Chapter 3
Sex Steroids and Their Influence in Lung Diseases Across the Lifespan

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Abstract  The economic burden of lung diseases continues to be on the rise, with increasing annual expenditures every year. However, the pathophysiology of lung diseases remains complex. Sex steroids are known to influence the development and the physiology of lungs across the life course. During puberty, there is a progressive increase in sex-steroid levels, which results in anatomical and physiological differences between the sexes, and the interactions are most likely causes of the observable sexual dimorphism in the incidence, prevalence, and severity of multiple lung pathologies. Notably, fluctuations during the menstrual cycle and pregnancy impact many lung pathologies, suggesting a link between female sex steroids and lung health. This chapter highlights the influence of sex steroids in lung diseases across the lifespan, adding to our understanding of their complex roles. Focusing on various time points, we aim to understand the following: (1) the inherent function of sex steroids in lung physiology, (2) their differential nature in lung diseases, (3) contribution of sex steroids in males versus females across the lifespan, (4) the implications of sex-steroid signaling, and (5) the probing questions on sex steroids and their interactions influencing the lungs. With the intention of appreciating the nuances of sex steroids in humans pertaining to epidemiological sex differences, we inform readers about the mechanisms involved in the sex–age interaction and sex steroids’ contributions in lung diseases across the lifespan.

Keywords  Adult lungs · Aging lungs · Estrogen · Progesterone · Sex differences · Testosterone

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3.1 Introduction

In the present-day era of omics and personalized medicine, we have overlooked and given less importance to the differential physiology and pathophysiology between males and females. This phenomenon is highly relevant and evident in pulmonary biology, where there has been limited sex-based research. A major factor in our understanding of sex-based physiology and pathophysiology is the sex steroids. The effects of sex steroids depend on their concentration, time of day, and site of action, as they vary across the life span of an individual. The goal of this chapter is to describe the influence of sex steroids in lung physiology and pathophysiology in males and females and across various life stages. Over the past two decades, studies on sex differences in health and disease have provided more information in this field. All this recent research has helped to bring about a consensus that sex should be taken into account as a biological variable, as opposed to just an observational feature, both in clinical research and clinical practice. Inherent sex differences are apparent right from the gestational age and manifest more as the lifespan progresses through adulthood to old age. Here, sex steroids (estrogens, progesterone, and testosterone) play a major modulatory role in all the life stages. Several in vivo and in vitro studies have established the critical role sex steroids play in sex differences in lung diseases. For example, the incidence, prevalence, and severity of asthma are higher in females (compared with males) after puberty, suggesting a role for sex steroids (Becklake and Kauffmann 1999; Carey et al. 2007b; Melgert et al. 2007). This is particularly important in major lung diseases—including asthma, chronic obstructive pulmonary disease (COPD), and pulmonary arterial hypertension (PAH)—in which epidemiological evidence suggests higher incidence, susceptibility, and severity in females than in males. This creates increased health care burdens, in the form of more physician visits, more hospitalizations, and a higher likelihood of death in some cases. Multiple observations in pulmonary research attribute the female sex as a significant risk factor for lung disease progression leading to death, which may differ in distinct pathologies. Studies addressing sex differences have been robust in the fields of cardiovascular (Lohff and Rieder 2004; Konhilas 2010; Leuzzi et al. 2010; Pérez-López et al. 2011), metabolic (Bigos et al. 2009; Greenhill 2011; Wang et al. 2011), and neurological health (Manson 2008; Janicki and Schupf 2010; Reddy 2010; Hines 2011; McEwen 2011; McEwen and Alves 2015). A better understanding of the biological role of sex steroids in mediating respiratory inflammation is needed. According to a recent report published by the American Thoracic Society, in a workshop by the National Heart, Lung, and Blood Institute, the National Institutes of Health (NIH) Office of Research on Women’s Health, and the NIH Office of Rare Diseases Research (“Female Sex and Gender in Lung/Sleep Health and Disease,” [Han et al. 2018]), clear emphasis was placed on the use of sex as a biological variable in both benchside-based laboratory research practices and clinical settings. This report critically reviewed the present understanding of the comprehensive implications of female sex on lung/sleep health and disease, addressing research gaps and
envisioning better health outcomes utilizing a specific and accurate management plan. A few noteworthy reviews regarding intrinsic sex differences in the respiratory physiology have been studied, and readers are referred to these topics (Gonzáles-Arenas and Agramonte-Hevia 2012; Townsend et al. 2012a; Martin and Pabelick 2014; Sathish et al. 2015; Fuentes and Silveyra 2018, 2019). Despite the highlighted publications reporting that sex steroids have more effects than a normal reproductive biological action, sex differences in lung diseases remain a subject of debate. Accordingly, it is imperative to summarize the contribution of sex steroids with respect to males versus females to better understand the potential role of sex steroids and their influence across the lifespan in the context of specific lung diseases.

Although there is limited knowledge on the effects of lung disease during the complete lifespan of an individual, there remains a hope for new collaborative studies to be able to shed light on the importance of considering sex steroids as a crucial determinant of lung development and function. Therefore, the primary purpose of this chapter is to emphasize the research done related to sex steroids and their role in lung diseases across different age groups of both sexes. Because the major research done to date has involved studies and investigations on adult lungs, which represent the majority of the health care burden, this chapter will focus on this aspect and highlight evidence of the subtle differences between males and females, with details about how sex-steroid effects on lungs begin early in life and are possibly amplified during the course of an adult’s lung disease. Readers will learn about some recent findings on sex-based and age-related sex-steroid dimorphism throughout this chapter, thus setting the stage to identify a novel paradigm of sex-based differences in lung diseases.

### 3.2 Biology of Sex Steroids

Classically, the normal reproductive function is what defines the role of sex steroids in the body. They are primarily produced by the three main organ systems—namely, the gonads, the adrenal glands, and the fetoplacental unit (Carey et al. 2007b, c). However, they have also been known to be metabolized in several nonendocrine peripheral tissues and organ systems (Koledova and Khalil 2007; Townsend et al. 2012a; Sathish et al. 2015; Frump and Lahm 2016; Fuentes and Silveyra 2019). The local production of sex steroids within specific tissues, mainly from nongonadal sources, depends on the concentration of the enzymes in cholesterol metabolism. The first step in the synthesis of sex steroids is the conversion of cholesterol to pregnenolone via the cholesterol side-chain cleavage enzyme (P450scc). After a cascade of downstream metabolic conversions, two active sex steroids are created, testosterone and 17β-estradiol (E2)—the male and female hormones, respectively. Several other estrogenic and androgenic precursors are assembled during the pathway which are metabolized into the active precursors by cytochrome P450 enzymes (Lahm et al. 2014). A detailed overview of sex hormone production and its regulation is explained in Fig. 3.1.
Fig. 3.1  Sex-steroid metabolism and regulation: a simplified overview of steroidogenesis, starting with the synthesis of estrogen, progesterone, and testosterone from cholesterol. Here, steroid hormones (luteinizing hormone [LH], follicle-stimulating hormone [FSH], and kisspeptin) regulate the release of the gonadal sex steroids, mainly by the hypothalamic–pituitary–gonadal axis. Cytochrome P450 (CYP) enzymes are particularly important and are a key modulator of the levels of sex steroids. Gonadotropin-releasing hormone (GnRH), neuropeptide Y (NPY), proopiomelanocortin (POMC), cholesterol side-chain cleavage enzyme (P450scc), cytochrome P450, family 11, subfamily A, polypeptide 1 (CYP11A1) gene, 3β-hydroxysteroid dehydrogenase (3β-HSD), cytochrome P450, family 17, subfamily A, polypeptide 1 (CYP17A1) gene, 17β-hydroxysteroid dehydrogenase (17β-HSD), cytochrome P450, family 19, subfamily A, polypeptide 1 (CYP19A1) gene, 16-hydroxyestrone (16-OHE1), 2-hydroxyestradiol (2-OHE2), 2-methoxyestradiol (2-ME2), 4-hydroxyestradiol (4-OHE2), 4-methoxyestradiol (4-ME2), cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) gene, cytochrome P450, family 42 N. A. Borkar and V. Sathish
All the sex-steroid receptors have been detected in human and murine lungs (Khosla et al. 1981; Couse et al. 1997). These sex steroids primarily interact with their receptors to mediate sex-steroid-dependent actions. Each of these sex-steroid hormones acts mainly through its receptor: estrogen receptor (ER, subtypes α and β), progesterone receptor (PR, subtypes A and B), and androgen receptor (AR) (Hewitt et al. 2005). Although the three major sex steroids—estrogen, progesterone, and testosterone—prompt the investigations pertaining to sex differences, a new possibility lies in studying other upstream regulators of sex-steroid metabolism regarding lung health and disease. The three hallmarks of the brain–reproductive axis are the brain, the pituitary, and the gonads. The hypothalamic-pituitary-gonadal (HPG) axis governs and amalgamates the complex interactions among these organ systems. Here, other hormones—such as gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and kisspeptin—play a role in regulating control over some aspects of sex-steroid function (Roseweir et al. 2009; Smith 2013). Recent studies from our group and others have suggested that lungs are capable of synthesizing and inactivating sex steroids, thereby modulating cellular-level sex-steroid actions (Ambhore et al. 2020; Townsend et al. 2012a; Fuentes and Silveyra 2018). What is currently not clear is whether local production occurs in the lungs at a differential level with respect to cell specifics and, if so, whether it is clinically relevant. Moreover, it is important to consider the ever-changing dynamics of life as various metamorphoses take place—for example, puberty in boys and girls, gestation and menopause in women, and aging-related changes in both sexes.

### 3.2.1 Estrogen

Being the principal female/ovarian sex steroid, estrogen’s role in physiology and sexual and reproductive development is sufficiently established. Estrogen has been implicated as a key hormone in the pathophysiology of many hormone-dependent diseases, especially breast cancer (Couse et al. 1997; Voltz et al. 2008; Bai and Gust 2009). Experimental evidence suggests that ERα and ERβ are the two main receptors governing estrogen signaling (Gustafsson 2003). The mechanisms governing these receptor-mediated effects vary depending on the nature of the bound ligand and the unique receptor conformation attained posthomodimerization, which may correspond to the pharmacological action.

The most effective estrogen endogenously synthesized in the body is 17β-estradiol (E2). Other weaker, although high affinity and potent ligands for ER

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**Fig. 3.1** (continued) 11, subfamily A, polypeptide 2 (CYP1A2) gene, cytochrome P450, family 11, subfamily B, polypeptide 1 (CYP1B1) gene, cytochrome P450, family 3, subfamily A, polypeptide 4 (CYP3A4) gene, and catechol-O-methyltransferase (COMT)

include estrone (E₁) and estriol (E₃) (Heldring et al. 2007). ERs are classically divided into two classes: the nuclear ERs—ERα (genetically coded by ESR1) and ERβ (genetically coded by ESR2)—and the membrane ERs, for example, G protein-coupled estrogen receptor 1 (GPER/GPR30) (Prossnitz et al. 2008). A newly added subtype, ERγ, has been found in fish (Hawkins et al. 2000; Ng et al. 2014). However, the role of estrogen signaling in lung function and disease states remains inconclusive because of the pleiotropic nature of ERs, with multiple studies reporting proinflammatory and/or anti-inflammatory effects in different cell types (Sathish et al. 2015). Accordingly, the cellular effects also vary depending on the nature and effects of the ligand binding (genomic versus nongenomic), which makes for more complicated signaling within the tissue (Gustafsson 2003; Deroo et al. 2006; Straub 2007; Burns and Korach 2017). Importantly, these actions are widespread in both sexes, with both in vitro and in vivo studies showing effects of estrogen in disease models of lungs. Studies of multiple groups, as well as our own, have observed differential expression and function of ERα and ERβ in the human airway smooth muscle (ASM) of lungs in the disease context of asthma. Interestingly, ERβ expression was significantly higher in the ASM of people with asthma compared with the ASM of others (Aravamudan et al. 2017). Another study showed that ERβ activation inhibits platelet-derived growth factor (PDGF)-induced proliferation in ASM cells, whereas ERα does not (Ambhore et al. 2018). Like the above, other studies suggest that the activation of ERα promotes proliferation (Maggioini et al. 2001; Teng et al. 2008), whereas ERβ activation inhibits proliferation by opposing ERα effects (Paruthiyil et al. 2004; Lahm et al. 2008; Rizza et al. 2014). This was also evident from studies in the pulmonary vasculature, wherein differential effects of ERα and ERβ were reported (Lindberg et al. 2003; Nikolic et al. 2007; O’Lone et al. 2007; Tsutsumi et al. 2008; Jayachandran et al. 2010). Estrogen and ERs regulate a multitude of known biological and physiological processes. The information obtained from past studies has helped and will continue to aid in the design and development of new therapeutic strategies to treat lung diseases contributing to new advances in precision medicine. It is believed that changes in levels of estrogen, as well as receptor-binding affinity, differ during development and in adult life. These discrepancies suggest a potential role of sex steroids in influencing the outcomes of developmental lung diseases and disease progression.

