Sex Steroid Hormone Effects in Normal and Pathologic Conditions in Lung Physiology

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Abstract: Progesterone and estradiol participate in the regulation of many pulmonary functions, for example progesterone mediates the fall of alveolar carbon dioxide tension observed in the luteal phase of the menstrual cycle and during pregnancy in humans, when progesterone levels are high. The treatment with estradiol diminishes vasoconstriction and hypoxia. Progesterone and estradiol in addition to participating in non-pathological functions such as vasodilation and lung maturation, also have influence on pathologies as asthma, cystic diseases and cancer. Therefore this review will provide an overview of the action and effects of these hormones in lung, their mechanism of action through their intracellular receptors and their influence over asthma, cystic lung diseases and cancer.

Keywords: Estradiol, estrogen receptor, lung, progesterone, progesterone receptor.

INTRODUCTION

Progesterone (P4) and estradiol (E2) participate in the regulation of many pulmonary functions. The administration of P4 induces hyperventilation [1-7] and also mediates the fall of alveolar carbon dioxide tension observed in the luteal phase of the menstrual cycle and during pregnancy in humans, when P4 levels are high [8, 9]. In women with cystic fibrosis lung function improves during the luteal phase of the menstrual cycle [10].

The treatment with E2 diminishes vasoconstriction and hypoxia in the adult rat lung [11-13] and increases the gas exchange by inducing the formation of alveoli [3]; E2 also has a protective role against chemical-induced acute inflammation in this tissue [14].

Many actions of P4 and E2 are mediated by specific intracellular receptors (PR and ER) that are members of the nuclear receptor family that activate transcription. Two PR isoforms have been described: a full-length form (PR-B, 120 kDa) and the N-terminally truncated one (PR-A, 80 kDa). There are also two ER isoforms, ER-α and ER-β, encoded by different genes and with a molecular weight of 66 and 54 kDa, respectively [15]. It has been shown that PR and ER isoforms are functionally distinct in terms of their ability to activate target genes in the same cell and regulate different physiological processes [16-18].

Both PR isoforms have been found in the rat and rabbit lung [19-21]. ER isoforms have also been detected in the lung [22, 23]. The expression of both steroid receptors (PRs and ERs) in lung suggests a genomic action of P4 and E2 in this tissue.

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PROGESTERONE AND ESTROGEN RECEPTORS IN LUNG

Many actions of P4 and E2 are mediated by specific intracellular receptors (PR and ER) that are members of the nuclear receptor family that activate transcription. In several tissues PR are up-regulated by E2 and down-regulated by P4 [24], while ER is negatively regulated by its ligand [25, 26].

Two PR isoforms have been described: a full-length form (PR-B, 120 kDa) and the N-terminally truncated one (PR-A, 80 kDa) [27]. Both PR isoforms are derived from a single gene and are generated from either alternative transcriptional or translational start sites [28, 29]. There are also two ER isoforms, ER-α and ER-β, encoded by different genes and with a molecular weight of 66 and 54 kDa, respectively [15]. It has been shown that PR and ER isoforms are functionally distinct in terms of their ability to activate target genes in the same cell and regulate different physiological processes [16-18].

Both PR isoforms have been found in rat and rabbit lung, and their expression in ovariectomized rats is regulated by E2 and P4 [19-21]. PR-A was the predominant isoform in the rat lung in an A:B ratio of 2:1 [19]. ER isoforms have also been detected in the lung; ER-β is the predominant isoform detected in this tissue (ER-β to ER-α ratio of 3.1 and 2.6 in female and male adult mice, respectively) [22, 23].

