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Review

The Endocrine-Respiratory Axis: Hormonal Regulation of Lung Development, Disease, and Repair

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Abstract

The respiratory system is increasingly recognized as a hormonally responsive organ whose development, immune homeostasis, and repair are tightly regulated by endocrine signals. Beyond classical neural and immune regulation, hormones such as glucocorticoids, thyroid hormones, and sex steroids exert profound effects on lung morphogenesis, epithelial integrity, immune responses, and tissue remodeling. Dysregulation of this endocrine-respiratory axis contributes to the pathogenesis and progression of diverse pulmonary diseases, including asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and pregnancy- or age-associated respiratory vulnerability. This review synthesizes current knowledge on hormonal control of lung biology, highlighting mechanisms by which cortisol, thyroid hormones, estrogen, progesterone, and androgens modulate lung development, inflammation, and repair. We further discuss how endocrine changes during pregnancy and aging reshape pulmonary immune responses and disease susceptibility. Understanding the endocrine-respiratory interface offers novel opportunities for precision therapies and improved management of lung diseases across the lifespan.

Keywords

Endocrine-respiratory axis, Lung development, Thyroid hormones, Sex hormones, Pulmonary immunity

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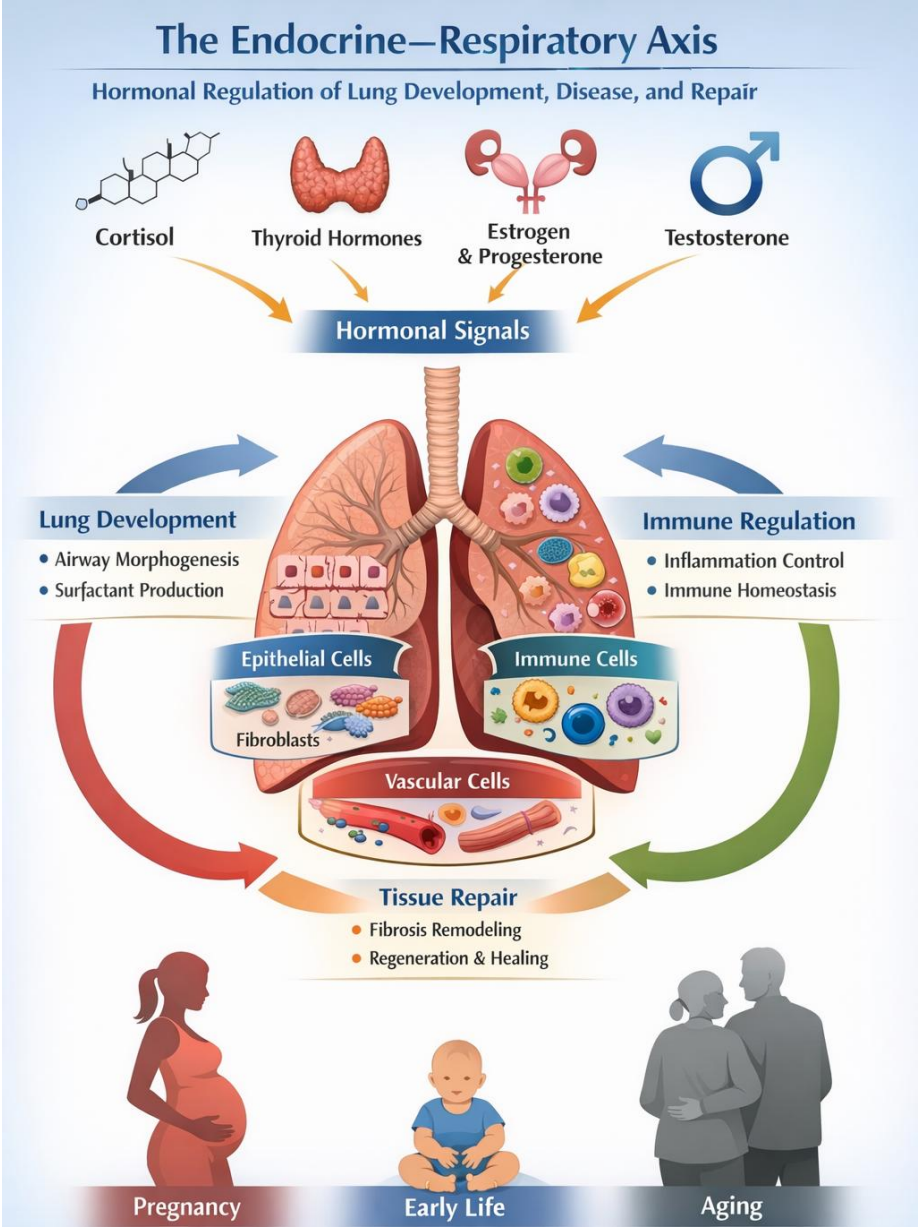
Graphical Abstract