### 3.2.2 Progesterone

The gonadal and nongonadal peripheral signaling and regulation of estrogen have been widely studied, but less is known about the role of progesterone in nongonadal function. It was discovered in the 20th century to be the second major female sex steroid, and it is mainly associated with puberty (Blaustein et al. 2017; Farello et al. 2019), the menstrual cycle (Xu et al. 2010), embryogenesis (Guennoun et al. 1987; Compagnone et al. 1995), and maintenance of pregnancy, also called myometrial quiescence (Condon et al. 2006; Xie et al. 2018). Progesterone is traditionally called
the “pregnancy hormone,” but accumulating data have shown its physiological actions to affect several nonreproductive functions in both males and females (Clarke and Sutherland 1996; Lydon et al. 1996; Conneely and Lydon 2000; González-Orozco and Camacho-Arroyo 2019). This hormone acts through progesterone receptor A (PR-A) and progesterone receptor B (PR-B) (Conneely and Lydon 2000). Under physiological conditions in humans, cells have equal distributions of PR-A and PR-B (Taraborrelli 2015). A third isoform, PR-C, exists in myometrial tissue (Condon et al. 2006). Evidence suggests there are differences in the functional activities of PR-A and PR-B, with A and B regulating different physiological target genes in response to progesterone. Progesterone is much more selective toward PR-A than it is toward PR-B (Lamont and Tindall 2010). Whereas estrogen is a strong proinflammatory agent in its reproductive capacity, progesterone exerts a strong anti-inflammatory response, mediated via PRs. In some tissues, PRs also act via ERs, suggesting the existence of a dual-hormone effect in normal physiology (Lydon et al. 1996). Consistent with this prediction, studies have demonstrated the selective knockout of PR-A in a certain PR-A-knockout (PRAKO) mouse model, indicating that PR-A is crucial for normal reproductive function in females (Conneely and Lydon 2000). Therefore, it becomes important to explore the influence of progesterone alone and within the context of estrogen in normal states and disease states (Asimakopoulos et al. 2006; Nikolettos et al. 2008; Tam et al. 2011).

### 3.2.3 Testosterone

Androgens are involved in a wide range of physiological processes and are known to play various anabolic (Kochakian 1975), metabolic (Pitteloud et al. 2005a, b, Frederiksen et al. 2012a, b), and cognitive (Bain 2007) roles, both in men and in women, other than their well-known functions, such as maintenance of spermatogenesis and pubertal sexual maturation in males and overall GnRH regulation (Tyagi et al. 2017). Although testosterone has traditionally been viewed as a male hormone, newer reports suggest a possible role of testosterone in normal female physiology—namely, regulating multiple functional aspects of nonreproductive organs, such as the heart (Mayer et al. 2010; Kelly and Jones 2013), lungs (Levesque et al. 2000), bones (Isidori et al. 2005), skeletal muscles (Bergamini et al. 1969; Kelley and Mandarino 2000), brain (Azad et al. 2003), liver (Sesti et al. 1992; Aguirre et al. 2002; Muthusamy et al. 2009, 2011), intestines (Olorunshola et al. 2012), and adipocytes (Mauras et al. 1998). In males, testosterone is known to be the main androgen secreted by the Leydig cells (Nieschlag 2017; Nieschlag and Nieschlag 2019). The other androgens include the three proandrogens—dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione (A)—which are converted to active sex-steroids; testosterone and dihydrotestosterone (DHT) (Burger 2002). Estrogen or DHT can be formed upon irreversible aromatization of testosterone (García-Arencibia et al. 2005). Testosterone, which is the most active and predominant form of circulating androgens in the physiological state, is
produced by the testes in males. The adrenal glands (particularly the adrenal cortex) produce the other androgens in relatively smaller quantities. In females, androgens are secreted mainly by the adrenal glands and the ovaries, including postmenopausal ovaries (Burger 2002). There are very limited data on the role and function of testosterone in the pulmonary vasculature, especially in the lungs, with recent studies claiming that testosterone plays a role in normal physiology (Fu et al. 2014) and in disease states (Verma et al. 2011). AR in the lungs acts through testosterone both genomically (Mikkonen et al. 2010) and nongenomically (Kouloumenta et al. 2006). Although more research is needed, a recent report said a ligand-dependent gene expression of AR was observed in non small-cell lung carcinoma (NSCLC) tissues and the cell line A549 (Mikkonen et al. 2010). Androgens have been reported to promote Th1-mediated inflammation, in combination with estrogens, in allergic mouse models. Here, more severe allergic reaction was observed in the female mice than in the male mice, suggesting a protective role of androgens in allergic lung inflammation (Hayashi et al. 2003; Koper et al. 2017). Other studies using C57BL/6 mice to assess airway hyperresponsiveness to lipopolysaccharide (LPS)-induced inflammation showed exaggerated inflammation in female mice (Markova et al. 2004; Carey et al. 2007b). Several studies, including our own, have investigated the nongenomic effects of testosterone in different cell types in the lungs using animal models and cells derived from both humans and nonhuman species (Espinoza et al. 2013; Mendoza-Milla et al. 2013). Interestingly, in human ASM cells, our studies indicated lower baseline expression of AR in females than in males, and the difference was even greater between females with asthma and males with asthma. This study was also the first to shed light on a sex-specific differential expression of AR in both nonasthmatic and asthmatic primary human ASM cells (Kalidhindi et al. 2019). Studies done on bronchial epithelium-denuded tracheal rings pretreated with testosterone abolished histamine-induced contraction, thus causing bronchial tissue relaxation (Kouloumenta et al. 2006).

3.2.4 Other Regulators of Sex Steroids

Estrogen, progesterone, and testosterone are the most widely known steroidal sex hormones in males and females. Although these are called sex steroids, they do more than just affect and regulate reproductive development. Sex steroids are mediated through nuclear receptors by genomic signaling, as well as through membrane-associated receptors and subsequent downstream signaling cascades by rapid nongenomic actions. Steroidogenesis of sex steroids is, by definition, sexually polymorphic, involving differences between the sexes both in hormone action and in temporal patterns of production and interactions. Despite the numerous differences, there are similarities among sex steroids that cause interactions among them on different levels, depending on the life stage (Dharmage et al. 2019; Han et al. 2019; Zein et al. 2019). Concentrations of the sex steroids are known to naturally fluctuate with the menstrual cycle in females (Hammes and Levin 2011). In males,
there must exist an altered concentration of sex steroids throughout the lifespan. Thus, sex steroids influence normal physiology. Steroid hormones typically regulate cellular processes by binding to steroid receptors present on the cytoplasm, which in turn undergo translocation into the nucleus and bind to appropriate response elements present on DNA to produce a subsequent biological effect, a process taking about 30–60 min (Robertson et al. 1985; O’Malley and Tsai 1992). Adding to this complexity of genomic signaling, steroid receptors can get activated rapidly at the nongenomic level, as well, and this nongenomic activation might eventually activate signaling at the nuclear level (independently of binding to hormone response elements), such as in the nucleus (Uht et al. 1997; Weatherman et al. 2001; Cato et al. 2002; Simoncini et al. 2004). These multiple modes of steroid hormone activation divericate as life advances to produce sex differences, both in the expression of behavior and in pathophysiology states. The knowledge about each of these individual signaling molecules is abundant; however, integrating them into disease physiology seems difficult, considering the complexities of the subsequent effects and underlying factors. Studies to link the rapid actions of sex steroids to definite biological processes are ongoing. Readers are referred to some of the best reviews by other groups on this topic (Watson and Gametchu 1999; Funder 2001; Sunny and Oommen 2001; Cato et al. 2002; Simoncini et al. 2004).

As mentioned previously, cholesterol from food sources is used by different cells in tissues of gonadal and nongonadal origin to synthesize the common precursor, pregnenolone. This cascade’s endpoint is a synthesis of androgens and estrogens used to elicit a biological effect. The gonads are responsible for the production of sex steroids under the influences of LH and FSH. LH and FSH are secreted by gonadotrophs, located in the anterior pituitary gland. The HPG axis can be regarded as the command center of the endocrine system, regulating the synthesis and secretion of hormones from other glands through the kisspeptin–neurokinin B–dynorphin (KNDy) neuronal network and GnRH-producing neurons. The absence of ERα on GnRH neurons raises the possibility of an intermediate signaling pathway that may be activated to mediate sex-steroid feedback mechanisms (Herbison and Theodosis 1992). Kisspeptins act as a crude proxy for GnRH, stimulating robust induction by integrating endocrine and metabolic signals via classic feedback loops, thus controlling the downstream HPG axis throughout the lifespan of an individual. Although the role of kisspeptins has been implicated in the estrogen-positive feedback mechanism, it is unclear how kisspeptin signaling would be affected by the same hormonal stimulus (Smith 2013).

The kisspeptin signaling pathway revolutionized our current understanding of the HPG axis. Kisspeptins are increasingly recognized as a critical factor for normal puberty, secretion of gonadotropin, and reproduction (Beltramo et al. 2014; Clarke et al. 2015). Some of the most recent updates have been discussed in greater detail in these review articles (Clarke et al. 2015; Abbara et al. 2018; Dudek et al. 2018; Wahab et al. 2018; Wolfe and Hussain 2018). Kisspeptins are involved in both the positive- and the negative-feedback regulation of GnRH, which has been highlighted in many of the initial studies (Irwig et al. 2004; Messager et al. 2005; Kirilov et al. 2013). Studies have shown that hunger impairs GnRH secretion and leptin secretion
from adipose tissue, which further affects LH production (Weigle et al. 1997; Bergendahl et al. 1998). GnRH neurons do not express leptin receptors; in stark contrast to this observation lies the fact that almost 40% of the arcuate kisspeptin neurons present in the HPG axis express leptin receptors (Roa et al. 2006; Quennell et al. 2009; Backholer et al. 2010). This has been validated using various disease and receptor-knockout animal models (Navarro et al. 2004; Roa et al. 2006; Smith 2013). Moreover, investigations on human-derived hypogonadism show mutations in leptin or the leptin receptor, indicating that there may be crosstalk between kisspeptin and leptin (Sadaf Farooqi and O’Rahilly 2009; Wahab et al. 2018). Proopiomelanocortin (POMC)-, neuropeptide Y (NPY)-, and ghrelin-expressing neurons, among others, have been linked to this process (Quennell et al. 2009; Yeo and Colledge 2018). The aforementioned neurons communicate with kisspeptin neurons to mediate the expression of relevant genes (Backholer et al. 2010). Studies have suggested that ghrelin interacts directly with hypothalamic neurons, leading to suppression of gonadotropin release, thus impairing fertility, an effect that is dependent on the estradiol milieu (Martini et al. 2006; Kluge et al. 2012; Frazão et al. 2014; Yeo and Colledge 2018). Considering this milieu of population-level biological factors and delineating the underlying contributions of sex (and sex steroids) in this neurocircuitry is complicated by innate difficulties related to epidemiology and confounding factors. Therefore, we are not certain whether kisspeptins and other regulators of sex steroids have any fundamentally unresolved functions in the context of lung physiology.

3.3 Functions of Sex Steroids Across the Lifespan: An Emphasis on Lung Diseases

Lungs continue to develop and change throughout a person’s life. Sex steroids are clearly shown to have effects on the lungs across the lifespan, from developing lungs to developed lungs. This signifies that sex steroids are a fundamental cause of observed disparities among various pathologies occurring during the course of an individual’s life. As part of this chapter, we aim to collect and integrate clinical and biomedical evidence regarding the inherent effects of sex steroids on lung health and disease during the life course.

3.3.1 Effects of Sex Steroids in Prenatal Lungs

Lung development is categorized into three main periods—namely, the embryonic period, the fetal period, and the postnatal lung development period. Studies of pulmonary immaturity leading to respiratory distress have indicated that the lungs of male infants are less developed than those of female infants at the same gestational
This sexual dimorphism in the immature lung may be caused by concomitant effects of gradually increasing levels of sex steroids (Carey et al. 2007c). The effects of sex within the context of sex hormone modulation may contribute to the incidence, susceptibility, and severity of multiple disease pathogeneses from the neonatal period through the adult era (Carey et al. 2007b). Boys have larger lung volume but smaller and narrower airways than girls. This may be a risk factor and could be the reason male neonates have higher incidences of respiratory morbidities than female neonates (Thurlbeck 1982). Age-matched lung function in boys seems worse than in girls from the neonatal stage to one year (Stocks et al. 1997; Thomas et al. 2006). This maturation seems to be more advanced in the females than in the males in several species in terms of mouth movement (Hepper et al. 1997) and higher phospholipid secretory profiles, reflecting the lungs’ surfactant production (Torday and Nielsen 1987). Female newborns have also been reported to have less susceptibility than male newborns to developing respiratory distress syndrome (RDS) or transient tachypnea during early development because of a much better airway structure and a higher airflow rate, which allows for better air exchange peripherally. Evidence suggests that the structural and functional dimorphism of neonatal lungs begins before the synthesis of pulmonary surfactants (McMillan et al. 1989). Preterm infants and neonates are at high risk of having PAH. For a fetus, the placenta, as opposed to the lungs, serves as the organ of gas exchange, and there can be a complicated transition to the lungs at birth, resulting in complications of bronchopulmonary dysplasia (BPD) (Steinhorn 2010). Male neonates suffer more severely from PAH than female neonates (Humbert et al. 2006; Benza et al. 2010). In the case of BPD, male sex is considered an independent prognostic factor associated with respiratory morbidities (Marshall et al. 1999). This occurs because androgens (particularly DHT), which adversely affect surfactant production (McMillan et al. 1989; Catlin et al. 1990), have a large impact on the developing male fetus (Torday and Nielsen 1987). Infants born preterm and with BPD or another obstructive lung disease are at higher risk of developing chronic diseases such as COPD in adulthood (Madurga et al. 2013; Caskey et al. 2016). Male neonates are more likely to have RDS, and this is associated with higher incidences of mortality caused by conditions such as BPD and chronic lung disease (CLD) (Bhandari and Bhandari 2009; Townsel et al. 2017; Kelly 2006; Lingappan et al. 2016; Balaji et al. 2018). Androgens also increased the incidence of inflammation and subsequent lung injury in a study performed on castrated 20-day-old male rats, and the rats had a significantly higher survival rate and abatement of lung injury under hypoxic conditions (Neriishi and Frank 1984), which suggests there may be a damaging role of androgens in neonates. The results from another study showed that the administration of DHT to rabbits reduced surfactant production, suggesting that an androgen-dependent mechanism via transforming growth factor-β (TGF-β) signaling may be involved in delayed maturation in males (McMillan et al. 1989; Dammann et al. 2000). Additionally, reports suggest that accelerated lung maturation may correlate to the rate at which levels of estrogen rise in neonatal females (Adamson et al. 1990). A study derived from a similar hypothesis suggested that fetal lungs isolated from rats that were 19 days pregnant showed enhanced
phospholipid synthesis after stimulation with estrogen (Gross et al. 1980). Treatment of pig fetuses with estrogen and progesterone receptor antagonists considerably impaired alveolar formation (Trotter et al. 2007). Postnatal estradiol treatment improved pulmonary function, structure, and growth (McCurnin et al. 2009). The reported inhibitory effects of androgens and protective effects of estrogen on fetal lung maturation suggest a definite physiological role for the sex steroids in the lungs in utero. In addition, a number of discrete modifications manifest in fetal lungs during the third trimester to prepare fetuses for extrauterine life. Such variations can often be attributed to the effects of sex steroids on the lungs, and also impact pulmonary outcomes for adults.