The content of PR mRNA changed according to the steroid hormonal environment. The treatment of ovariectomized rabbits with E2 induced a marked increase in PR mRNA content in the rabbit lung whereas the administration of P4 after E2 priming reduced it. During early pregnancy PR mRNA content markedly changed in rabbit lung. A significant increase in PR mRNA content was found on the first day of pregnancy when plasma P4 concentration was low; it then diminished progressively until it reached its lowest value on day 5 after a marked increase in plasma P4 concentration [21]. In the rat lung, E2 up-

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regulated mRNA and protein levels of total PR and down-regulated ER-β [19]. This sensitivity to E2 is associated with the presence of estrogen responsive elements located in the promoter regions of both PR isoforms [30]. These data suggest that ER-β should interact with its ligand to regulate PR transcription in the lung. It has been reported that the proteasome 26S degrades ER in a ligand dependent manner [31]. It is possible that the decrease in the content of ER-β produced by E2 could be due to its degradation by the proteasome. Interestingly, in the lung P4 exerted its maximal effect at mRNA level over total PR and PR-B at 12 and 48 h, respectively, while at protein level it did not significantly down-regulate PR isoforms at any time. These data showed that the regulation of PR isoforms in the lung at mRNA and protein levels is different, suggesting that PR isoforms expression should be regulated by its own ligand at transcriptional and at translational levels.

PR isoforms have also been detected in the rat lung during estrous cycle. PR-A was the predominant isoform. The maximal content of both PR isoforms was detected on the day of proestrus when serum E2 levels were the highest and P4 levels were low, whereas the lowest content of PR isoforms occurred on the day of estrus after a marked decrease in E2 levels [32] (Fig. **1**). The observed variations in PR isoforms in females across the estrous cycle could be related to the regulation of genes needed for the metabolic requirements for pregnancy to occur. In the adult rat lung the treatment with E2 induces the formation of smaller numerous alveoli that results in an increase in gas-exchange surface area [10], which is necessary for pregnancy when the O_2 volume increases to cover metabolic demands. The content of both PR isoforms was also determined in the lung of adult male rats; the PR isoforms expression was lower in males compared with females [32] (Fig. **1**). This sexual difference could be partly due to the low levels of E2 present in males compared with those in females. These results suggest that, under physiological conditions PR content in the lung depends on the concentration of sex steroid hormones.

Both PR isoforms are physiologically important and it has been reported that they regulate different genes [17, 33]. One of the genes regulated by P4 in lung is *CYP4A4*, which has a P4 responsive element [34]. It would be important to search for more P4 regulated genes in the lung as well as the participation of PR isoforms in the functions of this tissue.

In the adult mouse, the highest levels of ER-β in nonreproductive tissues were found in the lung [22]. In human lung fetus ER-α is almost undetectable compared to ER-β [35]. González-Arenas *et al*. showed that the lowest content of ER-β was found on the day of proestrus and increased again on the day of estrus as reported in other systems such as pituitary cells [25]. These data correlate with binding studies in female rats in which estrogen binding is higher at estrus [36]. In the lung of ovariectomized rats ER-β expression was down-regulated by E2 [19].

The content of ER-β was markedly lower in the lung of male rats than in that of females. Gender differences in ER isoforms have been reported in tumor and nontumor human lung [37]. In that study ER-β mRNA content in nontumor lung tissue of women was slightly higher than in men. A greater lung maturity has been reported in infant, rabbit and rat females than in males [38-40]. The maturation of this tissue could be related to sex differences in the content of ER.

Fig. (1). PR isoforms protein content in the lung of intact adult rats. A representative assay of four Western blot experiments is shown. Proteins from the rat lung (100 μg) were separated by electrophoresis on 7.5% SDS–PAGE. Gels were transferred to nitrocellulose membranes and then incubated with anti-PR antibody. The protein–antibody complex was detected by chemiluminescence (ECL). β-Actin was used to correct differences in the amount of total loaded protein. Metestrus (M), diestrus (D), proestrus (P), estrus (E) and intact males Modified from [32].

