile	Control Group (65)	Study Group (62)	p-value
1.	Mean Age (Yrs±SD)	23.03±3.99	27.70±4.09	0.23
2.	Mean Height (m±SD)	1.57±0.05	1.57±0.04	0.09
3.	Mean Weight (Kgs±SD)	52.97±6.13	53.10±8.06	0.84
4.	Mean BSA (m^2±SD)	1.52±0.09	1.52±0.12	0.76
5.	Mean BMI (Kg/m^2±SD)	21.44±2.66	21.61±3.24	0.19

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The mean PFT parameter recordings between study and control group is depicted in Table2. The results highlight a higher value of FEV_1, FVC, FEV_1/FVC, PEFR and $FEF_{25-75\%}$ among COCP users as compared to NCF and the difference was found to be statistically significant.

Table 2: Comparison of PFT parameters of the control & study group

Sl. No.	PFT variables	Controls (65)	Study group (62)	*t*	*df*	*p-value*
1	Mean FVC (L±SD)	2.5461±0.256	2.7010±0.311	-2.49325	125	**0.00698****
2	Mean FEV_1 (L±SD)	2.3625±0.249	2.5087±0.276	-2.49820	125	**0.00690****
3	Mean FEV_1/FVC (%±SD)	91.0698±4.321	93.2274±5.584	-2.07353	125	**0.02009***
4	Mean PEFR (L/sec±SD)	5.0548±0.696	5.2919±0.472	-1.72905	125	**0.04313***
5	Mean $FEF_{25-75\%}$ (L/sec±SD)	2.8874±0.417	3.6411±0.693	-6.16868	125	**0.00000****
**p highly significant (p<0.01), * p significant (p<0.05)						

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DISCUSSION: This study was conducted to assess the impact of COCP on PFT variables in women of reproductive age group. A total of one hundred and thirty participants were contacted, out of which one hundred and twenty-seven agreed to participate in the study, with sixty two females as COCP users (study group) and sixty five NCF (controls). The mean age of the study population was 25±3.99 years. The study group and controls were matched for age, height, BSA and BMI. The study yielded PFT values that align closely with those reported in several similar studies conducted by Resmi et al.,[16] Kumar et al.,[17] as well as Nandhini et al.[18] on Indian females. The study reflected comparatively higher values of all PFT variables including $FEV_{1,}$ FVC, FEV_1/FVC, mean PEFR and $FEF_{25-75\%}$among COCP users than to NCF. Moreover, the difference was found to be significant for FEV_1/FVC and mean PEFR parameters ($p<0.05$) whereas FEV_1, FVC and $FEF_{25-75\%}$ had a highly significant difference ($p<0.01$). On a similar note, Kumar et al. concluded higher values of FEV_1, FVC, FEV_1/FVC, PEFR and $FEF_{25-75\%}$ among COCP users as compared to non-users.[17] Farhana et al. also reported FEV_1 and FVC to be significantly higher but FEV_1/FVC as significantly lower in COCP users as compared to non-users.[19] Contrastingly, Reshmi et al. has concluded a significant decrease in FEV_1/FVC% and $FEF_{25-75\%}$ while a significant increase in VC and PEFR, in women on COCP as compared to non-users.[16]

The plausible explanation for aforementioned results could be attributed to the presence of exogenously administered synthetic steroid hormones, estrogen, and progesterone in varying proportions within COCP. The chief structural element which regulates the airway resistance and inherently the airway tone and calibre permitting adequate airflow is airway smooth muscle

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(ASM) layer. The SSH can regulate the tone of ASM as they influence the presence or levels of some agonist receptors, especially estrogen and progesterone receptors.[20] Researchers portray that the response to SSH can be either genomic or non-genomic.[4] The difference between the responses depends upon type of receptor involved, while generally nuclear and cytoplasmic receptors induce a genomic response, the membrane receptors activate a non-genomic pathway. Genomic pathways involve the enhancement of transcription factors, leading to long-term changes in cellular functions. On the other hand, non-genomic pathways are associated with the activation of intracellular signalling cascades mediated by G-proteins, resulting in more acute changes in cellular responses.[21] Out of the three primary naturally occurring estrogen in females, estradiol is the predominant estrogen in non-pregnant premenopausal women, estrone in menopausal women whereas estriol is the commonly occurring form in pregnant women. The precise role of estrogen and progesterone on ASM is elucidated in the following paragraphs.