### 3.3.2 Effects of Sex Steroids in Early Childhood

Lung development is invariably a continuous process, with anatomical and physiological differences observed in the lungs of boys and girls as age increases. Female fetuses show a lower specific airway resistance with an enhanced phospholipid profile in spite of the smaller lung size and volume. The first reason is the role of surfactant in maintaining an open and clear passage for air exchange in the airways (LoMauro et al. 2018; Becklake and Kauffmann 1999). The second reason is the increased susceptibility of lung infection in boys. Last but not least, is the underdeveloped nature of the airway epithelium in boys, which would be reason enough for a higher frequency of inflammation in immature male lungs. All these observations point to an altered lung structure (remodeling) in boys, especially in male neonates (Irvin 2000; Carey et al. 2007b; Voltz et al. 2008). Additionally, male sex is considered a major risk factor among the early childhood group, with the risk of developing chronic asthma being four-fold greater for boys than it is for girls until the age of 14 (Townsend et al. 2012a; Zein and Erzurum 2015; Yung et al. 2018). A number of studies have shown that respiratory allergic diseases are also prevalent in males during childhood, whereas they become more frequent and severe in females between adolescence and adulthood, indicating a major role of sex steroids as critical modulators of the immune response (Humbert et al. 2006; Martinez et al. 2012; Frump and Lahm 2016; Fuentes and Silveyra 2018; Barbagelata et al. 2019). Risk factors for childhood asthma include both genetic and environmental aspects—for example, prenatal complications in the infant breathing leading to RDS (Bonnet et al. 2009), child’s gender, and the presence of atopy (Trivedi and Denton 2019). While asthmatic phenotypes usually favor girls, PAH has an equal balance between boys and girls before pubertal age (Hansmann and Hoeper 2013). Thus, the anti-inflammatory effects of testosterone and the proinflammatory effects of estrogen should be examined separately. Evidence suggests that DHEA and its sulfate metabolite, DHEAS, a steroid prohormone that can further metabolize into testosterone and estrogen, decrease with age and also with multiple airway diseases (Kasperska-Zajac 2010; Mendoza-Milla et al. 2013). In this context, it is important to emphasize that how sex steroids affect the prepubertal age group is presently
unclear and warrants more studies. Further studies would help explain the gender switch observed in the prevalence and severity of a number of lung diseases during adolescence and likewise inform the differences in their mechanisms with subsequent maturation into puberty. An overview of sex-steroid levels during the lifespan of an individual, along with lung disease susceptibility, is shown in Fig. 3.2.

3.3.3 Effects of Sex Steroids in Late Childhood/Puberty

Puberty is a life stage at which sex steroids cause significant changes that lead to sexual maturation. An assessment of the mean age of puberty revealed that girls have a mean pubertal age of 10.5 years and boys have a mean pubertal age of 11.5 years (Brix et al. 2019; Limony et al. 2015; Marshall and Tanner 1969). Apart from the differences in males’ and females’ physical and sexual characteristics, there is an intriguing and potentially informative mechanism of sex steroids when it comes to lung health and disease. There are a higher number of lung-related hospital admissions for boys than for girls. But postpuberty, a gender switch occurs, a subject that requires further scrutiny and validation (Osman 2003). For example, in asthma cases followed prospectively from childhood, severity decreases postpuberty and into the
early stages of adulthood only among males. Asthma incidence begins to increase in females during late adolescence—a trend seemingly evident in the adult stage (Shah and Newcomb 2018). Overall, literature maintains a clear link between sex steroids and asthma (Foster et al. 1983; Beynon et al. 1988), and puberty is associated with fundamental hormonal fluctuations in both sexes (Sanfilippo 2008). Studies have indicated that the trend is more common in children with mild to moderate asthma, who tend to “outgrow” their asthma during puberty and subsequently into adulthood (Blair 1995; Gerritsen et al. 1990; Martin et al. 1980). For example, as mentioned in the previous section, DHEAS increases with puberty, inhibiting ASM and fibroblast proliferation (Koziol-White et al. 2012; Mendoza-Milla et al. 2013) and possibly contributing to epithelial–mesenchymal transition in the lungs (Xu et al. 2014), thereby alleviating chronic lung diseases. In boys, testosterone production, characterized by an increase in serum levels of DHEAS, leads to the initiation of puberty. This may explain the characteristic role of testosterone in ASM relaxation (Kouloumenta et al. 2006; Kalidhindi et al. 2019). Moreover, the occurrence of early-onset menarche in some females suggests a likely differential role of sex steroids among individuals, as females with early-onset menarche have cumulatively higher levels of estrogen and progesterone, along with lower serum hormone-binding globulin levels, than females with later-onset menarche (D. Apter et al. 1989; Salam et al. 2006). A certain correlation also exists between asthma status and corticosteroid treatment in pubertal children (Dorsey et al. 2006; DeBoer et al. 2018). Based on several cohort studies, early menarche is plausibly associated with the occurrence of asthma postpuberty because of estrogen and progesterone; however, the underlying mechanistic basis of this skewed pathobiology toward females is still unclear (Salam et al. 2006). In a study done on pubertal females, androgens associated positively with lung function, while estrogens associated negatively (a clear role of progesterone was not confirmed) (DeBoer et al. 2018). However, we cannot simply label this quest as testosterone vs. estrogen (or good vs. bad). Many things still need to be elucidated in the dynamics between late childhood and the pubertal age based on the nature, concentration, and fluctuation of sex steroids in an age-dependent context, on the cellular level (structural cells versus immune cells), and on the disease condition to come to a conclusion regarding sex-steroidal function in late childhood and puberty.

### 3.3.4 Effects of Sex Steroids in Adult Lungs

A major portion of respiratory diseases transforms into chronic states by the time an individual reaches the adult stage. Despite considerable progress in understanding developed adult lungs, how the pathogeneses of a spectrum of chronic pulmonary diseases—such as asthma, rhinitis, COPD, PAH, interstitial lung disease, and lung cancers—interplay with the modulating roles of sex steroids are complex and still under investigation. It is clear that the observed sexual disparity is caused by the physiology and pathophysiologically associated events brought about by sex
steroids (Townsend et al. 2012a). As we have discussed in earlier sections, sex differences and sex-steroid signaling in the lungs emerge as early as in utero and persist well into adulthood. Fundamentally, the cross-sectional area of the airways is higher in men than in women (Brooks and Strohl 1992). Furthermore, the literature suggests that significant differences in lung diseases also occur within the same sex (Barr and Camargo 2004; Barr et al. 2004; Koledova and Khalil 2007; Tam et al. 2011). Overall, a huge female-skewed ratio to men in several lung diseases, also hinting at worse health implications for women, emphasizes the need to understand the mechanism and the role of inherent sex differences versus how sex steroids act in lung disease pathophysiology. The evolution of respiratory diseases from childhood to adulthood has been the subject of multiple studies for many decades. The first prospective studies carried out in live subjects examined the reason males are more likely to have asthma in early adult life and confirmed the incidence of troublesome asthma in boys (Martin et al. 1980), as well as the tendency of asthmatic symptoms to be ameliorated by the age of 21 years (Johnstone 1968; Martin et al. 1980; Blair 1995; Roorda 1996). Though, those observations indicate that estrogen has to do with the remission of asthma, some studies have postulated otherwise (Roorda 1996). Physiological serum concentrations of sex steroids have also been implicated with lung diseases. In a study conducted in healthy and asthmatic females, serum concentrations of estradiol and progesterone differed outside of the normal range in approximately 80% of asthmatic females (Balzano et al. 2001). The severity of asthma is also suggested to fluctuate during the reproductive state, menstrual cycle, and pregnancy in females (Troisi et al. 1995). Given the well-known relationship between hormonal surges and lapses throughout the menstrual cycle, there is evidence of a relationship between sex steroids and aggravation of asthma (Frank 1931; Rees 1963; Eliasson 1981). One of the oldest studies that illustrated the crosstalk between sex steroids and respiratory dysfunctions reported a predisposition of asthma toward the menstrual cycle, wherein a woman was supposedly more prone to asthma attacks immediately before the start of her menses (Frank 1931). This hypothesis was made by several other groups in subsequent decades (Rees 1963; Hanley 1981; Gibbs et al. 1984; Eliasson et al. 1986). Some studies have, however suggested the contrary—that there is no relationship between airway function and the reproductive phase of an individual (Weinmann et al. 1987; Pauli et al. 1989). A study in patients with cystic fibrosis suggested that the disease symptoms were exacerbated during the menstrual cycle, while the same symptoms were abrogated in women administering oral contraceptives (Chotirmall et al. 2012). Interestingly, recent studies have suggested that hormonal status influences lung miRNA expression in ozone-induced lung inflammation, and there has been significant variability observed between males and females (Cabello et al. 2015; Fuentes et al. 2018). The theory that female sex hormones play a vital part in the circa rhythmicity of asthma, therefore, seems to be correct. Unlike the case with asthma, there is no consensus on whether there are sex differences in the prevalence of rhinitis, but some limited studies suggest a male predominance during childhood and a switch to a female predominance in adolescence and adulthood (Bertelsen et al. 2010; Barbagelata et al. 2019). Others suggest no clear outcome with respect to adult males and females.
Multiple studies have also reported a decrease in asthma symptoms and better asthma control in women who were administered oral contraceptives, either estrogen and/or GnRH analogs (Jenkins et al. 2006), although there have been some groups that have reported contradictory observations (Derimanov and Oppenheimer 1998).

Previous studies have shown the robust expression of ER$\alpha$ and ER$\beta$ in human lungs (Mollerup et al. 2002). The effects of estrogen in the airways have already been explored in vivo using specific estrogen receptor-knockout mouse models (Carey et al. 2007a; Riffo-Vasquez et al. 2007). Because there had been a limited number of studies to determine the mechanistic basis of differential ER$\alpha$ and ER$\beta$ signaling, our recent study using ER$\alpha$ KO mice and ER$\beta$ KO mice evaluated receptor-specific effects of endogenous estrogen in regulating the airway hyperresponsiveness (AHR) and remodeling. In this study, it was observed that ER$\beta$ KO mice showed exaggerated airway remodeling and AHR (Kalidhindi et al. 2020a). Th2-mediated allergic mouse models indicated a lesser infiltration of eosinophils and lymphocytes in mice treated with testosterone (Hayashi et al. 2003; Takeda et al. 2013). On the other hand, mice treated with estrogen and progesterone showed significantly increased interleukin-5 (IL-5) expression, immunoglobulin E (IgE) levels, and eosinophilic infiltration leading to increased AHR (Riffo-Vasquez et al. 2007; Fuseini and Newcomb 2017). Furthermore, reports on females suggest that estrogen (at periovulatory-to-pregnancy levels) and progesterone shift the immune response to a Th2 phenotype and suppress Th1 responses, whereas in males, testosterone is a Th2 suppressor, with an erratic pattern observed for Th1 responses (Straub 2007; Gilliver 2010; Koper et al. 2017; Han et al. 2018; Barbagelata et al. 2019). Our recent studies showed that testosterone via androgen receptor (AR) reduces ASM intracellular calcium ([Ca$^{2+}$]i) in the presence of proinflammatory cytokines and also highlighted a functional role of AR in both males and females (Kalidhindi et al. 2019). A study showed that DHT signaling via AR downregulates type 2 innate lymphoid cell (ILC2)-mediated cytokine expression and airway inflammation in mice of both sexes (Cephus et al. 2017). This was further supported by our histological findings, which implicated severe worsening of lung function and significantly increased airway remodeling (female>male) in a mixed allergen-induced mouse model of asthma (Ambhore et al. 2019a, b). The “estrogen puzzle” of PAH suggests that there is a better survival rate for female rats than for ovariectomized (OVX) female rats, which indicates a protective effect of estrogen (Al-Naamani and Ventetuolo 2019; Philip et al. 2019). While studies suggest there is a higher prevalence of PAH in females, animal models of PAH suggest otherwise, with estrogen significantly reducing pulmonary inflammation, thereby alleviating PAH, mediated via ER$\beta$ (Baker et al. 2004; Leventhal et al. 2006; Edvardsson et al. 2011). In addition, the rate of lung cancer mortality has been rising in women but not in men, with women being three times more likely to be diagnosed with lung cancer (there are notable histological sex differences in that there is a higher prevalence of squamous cell carcinoma in males and a higher prevalence of adenocarcinoma in females), implicating a possible hormonal component (LoMauro et al. 2018). A study on exposure to environmental tobacco smoke in a mouse model showed that
such exposure caused increased allergic sensitization and hyperreactivity in female mice (Seymour et al. 2002). Parallelly, in a clinical trial study, it was found that women were significantly more affected with COPD despite minimal tobacco smoke exposure (Han et al. 2007; Sørheim et al. 2010; Jenkins et al. 2017). This sex bias has led to a decrease in the mortality rate of men with COPD in the United States, while no change has occurred among females (LoMauro et al. 2018).