By examining ER-deficient (ERKO) mice, it was determined that both ER-α and ER-β are required for the formation of a full complement of alveoli in female mice, that ER-α mediates the sexual dimorphism of body mass-specific alveolar number and SA, and that absence of ER-β diminishes lung elastic tissue recoil [22, 41]. In male mice, ERs have a smaller effect on alveolar dimensions than in female mice [22]. Patrone *et al*. [42] investigated the alveolar defects in more detail and found deficiencies in platelet-derived growth factor A (PDGF-A) and granulocyte/ macrophage colony-stimulating factor (GM-CSF) in the lungs of adult βERKO mice. Since both PDGF-A and GM-CSF are critical factors in alveolar formation and surfactant production, and are controlled at the transcriptional level by ER-β, the authors concluded that the alveolar defects in the βERKO mice could be due to modifications in the expression of PDGF-A and GMCSF [42].

The expression of both PR isoforms and ER-β in the rat lung suggests a genomic action of P4 and E2 in this tissue. This could be supported by the fact that the functions regulated by P4 and E2 in the lung such as ventilation and lung maturation occurred at long latencies, usually more than 24 h, and most non-genomic actions of P4 and E2 occurred at short latencies (seconds or minutes). A direct effect of P4 in the lung is also supported by Waddell and O'Leary who recently demonstrated the presence of this steroid hormone in the rat lung in a major proportion compared with its metabolites (P4:metabolites ratio, 6:1) [43].

ESTROGEN AND PROGESTERONE PARTICIPATION IN LUNG DEVELOPMENT

It is well established in many species that lung maturation, as measured by surfactant production, is delayed in male fetuses compared with female fetuses [7, 39, 40]. Fetal plasma levels of estrogen are in abundance in the latter stages of gestation in many species [44-46]. Maternal administration of estrogen accelerates lung maturation and stimulates surfactant production in the fetal rabbit and rat [47-50]. In newborn piglets, prenatal estrogen deprivation significantly impairs alveolar formation and fluid clearance [51].

The chloride channel cystic fibrosis transmembrane conductance regulator (CFTR) and the epithelial sodium channel (ENaC) are important in lung development. The ENaC plays a critical role in the active reabsorption of alveolar fluid during pulmonary edema [52] and at birth, a process that is critical for the switch from placental to pulmonary delivery of O_2 [53]. CFTR is known to regulate other ion channels, including ENaC [54], and is thought to be important in the differentiation of the respiratory epithelium during development [55]. Sexually mature female rats have higher levels of mRNAs encoding ENaC and CFTR relative to males [56]. Combined, but not separate, administration of P4 and E2 augments mRNA levels of ENaC subunits or CFTR in sexually immature female rats [56]. This study concluded that increased expression of ENaC in the female lung may confer an advantage to females in better clearance of fetal lung liquid at birth or during pulmonary edema [56].

At the onset of sexual maturity, virgin female rats and mice have higher body mass specific gas-exchange surface area (SA) and smaller alveoli than age-matched males, although there is no difference in mass specific O_2 consumption [57]. The authors speculated that the differences in SA and alveolar size may have been selected for evolutionarily to help females meet the metabolic and O_2 demands of reproduction [57]. It was subsequently determined that estrogen is responsible for the sexual dimorphism in SA and alveolar size [58]. At 59 days, rats ovariectomized on day 21 have smaller SA and larger alveoli than sham ovariectomized rats [58]. Female rats treated with estrogen have smaller and more alveoli than females not receiving estrogen [58]. In mice, estrogen is also required for the maintenance of already-formed alveoli and induces alveolar regeneration after their loss in adult ovariectomized mice [3].

INFLUENCE OF ESTROGEN AND PROGESTERONE ON ASTHMA

There is considerable evidence to suggest that there is a role for sex and sex hormones in the pathogenesis of asthma [59-61]. Asthma prevalence in the general population is higher in women than in men, although several studies indicate distinctive changes in asthma prevalence and severity with age. Male children have asthma more frequently than female children, but a reversal of this incidence pattern occurs around the time of puberty, leading to a female predominance during middle age. The difference between the sexes is not apparent later in life (around the fifth or sixth decade), and some reports suggest that there is an increase once again in male prevalence [59-61]. These data collectively suggest a role for female sex hormones in promoting the asthmatic phenotype.