1. Introduction

The human lung has long been studied primarily through the lenses of immunology, environmental science, and infectious disease, with predominant emphasis placed on pathogen exposure, air pollution, allergens, and inflammatory processes [1]. These frameworks have yielded transformative insights into respiratory pathology, particularly in understanding the immunopathogenesis of diseases such as asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis. However, this focus has also imposed a somewhat reductionist view, often overlooking the endocrine system's pervasive and regulatory influence on pulmonary physiology. In recent years, a growing body of experimental, clinical, and molecular evidence has revealed that endocrine signaling represents a fundamental axis of lung regulation, extending beyond local immune and environmental interactions [2].

The lung is increasingly recognized not as a passive organ merely responding to systemic hormones but as an endocrine-responsive tissue equipped with a diverse array of hormone receptors [3]. These receptors are expressed on multiple lung-resident cell types, including epithelial and endothelial cells, fibroblasts, airway smooth muscle cells, and various immune cell populations [4,5]. Such broad receptor distribution enables the lung to dynamically sense and respond to endocrine cues, integrating systemic hormonal fluctuations into local physiological outcomes. Hormonal signals exert a critical influence over a spectrum of developmental and homeostatic processes, from airway branching morphogenesis and alveolar differentiation to surfactant synthesis, epithelial barrier maintenance, and vascular maturation [6].

During fetal and postnatal development, endocrine factors such as glucocorticoids and thyroid hormones are indispensable for the timing and maturation of pulmonary structures. Glucocorticoids primarily accelerate maturation of type II alveolar epithelial cells and stimulate the expression of surfactant-associated proteins, particularly SP-A and SP-B, which are essential for surfactant secretion and lung compliance at birth. Thyroid hormones, especially T3, contribute predominantly to phospholipid synthesis and surfactant lipid maturation while also promoting epithelial differentiation and structural lung development [7]. The coordinated actions of these endocrine pathways are critical for optimal pulmonary adaptation after delivery, and disruption of either pathway may increase susceptibility to neonatal respiratory distress syndrome (RDS) [8,9].

Endocrine signals also play a decisive role in maintaining immune homeostasis within the respiratory system [10,11]. Hormones modulate both innate and adaptive immune pathways, shaping macrophage polarization, lymphocyte trafficking, and cytokine expression patterns. For example, glucocorticoids and sex steroids can dampen excessive inflammation following injury, facilitating tissue repair, while hormonal dysregulation can lead to either exaggerated immune activation or impaired resolution [10]. These mechanisms underscore how systemic endocrine status profoundly influences susceptibility to and recovery from respiratory diseases. Physiological states such as pregnancy and aging exemplify this interplay: fluctuations in estrogen and progesterone during pregnancy can alter airway responsiveness and asthma severity, whereas age-related declines in sex steroid and thyroid hormone levels contribute to reduced regenerative capacity and chronic inflammatory states within aging lungs.

From this growing body of evidence has emerged the concept of an endocrine-respiratory axis, which captures the bidirectional and dynamic nature of interactions between systemic hormones and lung-resident cellular networks. Within this framework, endocrine signals are viewed as integrative modulators that align pulmonary function with broader physiological demands–including metabolic status, reproductive cycles, circadian rhythms, and stress responses. In return, the lung communicates back to the endocrine system through the release of cytokines, inflammatory mediators, and hypoxia-related signals that can influence endocrine gland activity and hormonal secretion patterns [12,13]. This reciprocal communication reflects a systems-level interdependence that transcends traditional organ-based boundaries, positioning the lung as both a target and participant within the body's endocrine regulatory network (Figure 1).