Overall, the present clinical and bench data showcase a contrasting nature of sex steroids, wherein there is no clarity on the nature of the sex steroids in the airways. Especially in the disease context of asthma, where there are several cyclical variations with respect to the reproductive age of the individual, it is of utmost importance to consider other variables, such as airway tone, ASM contractility, regulation of $[Ca^{2+}]_i$, and force contraction (Pabelick et al. 1995; Townsend et al. 2010). In vitro studies on human ASM have shown that acute exogenous exposure of E2 decreases $[Ca^{2+}]_i$ and influences cyclic adenosine monophosphate (cAMP) and cAMP-dependent protein kinase (PKA) (Townsend et al. 2012b). ASM is the main regulator of airway hyperreactivity and has become an important target within the lung for cell-specific studies (Loganathan et al. 2019). A precedent case showcasing estrogen-induced relaxation of smooth muscle has been widely recognized in the cardiovascular arena (Montgomery et al. 2003; Miller and Duckles 2008). The earliest report of experimental data on the relaxant properties of sex steroids in the lungs discussed the potentiation of isoproterenol-mediated relaxation of the porcine bronchus (Foster et al. 1983). Our recent studies have shown a higher expression of ER (α and β) in the ASM of those with asthma than in the ASM of nonasthmatics (Aravamudan et al. 2017). Here, long-term ERβ activation effectively reduces TNFα- or IL-13-induced $[Ca^{2+}]_i$ responses, particularly in the ASM of asthmatics, whereas ERα does not show significant effects (Bhallamudi et al. 2020). Furthermore, activation of ERβ downregulated PDGF-induced ASM proliferation by regulating Akt, ERK, and p38 MAPK pathways (Ambhore et al. 2018). Mechanistically, ERβ activation blunted TNFα- and PDGF-induced, ASM-derived extracellular matrix (ECM) production, and deposition via suppressing NF-κB signaling (Ambhore et al. 2019a, b).

In conclusion, these observations about the prevalence and severity of lung diseases suggest that gender affects airway inflammation and that this in turn is mediated by the congruity of sex steroids during an individual’s lifespan and subsequently play a critical role in disease development and progression. Despite experimental evidence from several in vitro studies and animal models, the specific mechanisms of action for sex steroids to promote or prevent lung diseases remain unclear. This can be evidenced by the current scenario of the COVID-19 pandemic that has afflicted people worldwide with reports suggesting a crucial role of sex steroids in COVID-19 pathophysiology via differentially expressed angiotensin converting enzyme-2 receptor (male > female) in human ASM cells (Kalidhindi et al. 2020b). Whether sex-steroidal manipulation is therapeutic or not, needs to be a separate study in order to determine whether there are therapeutic options in defined patient populations. In this regard, research is actively being pursued to consider
sex-steroid mechanisms via differential receptor signaling to gain insight into lung physiology, as well as pathology.

### 3.3.5 Effects of Sex Steroids in Aging Lungs

Sex differences also manifest in aging lungs. Physiologically, aging is a natural and unavoidable process wherein there is an observed decrease in elastic recoil of the lungs and large airways, resulting in increased alveolar air volume (Rodriguez-Roisin et al. 1999). Notably, the abundance of connective tissue increases (Turner et al. 1968; Gibson et al. 1976), also leading to a loss of lung integrity and impaired respiratory function (Rojas et al. 2015). These changes occur at a later age and appear less pronounced in females compared with males (Pride 2005). Aging has a bearing on individuals’ health-span (the period of disease-free living), depending on disease susceptibility, disease progression, and ongoing therapies. The lungs are no exception to this. In the past decade, we have learned that the relationship between higher age and a higher prevalence of lung diseases is more pronounced than previously thought. The mechanisms of this are not known (Selman et al. 2010; Sueblinvong 2012; Kapetanaki et al. 2013; Rojas et al. 2015; Thannickal et al. 2015). Aging is also known to influence other chronic lung diseases, such as acute lung injury, acute respiratory distress syndrome (ARDS), and asthma exacerbations (Eachempati et al. 2007; Tsai et al. 2013). The progressive nature of idiopathic pulmonary fibrosis (IPF) with unknown etiology occurs primarily in elderly adults, with a higher prevalence of the disease observed in men than in women (Raghu et al. 2006; Selman et al. 2010; King et al. 2011; Rojas et al. 2015). The prevalence of diseases such as IPF and COPD increases gradually as age advances, meaning they are much more common in the geriatric population, but there is no clear manifestation to determine whether there are sex differences (Ito and Barnes 2009). Whether aging women have increased risk for lung cancer is not certain (Cohen et al. 2007), as there have been no studies pertinent to the role of aging with respect to sex differences in lung cancer incidence. Inflammation caused by chronic cigarette smoke exposure in COPD is also associated with a gradual activation of immune cells in aging lungs over a certain period because of physiological changes, indicating a role for age-related inflammatory changes (John-Schuster et al. 2016). Interestingly, no difference in the survival rate was observed among aged men and women with PAH (Shapiro et al. 2012). Overall, in the context of respiratory diseases, remarkably little work has been done to investigate the effect of sex steroids on aging (Tulchinsky et al. 1972; Labrie et al. 1998; Townsend et al. 2012a). In aging, circulating concentrations of the sex-steroid prohormones DHEA and DHEAS (Buford and Willoughby 2008), as well as other sex steroids, decrease steeply. Likewise, menopause is known to be associated with lower levels of estrogen and progesterone and to coincide with the early stages of asthma (Rojas et al. 2015). This explains why postmenopausal women are less susceptible to suffering from asthma than aged men (Balzano et al. 2001).
It is believed that in the case of asthma, there is a major switch that takes place during the fifth or sixth decade—wherein there is a slightly greater prevalence in men, particularly asthma attributed to immune dysregulation (Zannolli et al. 1997). A study conducted on premenopausal and postmenopausal women suggested a higher risk of asthma in premenopausal women than in postmenopausal women (Troisi et al. 1995). This observation was however, in contrast to a cross-sectional study revealing a greater prevalence of asthma in aged males than in females (Zein et al. 2015), a result of possible “detoxification of androgens” (Blakemore and Naftolin 2016). This could result in an age-related decline in androgens corresponding to an increase in estrogen levels physiologically. Besides this, whether the conversion of testosterone to estrogen mediated by the cytochrome P450 enzyme aromatase (CYP19A1) creates a local imbalance in the levels of testosterone and estrogen and thus influences the development of lung disease still needs to be answered (Assaggaf and Felty 2017). Interestingly, studies have also reported conversely that with aging, discrepancies between male and female lung physiologies decrease. For example, a Swedish-based study showed that younger women had a lower total score on the Mini Asthma Quality of Life Questionnaire than similarly aged men, with no significant difference at older ages (Lisspers et al. 2013).

The above observations link aging-related respiratory morbidities with sex steroids. More clinical and experimental studies are required to specifically identify the consequences of aging on the lungs as a target organ. Because adults constitute the major age group of research in the current setting, we would like to take this opportunity to emphasize that more focus should also be placed on the geriatric population with lung disease, which also constitutes a major health care burden. Seeing as late adulthood is an important phase, it would be worthwhile to examine new strategies to delay aging’s impact on the course of diseases.

3.4 Conclusion and Future Scope

How sex steroids lead to gender and sex differences are relevant to more than just normal cellular biology and physiology. Sex steroids have fascinating roles that go far beyond the anatomical and physiological realms. The paraphrase “Sex matters to every cell of the body” (Young and Becker 2009) emphasizes the critical role of sex-steroid signaling in the structure and function of lungs at different life stages. Even though steroidogenesis is similar across both sexes, the subsequent molecular pathways each of the sex steroids undertake vary between males and females, leading to complex and scientifically unexplained actions and interactions within the lungs. Sex steroids typically regulate cellular processes by genomic/slow and nongenomic/rapid actions via nuclear- and membrane-associated receptors, respectively. The classic sex-steroid receptors—namely, ER (α or β), PR (A or B), and AR—are all nuclear receptors. Depending on their similarities and differences, crosstalk between these receptors can occur at multiple levels. For example, there
can be inter-receptor signaling (Hall and McDonnel 1999; Zhang and Teng 2000; Bennett et al. 2010), as well as downstream activation (Barchiesi et al. 2002; Dubey et al. 2009). Although the exact mechanism by which sex steroids exert effects through these divergent receptor-mediated actions is not yet fully characterized, it is evident that all the major cell types in the lungs are affected by these sex steroids. Moreover, the presence of tissue-specific metabolism and conversion in the lungs means that the qualitative effects of these sex steroids are radically different from the observed multifactorial effects. Overall, the importance of sex steroids in the lungs and their clinical implications were established in the earlier sections of this chapter. Although this chapter attempts to explain the effects of these sex steroids in different cell types, the effects are heterogeneous and often not entirely understood. However, what is known, is that the effects of these sex steroids are, as mentioned previously, concentration-, time-, context-, dose-, and site-specific. From a molecular perspective, understanding the numerous pathways begun independently or dependently by these sex steroids and their interactions are just the beginning of trying to understand this complex panoply of effects. As much as it is important to understand the individual contributions of sex steroids in the pathogeneses of lung diseases, it is equally important to emphasize that organisms and individuals are integrated entities fulfilling their specific functions. Therefore, even though it is important to classify the role of each sex steroid, the need of the hour is to be able to identify, as well as implement, the major players that cause the overall sex differences in various lung diseases. To establish this, supplementary work is needed to address biological mechanisms through which sex and age influence sex-steroid-related outcomes in lung diseases. As more and more experiments are conducted on males and females, underlying sex differences in the etiology of lung diseases will be highlighted, which will enable scientists to untangle alterations and develop specific therapeutic strategies against these lung diseases.

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References

Abbara A, Islam R, Clarke SA et al (2018) Clinical parameters of ovarian hyperstimulation syndrome following different hormonal triggers of oocyte maturation in IVF treatment. Clin Endocrinol (Oxf) 88:920–927. https://doi.org/10.1111/cen.13569
Adamson I, Bakowska J, McMillan E et al (1990) Accelerated fetal lung maturation by estrogen is associated with an epithelial-fibroblast interaction. In Vitro Cell Dev Biol 26:784–790. https://doi.org/10.1007/BF02623620
Aguirre V, Werner ED, Giraud J et al (2002) Phosphorylation of Ser307 in insulin receptor substrate-1 blocks interactions with the insulin receptor and inhibits insulin action. J Biol Chem 277:1531–1537. https://doi.org/10.1074/jbc.M101521200
Al-Naamani N, Ventetuolo CE (2019) Another piece in the estrogen puzzle of pulmonary hypertension. Am J Respir Crit Care Med 201:2019–2020. https://doi.org/10.1164/rccm.201910-1982ed
Ambhore NS, Katragadda R, Kalidhindi RSR et al (2018) Estrogen-receptor beta signaling inhibits PDGF-induced human airway smooth muscle proliferation. Mol Cell Endocrinol 476:37–47. https://doi.org/10.1016/j.mce.2018.04.007

Ambhore NS, Kalidhindi RSR, Pabelick CM et al (2019a) Differential estrogen-receptor activation regulates extracellular matrix deposition in human airway smooth muscle remodeling via NF-κB pathway. FASEB J 33(12):13935–13950. https://doi.org/10.1096/fj.201901340R

Ambhore NS, Kalidhindi RSR, Loganathan J et al (2019b) Role of differential estrogen-receptor activation in airway hyperreactivity and remodeling in a murine model of asthma. Am J Respir Cell Mol Biol. 61(4):469–480. https://doi.org/10.1165/rcmb.2018-0321OC

Ambhore NS, Bhallamudi S, Kalidhindi RSR et al (2020) Role of estrogen metabolites in regulating intracellular calcium in human airway smooth muscle cell. Am J Respir Crit Care Med 2020:A1237–A1237

Apter D, Reiniäl M, Reijo V (1989) Some endocrine characteristics of early menarche, a risk factor for breast cancer, are preserved into adulthood. Ital J Cancer E787:783–787. https://doi.org/10.1002/ijc.2910440506

Aravamudan B, Goorhouse KJ, Unnikrishnan G et al (2017) Differential expression of estrogen-receptor variants in response to inflammation signals in human airway smooth muscle. J Autism Dev Disord 47:549–562. https://doi.org/10.1097/CCM.0b013e31823da96d

Asimakopoulos B, Köster F, Felberbaum R et al (2006) Cytokine and hormonal profile in blood serum and follicular fluids during ovarian stimulation with the multidose antagonist or the long agonist protocol. Hum Reprod 21:3091–3095. https://doi.org/10.1093/humrep/dei207

Assaggaf H, Felty Q (2017) Gender, estrogen, and obliterative lesions in the lung. Int J Endocrinol. https://doi.org/10.1155/2017/8475701

Azad N, Pitale S, Barnes WE, Friedman N (2003) Testosterone treatment enhances regional brain perfusion in hypogonadal men. J Clin Endocrinol Metab 88:3064–3068. https://doi.org/10.1210/jc.2002-020632

Backholer K, Smith JT, Rao A et al (2010) Kisspeptin cells in the ewe brain respond to leptin and communicate with neuropeptide Y and proopiomelanocortin cells. Endocrinol 151:2233–2243. https://doi.org/10.1210/en.2009-1190

Bai Z, Gust R (2009) Breast cancer, estrogen receptor and ligands. Arch Pharm (Weinheim) 342:133–149. https://doi.org/10.1002/ardp.200800174

Bain J (2007) The many faces of testosterone. Clin Interv Aging 2:567–576. https://doi.org/10.2147/cia.s1417

Baker AE, Brautigam VM, Watters JJ (2004) Estrogen modulates microglial inflammatory mediator production via interactions with estrogen receptor β. Endocrinol 145:5021–5032. https://doi.org/10.1210/en.2004-0619

Balaji S, Dong X, Li H et al (2018) Sex-specific differences in primary neonatal murine lung fibroblasts exposed to hyperoxia in vitro: Implications for bronchopulmonary dysplasia. Physiol Genomics 50:940–946. https://doi.org/10.1152/physiolgenomics.00075.2018

Balzano G, Fuschillo S, Melillo GSB (2001) Asthma and sex hormones. Indian J Chest Dis Allied Sci 43:135–147. https://doi.org/10.1002/ardp.200800174