Asthma incidence is greater in boys during childhood and in girls during adolescence. There is no explanation for the change in gender related atopic disease to date. However, hormonal differences and their changes during adolescence have been considered to be contributing factors. It is well known that some female asthmatic patients experience aggravation of asthma symptoms during the premenstrual or menstrual phase of their cycle. This has been referred to as perimenstrual asthma (PMA). PMA has been documented in 30% to 40% of asthmatic women. This form of asthma can be severe and even life threatening with fatal cases were often reported. Therefore, prevention and treatment of PMA is of great interest. However, the underlying mechanisms associated with asthma exacerbation during the perimenstrual period and the related hormones have not been described [62-64].

Hoon Jeon *et al*. [65], investigated obesity, the menstrual cycle and lung function in adolescent girls. One hundred and three female high school girls (mean age: 15.9±0.8 yr) were enrolled. The investigation was performed using a questionnaire that included history of asthma, the menstrual cycle, other combined allergic disease and obesity. The skin prick and pulmonary function test during menstruation period and non-menstruation period. Analyses of these factors were compared. The forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) was significantly lower in the obese group compared to the non-obese group.

The FEV1 was significantly lower in the girls during menstruation period than in the girls who were not on menstruation. These results showed that changes of pulmonary function were related to menstrual cycle and obesity in Korean adolescent girls. The study showed that airflow limitation was present in the obese group, in girls with allergic disorders and during the menstrual phase as well as in girls who were sensitized to inhalant allergens. Further investigation into the relationship of sex hormones, leptin, lung function and asthma is needed in adolescent girls [65].

ESTROGEN AND PROGESTERONE ROLE IN CYSTIC LUNG DISEASES

Lymphangioleiomyomatosis (LAM) occurs sporadically in patients with no evidence of genetic disease and in approximately one third of women with tuberous sclerosis complex (TSC) [66-69]. LAM, is a disease affecting women and causing cystic lung lesions, and, in some instances, leading to respiratory failure and death, and it appears to be exacerbated by estrogens. Hence, hormonal therapy with P4 is frequently employed; Taveira-DaSilva *et al*. [70] determined whether P4 administration slowed the decline in lung function in LAM. The study population comprised 348 patients with LAM participating in a longitudinal research protocol. Declines in diffusion capacity of the lung for carbon monoxide (DLCO) and FEV1 were measured in

patients observed for approximately 4 years. The declines in DLCO and FEV1 of patients treated with P4 were compared with those of untreated patients. Patients treated with P4 tended to have lower rates of decline in FEV1 than patients without treatment. Rates of decline in DLCO were significantly higher in patients treated with P4 than in the untreated group. They concluded within the limitations of a retrospective study, that the data suggest that P4 therapy does not slow the decline in lung function in LAM [70].

Cystic fibrosis (CF) is a systemic disorder that develops in the gastrointestinal tract prior to birth but manifests in the lungs after birth. This delay in onset of airway obstruction opens a therapeutic window. CFTR is critically important to the airways and sinuses because it acts as a central regulator of periciliary ion and water content. Reducing or eliminating CFTR at the apical membrane of airway epithelial cells through genetic mutation, necrotizing infections, or experimentally by siRNA disrupts cAMPmediated Cl^- secretion and allows excessive epithelial Na^+ channel–mediated (ENaCmediated) Na^+ reabsorption. The net result is depleted airway surface liquid depth, poor ciliary function, impaired mucociliary clearance, and increased bacterial infections. It has long been hypothesized that parallel, non-CFTR mediated Cl^- conductance pathways might serve in a redundant capacity to carry Cl^- and promote fluid secretion when CFTR is absent. A proposed member of an alternative pathway of Cl^- conductance is the Ca^{2+}-activated Cl^- channel (CaCC) [71-73], which is the focus of the study reported by Coakley *et al*. [74].