Influence of Estrogen on ASM: Estrogen exerts its effects through nuclear (ERα and ERβ) and membrane (mERs) receptors. Studies in mice have revealed that both ERα and ERβ are essential for development of complete alveolar units in females.[22] Townsend et al. has depicted presence of both ERα and ERβ in ASM of female patients.[23] Extensive research on role of estrogen and its differential capacity to activate ERα and ERβ on ASM cells, reveals that estrogen modulates ASM tone through both genomic and non-genomic mechanisms, with a preference for non-genomic pathways.[21] Similar to other smooth muscles, the contractility of ASM is determined by the regulation of both intracellular calcium levels and force generation.[22] Townsend et al. have established that estrogen contributes to bronchodilation through a non-genomic mechanism by significantly reducing intracellular calcium ([Ca2+]i) within the physiological range of estrogen concentration. This reduction in calcium levels is facilitated by various proteins,

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including the inhibition of L-type calcium channels, the sodium-calcium exchanger efflux, and store-operated calcium channels via activation of the c-AMP/PKA pathway.[23] Furthermore, Rang et al. have shown that estrogen enhances the release of dilatory prostaglandins (PGE2) from tracheal smooth muscle cells, promoting c-GMP-mediated broncho-relaxation.[20] In humans, estradiol is the most potent ER agonist for both ERα and ERβ.[24]

Influence of Progesterone on ASM: Progesterone, another major female endogenous SSH, exerts its effects through progesterone receptors (PRα and PRβ).[22] Abraham et al. demonstrated the presence of PRs in the ASM of rats, while Perusquia et al. showed that progesterone and its metabolites induce non-genomic relaxation of the guinea pig trachea.[20,24] Oxytocin has been shown to increase cytosolic calcium levels in human ASM cells, promoting airway narrowing, as proposed by Amrani et al.[25] Conversely, progesterone inhibits oxytocin receptors and may impact ASM indirectly by interfering with oxytocin. Consequently, progesterone is observed to induce relaxation of bronchial smooth muscles, increasing the ventilatory capacity of individuals.[4] Dabhoiwala et al. found a strong positive correlation between serum progesterone and FVC and a negative correlation with FEV_1.[26] Bala et al. concluded that PEFR is significantly higher during the luteal phase compared to the menstrual phase due to elevated progesterone levels in the luteal phase.[27] Additionally, progesterone is known to enhance the sensitivity of the primary respiratory center to carbon dioxide.[28]

Over and above the considered facts, Abraham et al. demonstrated increased expression of ERα and ERβ in ASM of female rats following progesterone treatment.[20] Both 17β-estradiol and progesterone were found to potentiate the isoprenaline-induced relaxation of the pig bronchus by

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more than fourfold.[24] These findings confirm that additional SSH in the form of OCP can have a bronchodilatory effect, with progesterone enhancing the estrogen-induced bronchodilation.[20]

Influence of Nitric Oxide (NO): NO stimulates bronchodilation via cyclic guanosine monophosphate mediated decrease in intracellular calcium.[23] 17β-estradiol enhances endothelial NO synthase (eNOS) activity in a calcium-dependent manner, with this effect being completely inhibited by estrogen receptor antagonists. Progesterone has also been reported to mediate bronchodilation in female rats via this pathway.[20]

Under physiological conditions, from menarche to menopause, female SSH undergo cyclical changes, resulting in peak estrogen and progesterone levels during the luteal phase of the MC. These elevated SSH levels during the luteal phase have a measurable effect on bronchodilation. Mostafa S. et al. found that all PFT parameters, including FEV_1, FVC, and PEFR are elevated during the luteal phase of the menstrual cycle.[29] Similarly, Khan et al. concluded that FEV_1, FVC, and FEV_1/FVC are higher during the luteal phase compared to the follicular phase.[30]

Limitations: The participants from the study group and the controls could have constitutional differences leading to subject bias and thus pre and post interventional study could have led to scientifically congruous results. As the study was conducted at a single centre with small sample size, the results cannot be generalised. Further large cohort longitudinal studies are required to delineate the exact effects of SSH on pulmonary function parameters.

CONCLUSION: The study establishes the fact that pulmonary functions get affected by the presence of SSHs and the PFT parameters are higher among COCP users as compared to NCF. The possible explanation can lie in the fact that these COCP administer additional SSH which act

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individually as well as synergistically in a non-genomic manner to reduce the calcium levels and ultimately results in ASM relaxation and bronchodilation via various mechanisms as elucidated in our study. Future studies involving the role of SSH and its signalling pathways and interactions with other cell system including pulmonary physiology will help to identify novel therapeutic targets thereby providing scope for sex specific, individualised and precision based targeted treatment.

Clinical Significance: The outcomes of this study hints towards possible role of SSH supplementation in female patients of Chronic obstructive pulmonary disease, bronchial asthma and cystic fibrosis. The role of estrogen as bronchodilator via non-genomic, calcium signalling may have a potential application as β agonist sparing agent due to receptor insensitivity in long standing cases of asthma. Clinically, estrogen can be promoted for eNOS mediated bronchodilation. [25].

List of abbreviations: SSH: Sex Steroid hormones, OCP: Oral Contraceptive Pills, PFT: Pulmonary function tests, ASM: Airway smooth muscle cells, MC:Menstrual cycle, $FEV_{1:}$ forced expiratory volume in one second, FVC: forced vital capacity, $FEF_{25-75\%}$: forced expiratory flow between 25-75%, PEFR: peak expiratory flow rate, ER: Estrogen receptors. PR: Progesterone receptors, NO: Nitric oxide, NCF: Naturally cycling females

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