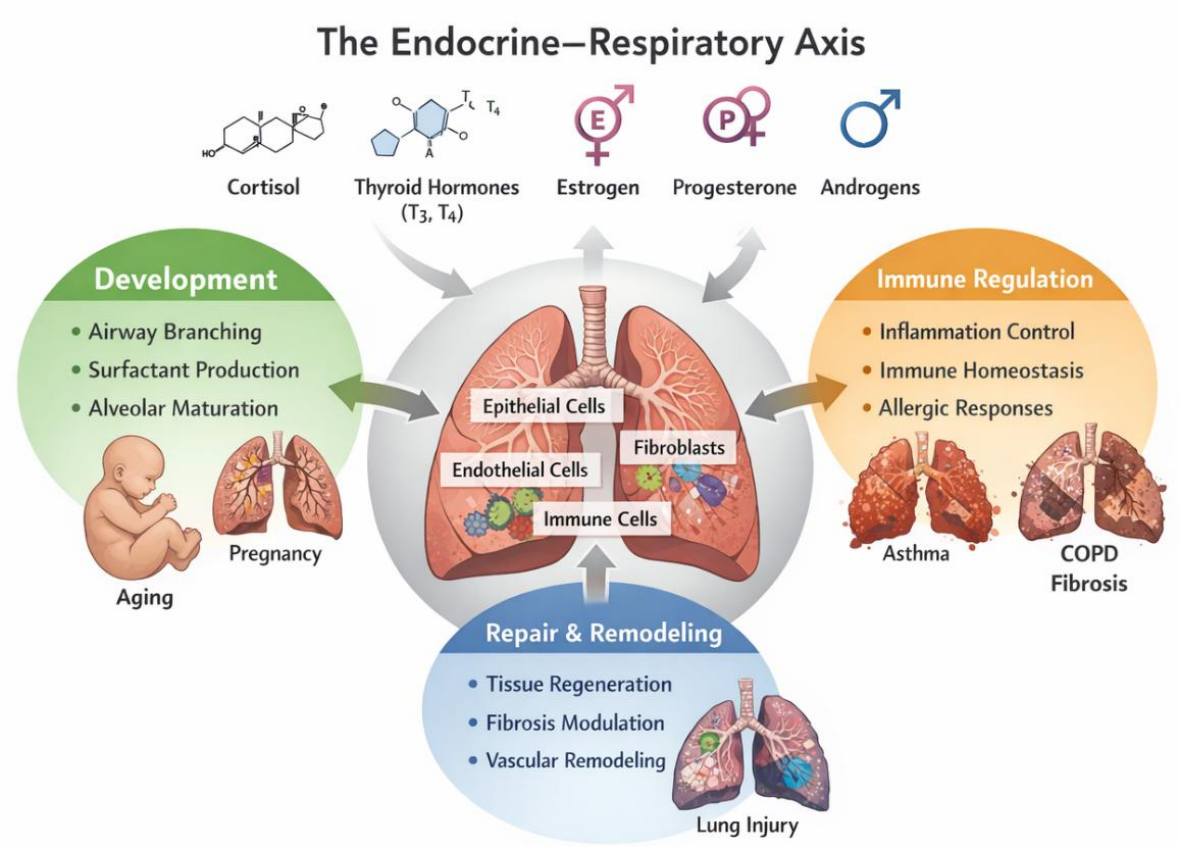


Figure 1. The conceptual overview of the endocrine-respiratory axis, depicting how systemic hormones interact with lung-resident epithelial, stromal, vascular, and immune cells to regulate development, immune balance, and tissue repair across different physiological states.

This review thus seeks to articulate a comprehensive understanding of the endocrine-respiratory interface, focusing on how key hormonal axes-glucocorticoid, thyroid, and sex steroid pathways–govern lung development, immune equilibrium, and tissue repair mechanisms. By synthesizing findings from developmental biology, molecular endocrinology, and pulmonary medicine, we aim to illuminate how hormonal fluctuations across the lifespan from

gestation to senescence shape respiratory health and disease vulnerability [14,15]. Particular attention is devoted to transitional life stages such as pregnancy and aging, during which endocrine remodeling exerts profound influences on pulmonary structure and immune function. Recognizing the lung as an endocrine-responsive organ opens new conceptual and therapeutic avenues, offering the potential for precision interventions that leverage hormonal modulation to restore or enhance respiratory resilience. A key contributor to Premenstrual Asthma is the rapid decline in progesterone levels during the late luteal phase. Progesterone withdrawal may influence airway physiology through both direct and indirect mechanisms. Directly, reduced progesterone signaling may diminish bronchodilatory effects on airway smooth muscle, thereby increasing bronchial responsiveness. Indirectly, progesterone withdrawal can promote a pro-inflammatory immune environment characterized by enhanced cytokine production, eosinophilic inflammation, and airway hyperreactivity. These combined effects may explain the increased frequency of asthma exacerbations observed during the premenstrual period and highlight the importance of hormonal fluctuations in asthma phenotypes.