The results of previously reported experiments performed at relatively high E2 concentrations suggest that estrogens and related molecules would have an impact on airway ion transport. The most common CF-associated mutation is the deletion of phenylalanine at residue 508 in CFTR (ΔF508 CFTR), and E2 at nM concentrations has been shown to rescue ΔF508 CFTR from proteasomal degradation and increase CFTR channel activity [75]. These authors identified the E2 target as Na^+/H^+ exchanger–regulator factor 1 (NHERF1). Raising E2 levels in the medium increased the levels of NHERF1, which facilitated the trafficking of mutant CFTR to the epithelial cell surface. Another group has studied CFTR expression in a rat model of human ovarian hyperstimulation syndrome (OHSS) [76]. OHSS occurs as a complication of assisted reproduction treatments that stimulate the ovaries. Using RT-PCR, Western blotting, and electrophysiologic techniques, this group demonstrated that CFTR expression is upregulated in this syndrome. Furthermore, estrogen but not P4 stimulated cAMP-mediated Cl^- secretion. Administration of P4 suppressed CFTR expression and alleviated symptoms in this animal model. Exogenous E2 but not P4 administered to ovariectomized rats increases CFTR expression in uterine tissue [77]. In extrapulmonary guinea pig ventricular myocytes, E2 has been shown to potentiate CFTR Cl^- currents [78]. The cAMP-activated Cl^- current in cardiac myocytes responds to exogenous E2 in a dose-dependent relationship at μM concentrations. However, there are opposing data regarding the effects of estrogens on CFTR-mediated Cl^- secretion.

Singh *et al*. [79] studied forskolin-activated (cAMP-activated) Cl^- currents in T84 human intestinal epithelial cells. The inhibition constant (*K*i) for E2 was 8 μM, which is unlikely to be experienced in vivo under normal circumstances. Synthetic estrogens and the selective estrogen receptor modulator tamoxifen also inhibited Cl^- currents in these cells. The balance of the data discussed here, which employed a variety of experimental systems, suggests that CFTR expression and function are stimulated by estrogens, except in the human colon carcinoma T84 cell line.

Recent studies suggest that the gap in lung function and prognosis between women and men is narrowing. If sex hormone cycling is leading to a significant reduction in airway mucociliary clearance, perhaps low-dose oral or patch contraceptives could be modified to reduce the disadvantage [80]. The results of the current study by Coakley *et al*. [74] reinforce that there is clearly a pressing need to raise awareness of sex-related differences in lung disease.

IMPLICATIONS OF ESTROGEN AND PROGESTERONE IN LUNG CANCER

There is substantial evidence for the presence of ER or ER-related proteins in pulmonary adenocarcinomas. Dabbs DJ, *et al*. [81] studied twenty-five resected solitary pulmonary nonmucinous bronchioalveolar carcinomas (15 female, 10 male) and 20 resected solitary pulmonary adenocarcinomas of no special type (12F, 8 mol/L) were studied by the immunohistochemical method using heat-induced epitope retrieval. Immunostaining was semiquantitated, and positive results included nuclear staining for ER and P4 receptor. The conclusion of the study was that the ER should not be used as a diagnostic tool to distinguish primary lung adenocarcinoma from metastatic breast carcinoma, because both tumors may be positive for ER, especially the ER 6F11 clone. The clinician and diagnostic pathologist need to be aware of the profound differences in immunoreactivity between the ER1D5 and 6F11 clones when examining tumors in the lung that are suspected of being a metastasis, especially from the breast [81].