Barr RG, Camargo CA (2004) Hormone replacement therapy and obstructive airway diseases. Treat Respir Med 3:1–7. https://doi.org/10.2165/00151829-200403010-00001

Barr RG, Wentowski CC, Grodstein F et al (2004) Prospective study of postmenopausal hormone use and newly diagnosed asthma and chronic obstructive pulmonary disease. Arch Intern Med 164:379–386. https://doi.org/10.1001/archinte.164.4.379
Becklake MR, Kauffmann F (1999) Gender differences in airway behaviour over the human life span. Thorax 54:1119–1138. https://doi.org/10.1136/thx.54.12.1119

Beltramo M, Dardente H, Cayla X, Caraty A (2014) Cellular mechanisms and integrative timing of neuroendocrine control of GnRH secretion by kisspeptin. Mol Cell Endocrinol 382:387–399. https://doi.org/10.1016/j.mce.2013.10.015

Bennett NC, Gardiner RA, Hooper JD et al (2010) Molecular cell biology of androgen receptor signalling. Int J Biochem Cell Biol 42:813–827. https://doi.org/10.1016/j.biocel.2009.11.013

Benza RL, Miller DP, Gomberg-Maitland M et al (2010) Predicting survival in pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation 122:164–172. https://doi.org/10.1161/CIRCULATIONAHA.109.898122

Bergamini E, Bombara G, Pellegrino C (1969) The effect of testosterone on glycogen metabolism in rat levator ani muscle. Biochimica et Biophysica Acta 177(2):220–234. https://doi.org/10.1016/0304-4165(69)90131-7

Bergendahl M, Aloi JA, Iranmanesh A et al (1998) Fasting suppresses pulsatile luteinizing hormone (LH) secretion and enhances orderliness of LH release in young but not older men. J Clin Endocrinol Metab 83:1967–1975. https://doi.org/10.1210/jc.83.6.1967

Bertelsen RJ, Instanes C, Granum B et al (2010) Gender differences in indoor allergen exposure and association with current rhinitis. Clin Exp Allergy 40:1388–1397. https://doi.org/10.1111/j.1365-2222.2010.03543.x

Beynon HLC, Garbett ND, Barnes PJ (1988) Severe premenstrual exacerbations of asthma: effect of intramuscular progesterone. Lancet 332:370–372. https://doi.org/10.1016/S0140-6736(88)92873-1

Bhallamudi S, Connell J, Pabelick CM et al (2020) Estrogen receptors differentially regulate intracellular calcium handling in human non-asthmatic and asthmatic airway smooth muscle cells. Am J Physiol Cell Mol Physiol 318:112–124. https://doi.org/10.1152/ajpcell.00206.2019

Bhandari A, Bhandari V (2009) Pitfalls, problems, and progress in bronchopulmonary dysplasia. Pediatrics 123:1562–1573. https://doi.org/10.1542/peds.2008-1962

Bigos KL, Pollock BG, Stankevich BA, Bies RR (2009) Sex differences in the pharmacokinetics and pharmacodynamics of antidepressants: an updated review. Gend Med 6:522–543. https://doi.org/10.1016/j.germ.2009.12.004

Blair H (1995) Natural history of childhood asthma. Pediatr Pulmonol 19:30–31. https://doi.org/10.1002/ppul.1950191117

Blakemore J, Naftolin F (2016) Aromatase: contributions to physiology and disease in women and men. Physiology 31:258–269. https://doi.org/10.1152/physiol.00054.2015

Blaustein JD, Ismail N, HM K (2017) Review: puberty as a time of remodeling the adult response to ovarian hormones. Physiol Behav 176:139–148. https://doi.org/10.1016/j.physbeh.2017.03.040

Bonnet S, Paulin R, Sutendra G et al (2009) Dehydroepiandrosterone reverses systemic vascular remodeling through the inhibition of the Akt/GSK3-β/NFAT Axis. Circulation 120:1231–1240. https://doi.org/10.1161/CIRCULATIONAHA.109.848911

Brooks LJ, Strohl KP (1992) Size and mechanical properties of the pharynx in healthy men and women. Am Rev Respir Dis 146:1394–1397. https://doi.org/10.1164/ajrccm.146.6.1394

Brix N, Ernst A, Lauridsen LLB et al (2019) Timing of puberty in boys and girls: a population-based study. Paediatr Perinat Epidemiol 33:70–78. https://doi.org/10.1111/ppe.12507

Buford TW, Willoughby DS (2008) Impact of DHEA(S) and cortisol on immune function in aging: a brief review. Appl Physiol Nutr Metab 33:429–433. https://doi.org/10.1139/H08-013

Burger HG (2002) Androgen production in women. Fertil Steril 309(Suppl 4):S3–S5. https://doi.org/10.1016/s0015-0282(02)02985-0

Burns KA, Korach KS (2017) Estrogen receptors and human disease: an update. Physiol Behav 176:139–148. https://doi.org/10.1016/j.physbeh.2017.03.040

Cabello N, Mishra V, Sinha U et al (2015) Sex differences in the expression of lung-inflammatory mediators in response to ozone. Am J Physiol - Lung Cell Mol Physiol 309:L1150–L1163. https://doi.org/10.1152/ajplung.00018.2015
Carey MA, Card JW, Bradbury JA et al (2007a) Spontaneous airway hyperresponsiveness in estrogen receptor-α-deficient mice. Am J Respir Crit Care Med 175:126–135. https://doi.org/10.1164/rccm.200509-1493OC

Carey MA, Card JW, Voltz JW et al (2007b) The impact of sex and sex hormones on lung physiology and disease: lessons from animal studies. Am J Physiol - Lung Cell Mol Physiol 293:272–278. https://doi.org/10.1152/ajplung.00174.2007

Carey MA, Card JW, Voltz JW et al (2007c) It’s all about sex: gender, lung development and lung disease. Trends Endocrinol Metab 18:308–313. https://doi.org/10.1016/j.tem.2007.08.003

Caskey S, Gough A, Rowan S et al (2016) Structural and functional lung impairment in adult survivors of bronchopulmonary dysplasia. Am Ann Thorac Soc 13:1262–1270. https://doi.org/10.1513/AnnalsATS.201509-578OC

Catlin EA, Powell SM, Manganaro TF et al (1990) Sex-specific fetal lung development and Mullerian-inhibiting substance. Am Rev Respir Dis 141:466–470. https://doi.org/10.1164/ajrccm/141.2.466

Cato ACB, Nestl A, Mink S (2002) Rapid actions of steroid receptors in cellular signaling pathways. Sci STKE 2002(138):re9. https://doi.org/10.1126/stke.2002.138.re9

Cephus JY, Stier MT, Fuseini H et al (2017) Testosterone attenuates group 2 innate lymphoid cell-mediated airway inflammation. Cell Rep 21:2487–2499. https://doi.org/10.1016/j.celrep.2017.10.110

Chotirmall SH, Smith SG, Gunaratnam C et al (2012) Effect of estrogen on pseudomonas mucoidy and exacerbations in cystic fibrosis. N Engl J Med 366:1978–1986. https://doi.org/10.1056/NEJMoa1106126

Clarke CL, Sutherland RL (1996) Progestin regulation of cellular proliferation. Adv Oncobiol 1:79–98. https://doi.org/10.1210/endo.136.6.7750493

Conmee OM, Lydon JP (2000) Progesterone receptors in reproduction: functional impact of the A and B isoforms. Steroids 65:571–577. https://doi.org/10.1016/S0039-128X(00)00115-X

Czer JF, Lindzey J, Grandien K et al (1997) Tissue distribution and quantitative analysis of estrogen receptor-α (ERα) and estrogen receptor-β (ERβ) messenger ribonucleic acid in the wild-type and ERo-knockout mouse. Endocrinol 138:4613–4621. https://doi.org/10.1210/endo.138.11.5496

Degmann CEL, Ramadurai SM, Mccants DD et al (2000) Androgen regulation of signaling pathways in late fetal mouse lung development. Endocrinology 141:2923–2929. https://doi.org/10.1210/endo.141.8.7615

DeBoer MD, Phillips BR, Mauger DT et al (2018) Effects of endogenous sex hormones on lung function and symptom control in adolescents with asthma. BMC Pulm Med 18:1–10. https://doi.org/10.1186/s12890-018-0612-x

Derimanov GS, Oppenheimer J (1998) Exacerbation of premenstrual asthma caused by an oral contraceptive. Ann Allergy Asthma Immunol 81:243–246. https://doi.org/10.1016/S1081-1206(10)62820-7
Deroo BJ, Korach KS, Deroo BJ, Korach KS (2006) Estrogen receptors and human disease. J Clin Invest 116:561–570. https://doi.org/10.1172/JCI27987

Dharmage SC, Perret JL, Custovic A (2019) Epidemiology of asthma in children and adults. Front Pediatr 7:1–15. https://doi.org/10.3389/fped.2019.00246

Dorsey MJ, Cohen LE, Phipatanakul W et al (2006) Assessment of adrenal suppression in children with asthma treated with inhaled corticosteroids: Use of dehydroepiandrosterone sulfate as a screening test. Ann Allergy Asthma Immunol 97:182–186. https://doi.org/10.1016/S1081-1206(10)60010-5

Dubey RK, Gillespie DG, Imthurn B et al (2009) Phytoestrogens inhibit growth and MAP kinase activity in human aortic smooth muscle cells. Hypertension. 33(1 Pt 2):177–182. https://doi.org/10.1161/01.hyp.33.1.177

Dudek M, Ziarniak K, Sliwowska JH (2018) Kisspeptin and metabolism: The brain and beyond. Front Endocrinol (Lausanne) 9:1–8. https://doi.org/10.3389/fendo.2018.00145

Eachempati SR, Hydo LJ, Shou J, Barie PS (2007) Outcomes of acute respiratory distress syndrome (ARDS) in elderly patients. J Trauma - Inj Infect Crit Care 63:344–350. https://doi.org/10.1097/TA.0b013e3180eea5a1

Edvardsson K, Ström A, Jonsson P et al (2011) Estrogen receptor \(\beta\) induces antiinflammatory and antitumorigenic networks in colon cancer cells. Mol Endocrinol 25:969–979. https://doi.org/10.1210/me.2010-0452

Eliasson O (1981) A cautionary tale about the investigations of the effect of the menstrual cycle on asthma. Bull Comed 33:89–92. https://doi.org/10.1353/boc.1981.0025

Eliasson O, Scherzer HH, DeGraff AC (1986) Morbidity in asthma in relation to the menstrual cycle. J Allergy Clin Immunol 77:87–94. https://doi.org/10.1016/0091-6749(86)90328-3

Espinoza J, Montaño LM, Perusquía M (2013) Nongenomic bronchodilating action elicited by dehydroepiandrosterone (DHEA) in a guinea pig asthma model. J Steroid Biochem Mol Biol 138:174–182. https://doi.org/10.1016/j.jsbmb.2013.05.009

Fagan JK, Scheff PA, Hryhorczuk D et al (2001) Prevalence of asthma and other allergic diseases in an adolescent population: Association with gender and race. Ann Allergy, Asthma Immunol 86:177–184. https://doi.org/10.1016/S1081-1206(10)62688-9

Farello G, Altieri C, Cutini M et al (2019) Review of the literature on current changes in the timing of pubertal development and the incomplete forms of early puberty. Front Pediatr 7:1–7. https://doi.org/10.3389/fped.2019.00147

Foster PS, Goldie RG, Paterson JW, Spina D (1983) Effect of hypothermia on \(\beta_1\)-adrenoceptor-mediated relaxation of pig bronchus. Br J Pharmacol 80:699–702. https://doi.org/10.1111/j.1476-5381.1983.tb10060.x

Frank RT (1931) The hormonal causes of premenstrual tension. Arch Neuropsych. 26 (5):1053–1057. https://doi.org/10.1001/archneurpsyc.1931.02230110151009

Frazão R, Dungan Lemko HM, da Silva RP et al (2014) Estradiol modulates Kiss1 neuronal response to ghrelin. Am J Physiol - Endocrinol Metab 306:606–614. https://doi.org/10.1152/ajpendo.00211.2013

Frederiksen L, Højlund K, Hougaard DM et al (2012a) Testosterone therapy decreases subcutaneous fat and adiponectin in aging men. Eur J Endocrinol 166:469–476. https://doi.org/10.1530/EJE-11-0565

Frederiksen L, Højlund K, Hougaard DM et al (2012b) Testosterone therapy increased muscle mass and lipid oxidation in aging men. Age (Dordr) 34:145–156. https://doi.org/10.1007/s11357-011-9213-9

Frump AL, Lahm T (2016) Sex-hormone signaling in the lung in health and disease: airways, parenchyma, and pulmonary vasculature. In: Hemnes A (ed) Gender, sex hormones and respiratory disease. Respiratory medicine. Humana Press, Cham, pp 27–62. https://doi.org/10.1007/978-3-319-23998-9_2

Fu L, Freishtat RJ, Gordish-Dressman H et al (2014) Natural progression of childhood asthma symptoms and strong influence of sex and puberty. Ann Am Thorac Soc 11:898–907. https://doi.org/10.1513/AnnalsATS.201402-084OC
3 Sex Steroids and Their Influence in Lung Diseases Across the Lifespan 63

Fuentes N, Silveyra P (2018) Endocrine regulation of lung disease and inflammation. Exp. Biol. Med. 243:1313–1322. https://doi.org/10.1177/1535370218816653

Fuentes N, Silveyra P (2019) Estrogen-receptor signaling mechanisms. Adv Protein Chem Struct Biol 116:135–170. https://doi.org/10.1016/bs.apcsb.2019.01.001

Fuentes N, Roy A, Mishra V et al (2018) Sex-specific microRNA expression networks in an acute mouse model of ozone-induced lung inflammation. Biol Sex Differ 9:1–14. https://doi.org/10.1186/s13293-018-0177-7

Funder JW (2001) Non-genomic actions of aldosterone: role in hypertension. Curr Opin Nephrol Hypertens 10:227–230. https://doi.org/10.1097/00041552-200103000-00011