2. Hormonal Regulation of Lung Development

Lung development is a complex, multistage process that begins in early embryogenesis and extends into postnatal life, requiring precise coordination of epithelial-mesenchymal interactions, angiogenesis, extracellular matrix (ECM) remodeling, and immune priming. While genetic and mechanical cues are essential drivers of this process, endocrine signals provide critical temporal and metabolic regulation that ensures appropriate lung maturation in anticipation of postnatal respiration [16,17].

Glucocorticoids are among the most extensively studied hormones in lung development and are indispensable for late gestational maturation. Acting primarily through the glucocorticoid receptor, these hormones promote alveolar epithelial differentiation, enhance surfactant protein synthesis, and accelerate thinning of the alveolar septa, thereby improving gas exchange capacity at birth [18,19]. This physiological role underpins the clinical use of antenatal corticosteroids to reduce the incidence of neonatal RDS in preterm infants. At the molecular level, glucocorticoids regulate transcriptional programs involved in lipid metabolism, antioxidant defense, and epithelial barrier formation, ensuring functional readiness of the neonatal lung.

Thyroid hormones, particularly triiodothyronine (T3) and thyroxine (T4), play complementary yet distinct roles in pulmonary development. These hormones regulate airway branching, alveolar septation, and postnatal lung growth by controlling metabolic rate, mitochondrial biogenesis, and structural gene expression [20]. Thyroid hormone receptors expressed in lung epithelial and mesenchymal cells modulate genes involved in cytoskeletal organization, ECM composition, and vascular development. Experimental models have demonstrated that both hypothyroidism and hyperthyroidism during gestation disrupt normal lung architecture, leading to impaired alveolarization and long-term reductions in pulmonary function.

Table 1. Hormonal regulation of lung development and maturation [4].

Hormone Group	Primary Source(s)	Key Receptors in Lung Tissue	Major Roles in Lung Development	Consequences of Dysregulation
Glucocorticoids (e.g., cortisol)	Fetal and maternal adrenal glands	Glucocorticoid receptor (GR) in epithelial and mesenchymal cells	Promote alveolar epithelial differentiation; stimulate surfactant protein synthesis; enhance alveolar septal thinning; prepare lung for postnatal gas exchange	Delayed lung maturation; reduced surfactant production; increased risk of neonatal RDS
Thyroid hormones (T3, T4)	Maternal and fetal thyroid gland	Thyroid hormone receptors (TRα, TRβ)	Regulate airway branching and alveolar septation; support mitochondrial biogenesis; control ECM organization and vascular development	Impaired alveolarization; abnormal lung architecture; long-term reduction in pulmonary function
Estrogens	Placenta, fetal gonads, postnatal ovaries	Estrogen receptors (ERα, ERβ)	Enhance epithelial proliferation; promote angiogenesis and vascular maturation; contribute to sex-specific lung growth patterns	Altered lung growth trajectories; increased susceptibility to airway disease
Androgens (e.g., testosterone)	Fetal and postnatal testes, adrenal glands	Androgen receptor (AR)	Modulate airway smooth muscle development; influence immune programming and airway caliber	Delayed lung maturation; increased neonatal respiratory morbidity
Progesterone	Placenta, corpus luteum	Progesterone receptor (PR)	Supports lung structural maturation; modulates inflammatory tone and smooth muscle responsiveness	Dysregulated airway development; altered respiratory mechanics
Combined endocrine balance	Maternal-fetal endocrine axis	Multiple nuclear hormone receptors	Ensures temporal coordination of lung growth, immune priming, and metabolic readiness	Increased risk of asthma, impaired lung growth, and reduced respiratory reserve later in life