Schwartz A., *et al* have identified differential nuclear ER-β expression in normal and lung tumor tissue, they were able to demonstrate that it is more frequent nuclear ER-β expression in men than in women particularly for adenocarcinomas, and survival differences in men by ER-β status. Nuclear ER-β expression was extremely common in these lung cancers opening up an avenue for translational research. Identifying ER-β status of a tumor may hold clinical value as a prognostic factor for predicting response to estrogen antagonists. Definitive conclusions pertaining to physiologic and tumorigenic consequences of ER-β expression in human lung await additional studies. Inclusion of risk factor data is important in this work because level and composition of circulating estrogens can be affected by smoking, age, race, oral contraceptive use, and hormone replacement therapy (HRT) use and may, therefore, be indirectly related to ER-β function through an estrogen mediated mechanism [82].

Canver *et al*. [83] investigated whether sex hormone receptors exist in the resected non-small-cell lung cancer in human beings and determined a link between the pulmonary

carcinogenesis and the sex receptor status of the lung cancer tissue, they reviewed the case histories of 64 patients who underwent resectional therapy for non-small-cell lung cancer between 1988 and 1990 (38 men and 26 women, mean age 65 years). Mouse monoclonal immunoglobulin G antibodies were used for immunohistochemical detection of estrogen receptors and P4 receptors in the acetone-fixed specimen. The control group consisted of normal lung tissue from the patients with and without bronchogenic carcinoma and breast cancer tissue from the patients with estrogen and P4 receptor immunoreactivity. No evidence of estrogen and P4 receptor immunoreactivity was present in the normal lung tissue. All but two patients had immunoreactivity (97%) for estrogen receptors in the lung cancer tissue [83].

Immunoreactivity for PR was absent or weak in the majority of patients. The differences for sex and for histologic subtypes were not statistically significant. Observed actuarial survival at 3 years was 83% for all patients with estrogen receptor immunoreactivity: 94% for women and 75% for men. They found no correlation between the hormone receptor status and the type, clinical features, or prognosis of the non-small-cell lung cancer. The conclusion was that an abundance of estrogen receptors is hosted only in cancerous tissue, not in normal pulmonary tissue. Improved identification and definition of estrogen receptors in the nontarget lung cancer tissue offers a possibility of antiestrogen therapy for patients with advanced bronchogenic carcinoma [83].

Hormone replacement therapy (HRT) compensates for the loss of endogenous estrogen that follows menopause and is typically prescribed to treat the symptoms related to it [84, 85]. However, HRT has also been associated with several additional putative health benefits including reductions in the risk of coronary heart disease and osteoporotic fractures, improved cognitive function, and reduced risk of colorectal cancer [86]. Nonetheless, controversy exists about the beneficial effects of HRT against recently suggested harmful effects that include risk of coronary heart disease, stroke, and thromboembolic events [87]. There are also concerns of whether HRT use may increase cancer risk. Although sex hormones are not genotoxic, it is known that they can stimulate or inhibit cell proliferation and, thus, theoretically modulate tumor development and progression [88], and their metabolites do have mutagenic potential. In addition some studies showed that estrogen metabolites could induce cancers of the breast, endometrium, kidney, and ovary [89]. Although recent data continue to support the association between HRT use and an increased risk for breast cancer, there have also been numerous other studies that did not demonstrate such an association [90-93].

To date, there have been relatively few data published regarding HRT use and lung cancer risk, and once again the data that have been published are inconsistent. For example, a Swedish study revealed a nonsignificantly slightly elevated risk of lung cancer in women taking estrogen replacement therapy. However, a small case-control analysis of 180 women with lung adenocarcinoma reported a 70% excess risk of lung cancer associated with estrogen replacement therapy (ERT) use [94]. There have also been studies showing no relationship between HRT use and lung cancer. A population study in Los Angeles County, CA, found no substantial relationship between HRT use in women with adenocarcinoma [95]. Ettinger *et al.* [96] observed a decrease in the risk of lung cancer mortality in a retrospective analysis of ERT users and nonusers. Likewise, a case-control study of female lung cancer patients showed a reduction in lung cancer risk associated with HRT use, this risk was additionally decreased among long-term users (7 years) when compared with nonusers [97].