Fuseini H, Newcomb DC (2017) Mechanisms driving gender differences in asthma. Curr. Allergy Asthma Rep. 17(3):19. https://doi.org/10.1007/s11882-017-0686-1

García-Arencibia M, Dávila N, Campión J et al (2005) Identification of two functional estrogen response elements complexed with AP-1-like sites in the human insulin-receptor gene promoter. J Steroid Biochem Mol Biol 94:1–14. https://doi.org/10.1016/j.jsbmb.2004.12.020

Gerritsen J, Koeter GH, Postma DS et al (1990) Prognosis of asthma from childhood to adulthood: reviewer’s comment. J Asthma 27:323. https://doi.org/10.3109/02770909009073346

Gibbs CJ, Coutts II, Lock R et al (1984) Premenstrual exacerbation of asthma. Thorax 39:833–836. https://doi.org/10.1136/thx.39.11.833

Gibson GJ, Pride NB, O’cain C, Quagliato R (1976) Sex and age differences in pulmonary mechanics in normal nonsmoking subjects. J Appl Physiol 41:20–25. https://doi.org/10.1152/jappl.1976.41.1.20

Gilliver SC (2010) Sex steroids as inflammatory regulators. J Steroid Biochem Mol Biol 120:105–115. https://doi.org/10.1016/j.jsbmb.2009.12.015

González-Arenas A, Agramonte-Hevia J (2012) Sex-steroid hormone effects in normal and pathologic conditions in lung physiology. Mini-Rev Med Chem 12:1055–1062. https://doi.org/10.2174/138955712802762194

González-Orozco JC, Camacho-Arroyo I (2019) Progesterone actions during central nervous system development. Front Neurosci 13:1–14. https://doi.org/10.3389/fnins.2019.00503

Greennhill C (2011) Metabolism: sex differences in fatty liver disease. Nat Rev Endocrinol 7:313. https://doi.org/10.1038/nrendo.2011.65

Gross I, Smith GJW, Wilson CM et al (1980) The influence of hormones on the biochemical development of fetal rat lung in organ culture. II. Insulin. Pediatr Res 14:834–838. https://doi.org/10.1203/00006450-198006000-00012

Guennoun R, Reyss-Brion M, Gasc JM (1987) Progesterone receptors in hypothalamus and pituitary during the embryonic development of the chick: regulation by sex-steroid hormones. Brain Res 465:1–9. https://doi.org/10.1016/0006-8993(87)90224-0

Gustafsson JÅ (2003) What pharmacologists can learn from recent advances in estrogen signalling. Trends Pharmacol Sci 24:479–485. https://doi.org/10.1016/S0165-6147(03)00229-3

Hall JM, McDonnel DP (1999) The estrogen receptor β isoform (ERβ) of the human estrogen receptor modulates ERα transcriptional activity and is a key regulator of the cellular response to estrogens and antiestrogens. Endocrinol 140:5566–5578. https://doi.org/10.1210/endo.140.12.7179

Hamnes SR, Levin ER (2011) Minireview: recent advances in extranuclear steroid-receptor actions. Endocrinol 152:4489–4495. https://doi.org/10.1210/en.2011-1470

Han MLK, Postma D, Mannino DM et al (2007) Gender and chronic obstructive pulmonary disease: why it matters. Am J Respir Crit Care Med 176:1179–1184. https://doi.org/10.1164/rcrm.200704-553CC

Han MLK, Arteaga-Solís E, Blenis J et al (2018) Female sex and gender in lung/sleep health and disease: increased understanding of basic biological, pathophysiological, and behavioral mechanisms leading to better health for female patients with lung disease. Am J Respir Crit Care Med 198:850–858. https://doi.org/10.1164/rcrm.201801-0168WS
Han YY, Forno E, Celedón JC (2019) Sex-steroid hormones and asthma in a nationwide study of U.S. adults. Am J Respir Crit Care Med 201:158–166. https://doi.org/10.1164/rccm.201905-0996oc

Hanley SP (1981) Asthma variation with menstruation. Br J Dis Chest 75:306–308. https://doi.org/10.1016/0007-0971(81)90010-3

Hansmann G, Hoerer MM (2013) Registries for paediatric pulmonary hypertension. Eur Respir J 42:580–583. https://doi.org/10.1183/09031936.00065713

Hawkins MB, Thornton JW, Crews D et al (2000) Identification of a third distinct estrogen receptor and reclassification of estrogen receptors in teleosts. Proc Natl Acad Sci 97:10751–10756. https://doi.org/10.1073/pnas.97.20.10751

Hayashi T, Adachi Y, Hasegawa K, Morimoto M (2003) Less sensitivity for late airway inflammation in males than females in BALB/c mice. Scand J Immunol 57:562–567. https://doi.org/10.1046/j.1365-3083.2003.01269.x

Heldring N, Pike A, Andersson S et al (2007) Estrogen receptors: how do they signal and what are their targets. Physiol Rev 87:905–931. https://doi.org/10.1152/physrev.00026.2006

Hepper PG, Shannon EA, Dorman JC (1997) Sex differences in fetal mouth movements. Lancet 350 (9094):1820. https://doi.org/10.1016/S0140-6736(92)90010-3

Herbison AE, Theodosis DT (1992) Localization of oestrogen receptors in preoptic neurons containing neurotensin but not tyrosine hydroxylase, cholecystokinin or luteinizing hormone-releasing hormone in the male and female rat. Neuroscience 50:283–298. https://doi.org/10.1016/0306-4522(92)90423-Y

Hewitt SC, Harrell JC, Korach KS (2005) Lessons in estrogen biology from knockout and transgenic animals. Annu Rev Physiol 67:285–308. https://doi.org/10.1146/annurev.physiol.67.040403.115914

Hines M (2011) Sex-related variation in human behavior and the brain. Trends Cogn Sci 14:448–456. https://doi.org/10.1016/j.tics.2010.07.005

Humbert M, Sitbon O, Chaouat A et al (2006) Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 173:1023–1030. https://doi.org/10.1164/rccm.200510-1668OC

Irvin CG (2000) Interaction between the growing lung and asthma: role of early intervention. J Allergy Clin Immunol 105:540–546. https://doi.org/10.1016/S0091-6749(00)90058-7

Irwig MS, Fraley GS, Smith JT et al (2004) Kisspeptin activation of gonadotropin-releasing hormone neurons and regulation of KISS-1 mRNA in the male rat. Neuroendocrinology 80:264–272. https://doi.org/10.1159/000083140

Isidori AM, Giannetta E, Greco EA et al (2005) Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol (Oxf) 63:280–293. https://doi.org/10.1111/j.1365-2265.2005.02339.x

Ito K, Barnes PJ (2009) COPD as a disease of accelerated lung aging. Chest 135:173–180. https://doi.org/10.1378/chest.08-1419

Janicki SC, Schupf N (2010) Hormonal influences on cognition and risk for Alzheimer’s disease. Curr Neurol Neurosci Rep 10:359–366. https://doi.org/10.1007/s11910-010-0122-6

Jayachandran M, Preston CC, Hunter LW et al (2010) Loss of estrogen receptor β decreases mitochondrial energetic potential and increases thrombogenicity of platelets in aged female mice. Age (Omaha) 32:109–121. https://doi.org/10.1007/s11357-009-9119-y

Jenkins MA, Dharmage SC, Flander LB et al (2006) Parity and decreased use of oral contraceptives as predictors of asthma in young women. Clin Exp Allergy 36:609–613. https://doi.org/10.1111/j.1365-2222.2006.02475.x

Jenkins CR, Chapman KR, Donohue JF et al (2017) Improving the management of COPD in women. Chest 151:686–696. https://doi.org/10.1016/j.chest.2016.10.031

John-Schuster G, Günter S, Hager K et al (2016) Inflammaging increases susceptibility to cigarette smoke-induced COPD. Oncotarget 7:30068–30083. https://doi.org/10.18632/oncotarget.4027

Johnstone DE (1968) A study of the natural history of bronchial asthma in children. Am J Dis Child 115:213–216. https://doi.org/10.1001/archpedi.1968.0210010215010
Kalidhindi RSR, Katragadda R, Beauchamp KL et al (2019) Androgen receptor-mediated regulation of intracellular calcium in human airway smooth muscle cells. Cell Physiol Biochem 53:215–228. https://doi.org/10.33594/000000131

Kalidhindi RSR, Ambhore NS, Bhallamudi S (2020a) Role of estrogen receptors α and β in a murine model of asthma: exacerbated airway hyperresponsiveness and remodeling in ERβ-Knockout mice. Front Pharmacol 10:1–15. https://doi.org/10.3389/fphar.2019.01499

Kalidhindi RSR, Borkar NA, Ambhore NS et al (2020b) Sex steroids skew ACE2 expression in human airway: a contributing factor to sex differences in COVID-19? Am J Physiol Lung Cell Mol Physiol 319:L843–L847. https://doi.org/10.1152/ajplung.00391.2020

Kapetanaki MG, Mora AL, Rojas M (2013) Influence of age on wound healing and fibrosis. J Pathol 229:310–322. https://doi.org/10.1002/path.4122

Kasperska-Zajac A (2010) Asthma and dehydroepiandrosterone (DHEA): facts and hypotheses. Inflammation 33:320–324. https://doi.org/10.1007/s10753-010-9188-1

Kelley DE, Mandarino LJ (2000) Fuel selection in human skeletal muscle in insulin resistance: a reexamination. Diabetes 49:677–683. https://doi.org/10.2337/diabetes.49.5.677

Kelly MM (2006) The basics of prematurity. J Pediatr Heal Care 20:238–244. https://doi.org/10.1016/j.pedhc.2006.01.001

Kelly DM, Jones TH (2013) Testosterone: a metabolic hormone in health and disease. J Endocrinol 217:R25–R45. https://doi.org/10.1530/JOE-12-0455

Khosla SS, Smith GJW, Parks PA, Rooney SA (1981) Effects of estrogen on fetal rabbit lung maturation: morphological and biochemical studies. Pediatr Res 15:1274–1281. https://doi.org/10.1203/00006450-198109000-00010

King TE, Parдо A, Selman M (2011) Idiopathic pulmonary fibrosis. Lancet 378:1949–1961. https://doi.org/10.1016/S0140-6736(11)60052-4

Kirilov M, Clarkson J, Liu X et al (2013) Dependence of fertility on kisspeptin-Gpr54 signaling at the GnRH neuron. Nat Commun 4:2492. https://doi.org/10.1038/ncomms3492

Kluge M, Schüssler P, Schmidt D et al (2012) Ghrelin suppresses secretion of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) in women. J Clin Endocrinol Metab 97:448–451. https://doi.org/10.1210/jc.2011-2607

Kochakian CD (1975) Definition of androgens and protein anabolic steroids. Pharmacol Ther Part B Gen Syst 1:149–177. https://doi.org/10.1016/S0306-039X(75)90002-1

Koledova VV, Khalil RA (2007) Sex-hormone replacement therapy and modulation of vascular function in cardiovascular disease. Expert Rev Cardiovasc Ther 5:777–789. https://doi.org/10.1586/147797072.5.4.777

Konhilas JP (2010) What we know and do not know about sex and cardiac disease. J Biomed Biotechnol 2010:562051. https://doi.org/10.1186/1472-6750-10-562051

Koper I, Hufnagl K, Ehmann R (2017) Gender aspects and influence of hormones on bronchial asthma – secondary publication and update. World Allergy Organ J 10:1–7. https://doi.org/10.1186/s40413-017-0177-9

Kouloumenta V, Hatziefthimiou A, Paraskeva E et al (2006) Non-genomic effect of testosterone on airway smooth muscle. Br J Pharmacol 149:1083–1091. https://doi.org/10.1039/bj107069l

Koziol-White CJ, Goncharova EA, Cao G et al (2012) DHEA-S inhibits human neutrophil and human airway smooth muscle migration. Biochim Biophys Acta - Mol Basis Dis 1822:1638–1642. https://doi.org/10.1016/j.bbadis.2012.06.012

Labrie F, Bélanger A, Luu-The V et al (1998) DHEA and the intracrine formation of androgens and estrogens in peripheral target tissues: Its role during aging. Steroids 63:322–328. https://doi.org/10.1016/S0039-128X(98)00007-5

Lahm T, Crisostomo PR, Markel TA et al (2008) The effects of estrogen on pulmonary artery vasoactivity and hypoxic pulmonary vasoconstriction: Potential new clinical implications for an old hormone. Crit Care Med 36:2174–2183. https://doi.org/10.1097/CCM.0b013e31817d1a92
LaHm T, Tuder RM, PetracHe I (2014) Progress in solving the sex-hormone paradox in pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 307:L7–L26. https://doi.org/10.1152/ajplung.00337.2013

Lamont KR, Tindall DJ (2010) Androgen regulation of gene expression. Adv Cancer Res 107:137–162. https://doi.org/10.1016/S0065-230X(10)07005-3

Leuzzi C, Sangiorgi GM, Modena MG (2010) Gender-specific aspects in the clinical presentation of cardiovascular disease. Fundam Clin Pharmacol 24:711–717. https://doi.org/10.1111/j.1472-8206.2010.00873.x

Leventhal L, Brandt MR, Cummons TA et al (2006) An estrogen receptor-β agonist is active in models of inflammatory and chemical-induced pain. Eur J Pharmacol 553:146–148. https://doi.org/10.1016/j.ejphar.2006.09.033

Levesque BM, Vosatka RJ, Nielsen HC (2000) Dihydrotestosterone stimulates branching morphogenesis, cell proliferation, and programmed cell death in mouse embryonic lung explants. Pediatr Res 47:481–491. https://doi.org/10.1203/00006450-200004000-00012

Limony Y, Koziel S, Friger M (2015) Age of onset of a normally timed pubertal growth spurt affects the final height of children. Pediatr Res 78:351–355. https://doi.org/10.1007/pr.2015.104