Sex hormones further contribute to lung development by shaping growth trajectories and structural dimorphism. Estrogens, androgens, and progesterone influence lung size, airway caliber, and elastic recoil, contributing to sex-specific differences in lung function that emerge early in life and persist into adulthood [21]. Estrogen signaling has been shown to promote epithelial proliferation and vascularization, while androgens modulate airway smooth muscle development and immune programming (Table 1). These effects are not limited to fetal life; pubertal hormonal surges further refine lung structure and function, highlighting the prolonged influence of endocrine signaling on respiratory development [22]. Disruption of hormonal signaling during critical windows of lung development can result in persistent respiratory vulnerability. Prenatal exposure to endocrine imbalances, whether due to maternal stress, thyroid dysfunction, or altered sex hormone levels, has been associated with increased risk of asthma, impaired lung growth, and reduced respiratory reserve later in life [23]. These observations underscore the importance of endocrine integrity during gestation and early postnatal periods for establishing lifelong respiratory health.

3. Cortisol and Glucocorticoid Signaling in Lung Homeostasis

Cortisol, the primary endogenous glucocorticoid in humans, is a pivotal regulator of pulmonary homeostasis, orchestrating immune balance, epithelial integrity, and adaptive responses to physiological and environmental stress [7]. In the lung, glucocorticoid signaling operates through the glucocorticoid receptor, a ligand-activated transcription factor expressed in airway epithelial cells, alveolar macrophages, endothelial cells, and infiltrating immune populations. Through genomic and non-genomic mechanisms, cortisol fine-tunes inflammatory thresholds while preserving essential host defense functions, thereby maintaining respiratory equilibrium in both steady-state and stress conditions [24,25].

3.1 Anti-Inflammatory and Immunomodulatory Effects

At the molecular level, glucocorticoids exert potent anti-inflammatory effects by repressing the transcription of pro-inflammatory genes while promoting anti-inflammatory pathways. Cortisol suppresses the expression of key cytokines such as interleukin-1β, tumor necrosis factor-α, and interleukin-6 by inhibiting transcription factors including NF-κB and AP-1 [26,27]. Concurrently, it enhances the expression of anti-inflammatory mediators such as interleukin-10 and annexin A1, contributing to the resolution of inflammation. In the pulmonary microenvironment, this regulatory balance is essential to prevent excessive immune activation in response to inhaled pathogens, allergens, or pollutants. Glucocorticoids also modulate immune cell trafficking by reducing endothelial adhesion molecule expression, thereby limiting leukocyte infiltration into airway tissues. Through these coordinated actions, cortisol preserves lung architecture and gas exchange efficiency while minimizing immune-mediated tissue damage.

3.2 Role in Lung Disease

Despite their critical homeostatic role, disruptions in glucocorticoid signaling are increasingly recognized as contributors to chronic lung disease pathogenesis. Exogenous glucocorticoids remain cornerstone therapies for asthma, acute lung injury, and certain interstitial lung diseases due to their capacity to rapidly suppress inflammation [28,29]. However, prolonged exposure or intrinsic dysregulation of cortisol signaling can lead to glucocorticoid resistance, a phenomenon commonly observed in severe asthma and COPD. Mechanistically, this resistance involves altered glucocorticoid receptor expression, post-translational modifications, and impaired nuclear translocation, resulting in diminished anti-inflammatory efficacy [30-32]. Emerging evidence suggests that systemic endocrine aging may further contribute to glucocorticoid resistance in COPD. Declining levels of dehydroepiandrosterone (DHEA) and growth hormone/insulin-like growth factor-1 (GH/IGF-1) are associated with increased oxidative stress, impaired tissue repair, and persistent low-grade inflammation. These endocrine alterations may indirectly exacerbate HDAC2 dysfunction and reduce corticosteroid responsiveness, highlighting a potential interaction between endocrine senescence and steroid resistance in chronic airway disease. Furthermore, chronic glucocorticoid imbalance compromises epithelial repair processes, weakens mucosal barrier integrity, and increases susceptibility to respiratory infections. These findings underscore the dualistic nature of cortisol in lung disease, where precise temporal and spatial regulation is required to harness therapeutic benefit without exacerbating long-term pathology.