Recently a study in Swedish women found that HRT use was associated with a decrease in the incidence of lung cancer and long-term HRT users who smoked had a decrease in the incidence of smoking-related cancers, including head and neck, lung, cervix, and bladder [98]. The use of ERT alone was associated with a 35% reduction in lung cancer risk and the use of combination therapy (estrogen and progestin) was associated with a 39% reduction in lung cancer risk. HRT use was also associated with a statistically significantly reduced risk of lung cancer in current smokers, but the risk estimates were not statistically significant in never or former smokers [99]. Decreased lung cancer risks were also evident when the data were stratified by age, ethnicity, and body mass index. The joint effects of HRT use and mutagen sensitivity suggest that HRT use modifies lung cancer risk for genetically susceptible women. HRT use was also associated with a lower risk of death and improved survival compared with the women not taking HRT [99]. The biological role of HRT in lung cancer remains understudied, and only extensive research can yield new insights into the mechanisms underlying a protective effect of HRT for lung cancer.

Oral contraceptives are associated with an increased risk of some cancers and a decreased risk of others. The absolute overall balance of incident cancer associated with oral contraception is unknown. Two large cohort studies reported on the overall risk of death from cancer among ever and never users of oral contraception; neither found significant differences between the groups [100, 101]. A Norwegian cohort study found no significant association between oral contraceptive use and the combined risk of breast, endometrial, and ovarian cancer [102]. A neutral balance of invasive genital cancers among ever and never users of oral contraception was found in the Royal College of General Practitioners' oral contraception study in the late 1980s [103]. Hannaford *et al.* examined the absolute risks or benefits on cancer associated with oral contraception, using incident data. In this study they found that ever users compared with never users had statistically significant lower rates of cancers of the large bowel or rectum, uterine body, and ovaries, tumors of unknown site, and other malignancies. The relative risk for any cancer in the smaller general practitioner observation dataset was not significantly reduced. Statistically significant trends of increasing risk of cervical and central nervous system or pituitary cancer, and decreasing risk of uterine body and ovarian malignancies, were seen with increasing duration of oral contraceptive use. Reduced relative risk were observed for ovarian and uterine body cancer many years after stopping oral contraception, although some were not statistically significant [104]. The balance of cancer risks and benefits may vary internationally,

depending on patterns of oral contraception usage and the incidence of different cancers.

CONCLUSIONS AND PERSPECTIVES

The effects of P4 and E2 in the lung appear to be of a great variability. The action of these hormones in lung development is very clear, the maturation of this organ through an increase in the production of surfactant liquid and in the number of alveoli increases as a result of P4 and E2 effect. In cystic diseases like LAM and cystic fibrosis, E2 may participate in the progress of these, while P4 seems to have no role in the development or decline of these diseases. In conditions such as asthma the role of E2 and P4 is unclear because although it has been observed that this condition occurs more often in men than in women, suggesting the involvement of P4 and E2 in the development of this illness, PMA syndrome (where hormone levels are very low) suggests that the absence of these hormones increased the severity of asthma attacks. In cancer the effects of E2 and P4 are controversial; several studies of women who have used oral contraceptives or HRT showed lower risk of developing lung cancer compared with women who never were subjected to these treatments, however other works have suggested higher risk of developing this pathology.

P4 and E2 participate in the regulation of many pulmonary functions and many studies suggest that many of these actions could be mediated by their specific intracellular receptors. The content of proteins involved in lung development like CYP4A4 prostaglandin ω hydroxylase or CFTR is regulated by P4 and E2 respectively, however it would be important to search for more P4 and E2 regulated genes and proteins in the lung as well as the participation of PR and ER isoforms and its mechanisms of action in the functions of this tissue.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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