Lindberg MK, Mové rare S, Skrtic S et al (2003) Estrogen receptor (ER)-β reduces ERα-regulated gene transcription, supporting a “Ying Yang” relationship between ERα and ERβ in mice. Mol Endocrinol 17:203–208. https://doi.org/10.1210/me.2002-0206

Lingappan K, Jiang W, Wang L, Moorthy B (2016) Sex-specific differences in neonatal hyperoxic lung injury. Am J Physiol - Lung Cell Mol Physiol 311:L481–L493. https://doi.org/10.1152/ajplung.00047.2016

Lisspers K, Stubbeng B, Janson C et al (2013) Sex differences in quality of life and asthma control in Swedish asthma patients. J Asthma 50:1090–1095. https://doi.org/10.3109/02770903.2013.834502

Loganathan J, Pandey R, Ambhore NS et al (2019) Laser-capture microdissection of murine lung for differential cellular RNA analysis. Cell Tissue Res 376:425–432. https://doi.org/10.1007/s00441-019-02995-y

Lohff B, Rieder A (2004) Gender medicine. Wiener Medizinische Wochenschrift 154:391–393. https://doi.org/10.1007/s10354-004-0092-x

LoMauRo A, Aliverti A, Are M, Are W (2018) Sex differences in respiratory function. Physiology masterclass. 14:131–140. https://doi.org/10.1183/20734735.000318

Lydon JP, DeMayo FJ, Conneely OM, O’Malley BW (1996) Reproductive phenotypes of the progesterone receptor null mutant mouse. J Steroid Biochem Mol Biol 56:67–77. https://doi.org/10.1016/0960-0760(95)00254-5

Madurga A, Mižíková I, Ruiz-Camp J, Morty RE (2013) Recent advances in late lung development and the pathogenesis of bronchopulmonary dysplasia. Am J Physiol - Lung Cell Mol Physiol 305:L893–L905. https://doi.org/10.1152/ajplung.00267.2013

Maggiolini M, Bonofiglio D, Marsico S et al (2001) Estrogen receptor α mediates the proliferative but not the cytotoxic dose-dependent effects of two major phytoestrogens on human breast cancer cells. Mol Pharmacol 60:595–602

Manson JAE (2008) Prenatal exposure to sex-steroid hormones and behavioral/cognitive outcomes. Metabolism 57:16–21. https://doi.org/10.1016/j.metabol.2008.07.010

Markova MS, Zeskand J, McEntee B et al (2004) A role for the androgen receptor in collagen content of the skin. J Invest Dermatol 123:1052–1056. https://doi.org/10.1111/j.0022-202X.2004.23494.x

Marshall WA, Tanner JM (1969) Variations in pattern of pubertal changes in girls. Arch Dis Child 44:291–303. https://doi.org/10.1136/adc.44.235.291

Marshall DD, Kotelchuck M, Young TE et al (1999) Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. Pediatrics 104:1345–1350. https://doi.org/10.1542/peds.104.6.1345
Martin YN, Pabelick CM (2014) Sex differences in the pulmonary circulation: implications for pulmonary hypertension. Am J Physiol - Hear Circ Physiol 306:H1253–H1264. https://doi.org/10.1152/ajpheart.00857.2013

Martin AJ, McLennan LA, Landau LI, Phelan PD (1980) The natural history of childhood asthma to adult life. Br Med J 280:1397. https://doi.org/10.1136/bmj.280.6229.1397

Martínez CH, Raparla S, Plauschinat CA et al (2012) Gender differences in symptoms and care delivery for chronic obstructive pulmonary disease. J Women’s Heal 21:1267–1274. https://doi.org/10.1089/jwh.2012.3650

Martíni AC, Fernández-Fernández R, Tovar S et al (2006) Comparative analysis of the effects of ghrelin and unacylated ghrelin on luteinizing hormone secretion in male rats. Endocrinology 147:2374–2382. https://doi.org/10.1210/en.2005-1422

Mauras N, Hayes V, Welch S et al (1998) Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. J Clin Endocrinol Metab 83:1886–1892. https://doi.org/10.1210/jc.83.6.1886

Mayer C, Acosta-Martínez M, Dubois SL et al (2010) Timing and completion of puberty in female mice depend on estrogen receptor α-signaling in kisspeptin neurons. Proc Natl Acad Sci 107:22693–22698. https://doi.org/10.1073/pnas.1012406108

McCurnin DC, Pierce RA, Willis BC et al (2009) Postnatal estradiol up-regulates lung nitric oxide synthases and improves lung function in bronchopulmonary dysplasia. Am J Respir Crit Care Med 179:492–500. https://doi.org/10.1164/rccm.200805-794OC

McEwen BS (2011) Stress, sex and neural adaptation to a changing environment: mechanisms of neuronal remodeling. Ann NY Acad Sci 1204:1–30. https://doi.org/10.1111/j.1749-6632.2010.05568

McEwen BS, Alves SE (2015) Estrogen actions in the nervous system. Neurology 85:263–273. https://doi.org/10.1212/WNL.0000000000001776

McMillan EM, King GM, Adamson IYR (1989) Sex hormones influence growth and surfactant production in fetal lung explants. Exp Lung Res 15:167–179. https://doi.org/10.3109/01902148909087851

Melgert BN, Ray A, Hylkema MN et al (2007) Are there reasons why adult asthma is more common in females? Curr Allergy Asthma Rep 7:143–150. https://doi.org/10.1007/s11882-007-0012-4

Mendoza-Milla C, Jiménez AV, Rangel C et al (2013) Dehydroepiandrosterone has strong anti-fibrotic effects and is decreased in idiopathic pulmonary fibrosis. Eur Respir J 42:1309–1321. https://doi.org/10.1183/09031936.00027412

Messer S, Chatzidaki EE, Ma D et al (2005) Kisspeptin directly stimulates gonadotropin-releasing hormone release via G protein-coupled receptor 54. Proc Natl Acad Sci. 102 (5):1761–1766. https://doi.org/10.1073/pnas.0409330102

Mikkonen L, Pihlajamaa P, Sahu B et al (2010) Androgen receptor and androgen-dependent gene expression in lung. Mol Cell Endocrinol 317:14–24. https://doi.org/10.1016/j.mce.2009.12.022

Miller VM, Duckles SP (2008) Vascular actions of estrogens: functional implications. Pharmacol Rev 60:210–241. https://doi.org/10.1124/pr.107.08002

Mollerup S, Jørgensen K, Berge G, Haugen A (2002) Expression of estrogen receptors α and β in human lung tissue and cell lines. Lung Cancer 37:153–159. https://doi.org/10.1016/S0169-5002(02)00039-9

Montgomery S, Shaw L, Pantelides N et al (2003) Acute effects of oestrogen receptor subtype-specific agonists on vascular contractility. Br J Pharmacol 139:1249–1253. https://doi.org/10.1038/sj.bjp.0705368

Muthusamy T, Murugesan P, Balasubramanian K (2009) Sex-steroids deficiency impairs glucose transporter 4 expression and its translocation through defective Akt phosphorylation in target tissues of adult male rat. Metabolism 58:1581–1592. https://doi.org/10.1016/j.metabol.2009.05.010

Muthusamy T, Murugesan P, Srinivasan C, Balasubramanian K (2011) Sex steroids influence glucose oxidation through modulation of insulin receptor expression and IRS-1 serine
phosphorylation in target tissues of adult male rat. Mol Cell Biochem 352:35–45. https://doi.org/10.1007/s11010-011-0737-1

Navarro VM, Castellano JM, Fernández-Fernández R et al (2004) Developmental and hormonally regulated messenger ribonucleic acid expression of KiSS-1 and its putative receptor, GPR54, in rat hypothalamus and potent luteinizing hormone-releasing activity of KiSS-1 peptide. Endocrinol 145:4565–4574. https://doi.org/10.1210/en.2004-0413

Neriishi K, Frank L (1984) Castration prolongs tolerance of young male rats to pulmonary O2 toxicity. Am J Physiol 247:R475. https://doi.org/10.1152/ajpregu.1984.247.3.r475

Ng HW, Perkins R, Tong W, Hong H (2014 Sep) Versatility or promiscuity: the estrogen receptors, control of ligand selectivity and an update on subtype selective ligands. Int J Environ Res Public Health ii(9):8709–8742. https://doi.org/10.3390/ijerph110908709

Nieschlag E (2017) The history of testosterone and the тестес: from antiquity to modern times. In: Hohl A (ed) Testosterone: from basic to clinical aspects. Springer, Cham, pp 161–168

Nieschlag E, Nieschlag S (2019) The history of discovery, synthesis and development of testosterone for clinical use. Eur J Endocrinol 180:R201–R212. https://doi.org/10.1530/EJE-19-0071

Nikolettos N, Asimakopoulos B, Köster F et al (2008) Cytokine profile in cases with premature elevation of progesterone serum concentrations during ovarian stimulation. Physiol Res 57:215–224

Nikolic I, Liu D, Bell JA et al (2007) Treatment with an estrogen receptor-beta-selective agonist is cardioprotective. J Mol Cell Cardiol 42:769–780. https://doi.org/10.1016/j.yjmcc.2007.01.014

O’Lone R, Knorr K, Jaffe IZ et al (2007) Estrogen receptors α and β mediate distinct pathways of vascular gene expression, including genes involved in mitochondrial electron transport and generation of reactive oxygen species. Mol Endocrinol 21:1281–1296. https://doi.org/10.1210/me.2006-0497

O’Malley BW, Tsai M-J (1992) Molecular pathways of steroid receptor action. Biol Reprod 46:163–167. https://doi.org/10.1095/biolreprod46.2.163

Olorunshola KV, Aliyu OF, Achi LN (2012) Testosterone and orchidectomy modulate intestinal fluid and glucose transport in albino wistar rat. Eur J Sci Res 81:78–84

Osman M (2003) Therapeutic implications of sex differences in asthma and atopy. Arch Dis Child 88:587–590. https://doi.org/10.1136/adc.88.7.587

Pabelick CM, Jones KA, Street K et al (1995) Calcium concentration-dependent mechanisms through which ketamine relaxes canine airway smooth muscle. Anesthesiology 31:305–309. https://doi.org/10.1097/00000542-199705000-00014

Paruthiyil S, Parmar H, Kerekatte V et al (2004) Estrogen receptor β Inhibits human breast cancer cell proliferation and tumor formation by causing a G2 cell cycle arrest. Cancer Res 64:423–428. https://doi.org/10.1158/0008-5472.CAN-03-2446

Pauli BD, Reid RL, Munt PW et al (1989) Influence of the menstrual cycle on airway function in asthmatic and normal subjects. Am Rev Respir Dis 140:358–362. https://doi.org/10.1164/ajrccm/140.2.358

PausJenssen ES, Cockcroft DW (2003) Sex differences in asthma, atopy, and airway hyperresponsiveness in a university population. Ann Allergy, Asthma Immunol 91:34–37. https://doi.org/10.1016/S1081-1206(10)62055-8

Pérez-López FR, Larrad-Mur L, Kallen A, Chedraui P, Taylor HSM (2011) Gender differences in cardiovascular disease: hormonal and biochemical influences. Immunology 17:511–531. https://doi.org/10.1177/19337191110367829

Philip JL, Tabima DM, Wolf GD et al (2019) Exogenous estrogen preserves distal pulmonary arterial mechanics and prevents pulmonary hypertension in rats. Am J Respir Crit Care Med 102 (5):1761–1766. https://doi.org/10.1164/rcrm.201906-1217L

Pitteloud N, Hardin M, Dwyer AA et al (2005a) Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. J Clin Endocrinol Metab 90:2636–2641. https://doi.org/10.1210/jc.2004-2190
Pitteloud N, Mootha VK, Hardin M et al (2005b Jul) Relationship between testosterone levels, insulin sensitivity and mitochondrial function in men. Diabetes Care. 28(7):1636–1642. https://doi.org/10.2337/diacare.28.7.1636

Pride NB (2005) Ageing and changes in lung mechanics. Eur Respir J 26:563–565. https://doi.org/10.1183/09031936.05.00079805

Prossnitz ER, Arterburn JB, Smith HO et al (2008) Estrogen signaling through the transmembrane G protein-coupled receptor GPR30. Annu Rev Physiol 70:165–190. https://doi.org/10.1146/annurev.physiol.70.113006.100518

Quennell JH, Mulligan AC, Tups A et al (2009) Leptin indirectly regulates gonadotropin-releasing hormone neuronal function. Endocrinol 150:2805–2812. https://doi.org/10.1210/en.2008-1693

Raghu G, Weycker D, Edelsberg J et al (2006) Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 174:810–816. https://doi.org/10.1164/rccm.200602-163OC

Reddy DS (2010) Neurosteroids. Endogenous role in the human brain and therapeutic potentials. Prog Brain Res 186:113–137. https://doi.org/10.1016/B978-0-444-53630-3.00008-7

Rees L (1963) An aetiological study of premenstrual asthma. J Psychosom Res 7:191–197. https://doi.org/10.1016/0022-3999(63)90003-5

Riffo-Vasquez Y, Ligeiro De Oliveira AP, Page CP et al (2007) Role of sex hormones in allergic inflammation in mice. Clin Exp Allergy 37:459–470. https://doi.org/10.1111/j.1365-2222.2007.02670.x

Rizza P, Barone I, Zito D et al (2014) Estrogen receptor beta as a novel target of androgen receptor action in breast cancer cell lines. Breast Cancer Res 16:1–13. https://doi.org/10.1186/bcr3619

Roa J, Vigo E, Castellano JM et al (2006) Hypothalamic expression of KiSS-1 system and gonadotropin-releasing effects of kisspeptin in different reproductive states of the female rat. Endocrinol 147:2864–2878. https://doi.org/10.1210/en.2005-1463

Robertson HA, Dwyer RJ, King GJ (1985) Oestrogens in fetal and maternal fluids throughout pregnancy in the pig and comparisons with the ewe and cow. J Endocrinol 106:355–360. https://doi.org/10.1677/joe.0.1060355

Rodriguez-Roisin R, Burgos F, Roca J et al (1999) Physiological changes in respiratory function associated with ageing. Eur Respir J 14:1454–1456. https://doi.org/10.1183/09031936.99.14614549

Rojas M, Mora AL, Kapetanaki M et al (2015) Aging and lung disease: clinical impact and cellular and molecular pathways. Ann Am Thorac Soc 12:S222–S227. https://doi.org/10.1513/AnnalsATS.201508-484PL

Roorda RJ (1996) Prognostic factors for the outcome of childhood asthma in adolescence. Thorax 51:S7–S12. https://doi.org/10.1136/thx.51.suppl_1.s7

Roseweir AK, Kaufman AS, Smith JT et al (2009) Discovery of potent kisspeptin antagonists delineates physiological mechanisms of gonadotropin regulation. J Neurosci 29(12):3920–3929. https://doi.org/10.1523/jneurosci.5740-08.2009

Sadaf Farooqi I, O’Rahilly S (2009) Leptin: a pivotal regulator of human energy homeostasis. Am J Clin Nutr 89:980–984. https://doi.org/10.3945/ajcn.2008.26788C

Salam MT, Wenten M, Gilliland FD (2006) Endogenous and exogenous sex-steroid hormones and asthma and wheeze in young women. J Allergy Clin Immunol 117:1001–1007. https://doi.org/10.1016/j.jaci.2006.02.004

Sanfilippo (2008) Physiology of puberty. Hippokrates 34:549–556. https://doi.org/10.3843/GLOWM.10286

Sathish V, Martin YN, Prakash YS (2015) Sex-steroid signaling: implications for lung diseases. Pharmacol. Ther. 150:94–108. https://doi.org/10.1016/j.pharmthera.2015.01.007

Selman M, Rojas M, Mora AL, Pardo A (2010) Aging and interstitial lung diseases: unraveling an old forgotten player in the pathogenesis of lung fibrosis. Semin Respir Crit Care Med 31:607–617. https://doi.org/10.1055/s-0030-1265901
Senthilselvan A, Rennie D, Chénard L et al (2008) Association of polymorphisms of toll-like receptor 4 with a reduced prevalence of hay fever and atopy. Ann Allergy Asthma Immunol 100:463–468. https://doi.org/10.1016/S1081-1206(10)60472-3

Sesti G, Marini MA, Briata P et al (1992) Androgens increase insulin receptor mRNA levels, insulin binding, and insulin responsiveness in HEp-2 larynx carcinoma cells. Mol Cell Endocrinol 86:111–118. https://doi.org/10.1016/0303-7207(92)90181-5

Seymour BWP, Friebertshauser KE, Peake JL et al (2002) Gender differences in the allergic response of mice neonatally exposed to environmental tobacco smoke. Dev Immunol 9:47–54. https://doi.org/10.1080/1044667021000003989

Shah R, Newcomb DC (2018) Sex bias in asthma prevalence and pathogenesis. Front Immunol 9:2997. https://doi.org/10.3389/fimmu.2018.02997

Shapiro S, Traiger GL, Turner M et al (2012) Sex differences in the diagnosis, treatment, and outcome of patients with pulmonary arterial hypertension enrolled in the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Chest 141:363–373. https://doi.org/10.1378/chest.10-3114

Simoncini T, Mannella P, Fornari L et al (2004) Genomic and non-genomic effects of estrogens on endothelial cells. Steroids 69:537–542. https://doi.org/10.1016/j.steroids.2004.05.009

Smith JT (2013) In: Kauffman AS, Smith JT (eds) Kisspeptin signaling in reproductive biology. Springer, London, pp 275–295

Sørheim IC, Johannessen A, Gulsvik A et al (2010) Gender differences in COPD: Are women more susceptible to smoking effects than men? Thorax 65:480–485. https://doi.org/10.1136/thx.2009.122002

Steinhorn RH (2010) Neonatal pulmonary hypertension. Pediatr Crit Care Med 11:1–14. https://doi.org/10.1097/PCC.0b013e3181c7edc

Stocks J, Henschen M, Hoo AF et al (1997) Influence of ethnicity and gender on airway function in preterm infants. Am J Respir Crit Care Med 156:1855–1862. https://doi.org/10.1164/ajrccm.156.6.9607056

Straub RH (2007) The complex role of estrogens in inflammation. Endocr Rev 28:521–574. https://doi.org/10.1210/er.2007-0001

Sueblinvong V (2012) Predisposition for disrepair in the aged lung. Bone 23:1–7. https://doi.org/10.1038/jid.2014.371

Sunny F, Oommen OV (2001) Rapid action of glucocorticoids on branchial ATPase activity in Oreochromis mossambicus: an in vivo and in vitro study. Comp Biochem Physiol - B Biochem Mol Biol 130:323–330. https://doi.org/10.1016/S1096-4959(01)00438-9

Takeda M, Tanabe M, Ito W et al (2013) Gender difference in allergic airway remodelling and immunoglobulin production in mouse model of asthma. Respirology 18:797–806. https://doi.org/10.1111/resp.12078

Tam A, Morrish D, Wadsworth S et al (2011) The role of female hormones on lung function in chronic lung diseases. BMC Womens Health 11:24. https://doi.org/10.1186/1472-6874-11-24

Taraborrelli S (2015) Physiology, production and action of progesterone. Acta Obstet Gynecol Scand 94:8–16. https://doi.org/10.1111/aogs.12771

Teng J, Wang ZY, Jarrard DF, Bjorling DE (2008) Roles of estrogen receptor α and β in modulating urothelial cell proliferation. Endocr Relat Cancer 15:351–364. https://doi.org/10.1677/erc.1.01255

Thannickal VJ, Murthy M, Balch WE et al (2015) Blue journal conference: aging and susceptibility to lung disease. Am J Respir Crit Care Med 191:261–269. https://doi.org/10.1164/rcrm.201410-1876PP

Thomas MR, Marston L, Rafferty GF et al (2006) Respiratory function of very prematurely born infants at follow up: influence of sex. Arch Dis Child Fetal Neonatal Ed 91:197–201. https://doi.org/10.1136/adc.2005.081927

Thurlbeck WM (1982) Postnatal human lung growth. Thorax 37:564–571. https://doi.org/10.1136/thx.37.8.564
Torday JS, Nielsen HC (1987) The sex difference in fetal lung surfactant production. Exp Lung Res 12:1–19. https://doi.org/10.3109/01902148709068811

Townsel CD, Emmer SF, Campbell WA, Hussain N (2017) Gender differences in respiratory morbidity and mortality of preterm neonates. Front Pediatr 5:1–6. https://doi.org/10.3389/fped.2017.00006

Townsend EA, Thompson MA, Pabelick CM, Prakash YS (2010) Rapid effects of estrogen on intracellular Ca2+ regulation in human airway smooth muscle. Am J Physiol - Lung Cell Mol Physiol 298:L521–L530. https://doi.org/10.1152/ajplung.00287.2009

Townsend EA, Miller VM, Prakash YS (2012a) Sex differences and sex steroids in lung health and disease. Endocr. Rev. 33:1–47. https://doi.org/10.1210/er.2010-0031

Townsend EA, Sathish V, Thompson MA et al (2012b) Estrogen effects on human airway smooth muscle involve cAMP and protein kinase A. Am J Physiol - Lung Cell Mol Physiol 303:923–928. https://doi.org/10.1152/ajplung.00023.2012

Trivedi M, Denton E (2019, June 1–15) Asthma in children and adults—what are the differences and what can they tell us about asthma? Front Pediatr, 7:256. https://doi.org/10.3389/fped.2019.00256

Troisi RJ, Speizer FE, Willett WC et al (1995) Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma: a prospective Cohort study. Am J Respir Crit Care Med 152:1183–1188. https://doi.org/10.1164/ajrccm.152.4.7551368

Trotter A, Maier L, Kron M, Pohlant F (2007) Effect of oestradiol and progesterone replacement on bronchopulmonary dysplasia in extremely preterm infants. Arch Dis Child Fetal Neonatal Ed 92:94–99. https://doi.org/10.1136/adc.2006.097170

Tsai CL, Delclos GL, Huang JS et al (2013) Age-related differences in asthma outcomes in the United States, 1988-2006. Ann Allergy Asthma Immunol 110:240–246.e1. https://doi.org/10.1016/j.anai.2013.01.002

Tsutsumi S, Zhang X, Takata K et al (2008) Differential regulation of the inducible nitric oxide synthase gene by estrogen receptors 1 and 2. J Endocrinol 199:267–273. https://doi.org/10.1677/JOE-07-0292

Tulchinsky D, Hobel CJ, Yeager E, Marshall JR (1972) Plasma estrone, estradiol, estriol, progesterone, and 17-hydroxyprogesterone in human pregnancy. I. Normal pregnancy. Am J Obstet Gynecol 112:1095–1100. https://doi.org/10.1016/0002-9378(72)90185-8

Turner JM, Mead J, Wohl ME (1968) Elasticity of human lungs in relation to age. J Appl Physiol 25:664–671. https://doi.org/10.1152/jappl.1968.25.6.664

Tyagi V, Scordo M, Yoon RS et al (2017) Revisiting the role of testosterone: are we missing something? Rev Urol 19:16–24. https://doi.org/10.3909/riu0716

Uht RM, Anderson CM, Webb P, Kushner PJ (1997) Transcriptional activities of estrogen and glucocorticoid receptors are functionally integrated at the AP-1 response element. Endocrinol 138:2900–2908. https://doi.org/10.1210/endo.138.7.5244

Verma MK, Miki Y, Sasano H (2011) Sex-steroid receptors in human lung diseases. J Steroid Biochem Mol Biol 127:216–222. https://doi.org/10.1016/j.jsbmb.2011.07.013

Voltz JW, Card JW, Carey MA et al (2008) Male sex hormones exacerbate lung function impairment after bleomycin-induced pulmonary fibrosis. Am J Respir Cell Mol Biol 39:45–52. https://doi.org/10.1165/rcmb.2007-0340OC

Wahab F, Atika B, Ullah F et al (2018) Metabolic impact on the hypothalamic kisspeptin-kiss1r signaling pathway. Front Endocrinol (Lausanne) 9:123. https://doi.org/10.3389/fendo.2018.00123

Wang X, Magkos F, Mittendorfer B (2011) Sex differences in lipid and lipoprotein metabolism: It’s not just about sex hormones. J Clin Endocrinol Metab 96:885–893. https://doi.org/10.1210/jc.2010-2061

Watson CS, Gametchu B (1999) Membrane-initiated steroid actions and the proteins that mediate them. Proc Soc Exp Biol Med 220:9–19. https://doi.org/10.3181/00379727-220-44338
Weatherman RV, Clegg NJ, Scanlan TS (2001) Differential SERM activation of the estrogen receptors (ERα and ERβ) at AP-1 sites. Chem Biol 8:427–436. https://doi.org/10.1016/S1074-5521(01)00025-4

Weigle DS, Duell PB, Connor WE et al (1997) Effect of fasting, refeeding, and dietary fat restriction on plasma leptin levels. J Clin Endocrinol Metab 82:561–565. https://doi.org/10.1210/jc.82.2.561

Weinmann GG, Zacur H, Fish JE (1987) Absence of changes in airway responsiveness during the menstrual cycle. J Allergy Clin Immunol 79:634–638. https://doi.org/10.1016/S0091-6749(87)80160-4

Wolfe A, Hussain MA (2018) The emerging role(s) for kisspeptin in metabolism in mammals. Front. Endocrinol. (Lausanne) 9:184. https://doi.org/10.3389/fendo.2018.00184

Xie H, Wu L, Deng Z et al (2018) Emerging roles of YAP/TAZ in lung physiology and diseases. Life Sci 214:176–183. https://doi.org/10.1016/j.lfs.2018.10.062

Xu X, Yang W, Li Y, Wang Y (2010) Discovery of estrogen receptor modulators: a review of virtual screening and SAR efforts. Expert Opin Drug Discov 5:21–31. https://doi.org/10.1517/1746040903490395

Xu L, Xiang X, Ji X et al (2014) Effects and mechanism of dehydroepiandrosterone on epithelial-mesenchymal transition in bronchial epithelial cells. Exp Lung Res 40:211–221. https://doi.org/10.3109/01902148.2013.879966

Yeo SH, Colledge WH (2018) The role of Kiss1 neurons as integrators of endocrine, metabolic, and environmental factors in the hypothalamic-pituitary-gonadal axis. Front Endocrinol (Lausanne) 9:188. https://doi.org/10.3389/fendo.2018.00188

Young EA, Becker JB (2009) Perspective: sex matters: gonadal steroids and the brain. Neuropsychopharmacology 34:537–538. https://doi.org/10.1038/npp.2008.221

Yung JA, Fuseini H, Newcomb DC (2018) Hormones, sex, and asthma. Ann Allergy Asthma Immunol 120:488–494. https://doi.org/10.1016/j.anai.2018.01.016

Zannolli R, Morgese G, Morgese G (1997 Jan) Does puberty interfere with asthma? Med Hypotheses 48(1):27–32. https://doi.org/10.1016/s0306-9877(97)90020-7

Zein JG, Erzurum SC (2015) Asthma is different in women. Curr Allergy Asthma Rep 15:1–16. https://doi.org/10.1007/s11882-015-0528-y

Zein JG, Dweik RA, Comhair SA et al (2015) Asthma is more severe in older adults. PLoS One 10:1–13. https://doi.org/10.1371/journal.pone.0133490

Zein JG, Denson JL, Wechsler ME (2019) Asthma over the adult life course: gender and hormonal influences. Clin Chest Med 40:149–161. https://doi.org/10.1016/j.ccm.2018.10.009

Zhang Z, Teng CT (2000) Estrogen receptor-related receptor interacts with coactivator and constitutively activates the estrogen response elements of the human lactoferrin gene. J Biol Chem 275:20837–20846. https://doi.org/10.1074/jbc.M001880200