4. Thyroid Hormones and Pulmonary Metabolism

Thyroid hormones, principally T3 and T4, exert far-reaching effects on pulmonary physiology by regulating cellular metabolism, differentiation, and energy homeostasis within the lung. Acting through thyroid hormone receptors (TRα and TRβ), which are expressed across multiple pulmonary cell types—including airway epithelial cells, alveolar type I and II pneumocytes, endothelial cells, and fibroblasts—these hormones orchestrate gene networks that sustain respiratory structure and function. The lung's intrinsic capacity for thyroid hormone metabolism, mediated by deiodinase enzymes (DIO1, DIO2, and DIO3), allows local conversion of the prohormone T4 to the bioactive T3 or its inactive metabolite reverse T3, thereby providing precise spatial and temporal regulation of thyroid signaling within pulmonary tissue [33]. At the cellular level, T3 functions as a potent regulator of mitochondrial biogenesis and oxidative phosphorylation, processes essential for the high energy demands of alveolar cells engaged in gas exchange and surfactant production. T3 enhances transcription of mitochondrial transcription factor A and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), thereby driving mitochondrial replication and respiratory

chain enzyme synthesis [34]. In alveolar type II pneumocytes, this hormonal signaling promotes lipid metabolism and phospholipid synthesis, facilitating the generation of pulmonary surfactant components such as dipalmitoylphosphatidylcholine (DPPC). Adequate surfactant synthesis ensures alveolar stability, prevents collapse at end-expiration, and supports efficient oxygen diffusion.

Beyond metabolic regulation, thyroid hormones influence cellular differentiation and tissue remodeling throughout lung development and repair. During fetal lung maturation, T3 and T4 act synergistically with glucocorticoids to accelerate alveolar septation, vascularization, and epithelial differentiation, thereby optimizing the transition to air breathing at birth. In adult lungs, thyroid hormone signaling maintains epithelial turnover and barrier integrity by modulating keratinocyte growth factor, transforming growth factor-beta (TGF-β), and ECM components [35]. Dysregulation of this signaling balance—whether due to systemic thyroid disease, inflammation, or altered deiodinase activity—can shift the pulmonary milieu toward fibrosis, impaired regeneration, or metabolic insufficiency.

Clinical and experimental evidence underscores the sensitivity of the respiratory system to changes in thyroid hormone homeostasis. Hypothyroidism is frequently associated with reduced ventilatory drive, diminished respiratory muscle strength, and impaired lung compliance, all of which contribute to hypoventilation and reduced oxygenation [36]. On a molecular level, decreased thyroid hormone availability attenuates β-adrenergic responsiveness and mitochondrial ATP production, thereby compromising diaphragmatic contractility and alveolar ventilation. In contrast, hyperthyroidism induces a state of heightened metabolism and oxygen consumption. Patients often present with dyspnea, tachypnea, and increased pulmonary blood flow, consequences of elevated cardiac output and metabolic rate [37]. The accompanying respiratory alkalosis and increased minute ventilation reflect the systemic overstimulation of oxygen utilization pathways. Beyond these systemic manifestations, emerging data suggest that thyroid hormones directly influence pathological remodeling of lung tissue. Preclinical studies demonstrate that aberrant thyroid receptor signaling promotes fibroblast activation, myofibroblast differentiation, and ECM deposition, processes central to pulmonary fibrosis (Figure 2). Conversely, appropriate thyroid hormone signaling appears to limit fibrosis by downregulating profibrotic mediators such as TGF-β1 and connective tissue growth factor, while upregulating antioxidant enzymes that mitigate oxidative stress [38]. Moreover, experimental models of lung injury indicate that exogenous T3 administration can enhance epithelial regeneration, accelerate wound closure, and restore surfactant function, suggesting a reparative role for thyroid hormones in both acute and chronic lung injury contexts. Collectively, these findings position thyroid hormones as key metabolic and regenerative regulators within the respiratory system. Their influence extends from developmental morphogenesis to adult homeostasis and disease pathogenesis, linking systemic endocrine status to local pulmonary health [39-41]. The emerging appreciation of this thyroid-lung axis underscores the potential therapeutic relevance of modulating thyroid hormone activity in respiratory diseases characterized by metabolic dysregulation, impaired repair, or fibrotic progression. Future research into targeted modulation of thyroid hormone receptors and deiodinase enzymes may yield innovative approaches for restoring metabolic balance and promoting recovery in diverse pulmonary disorders.

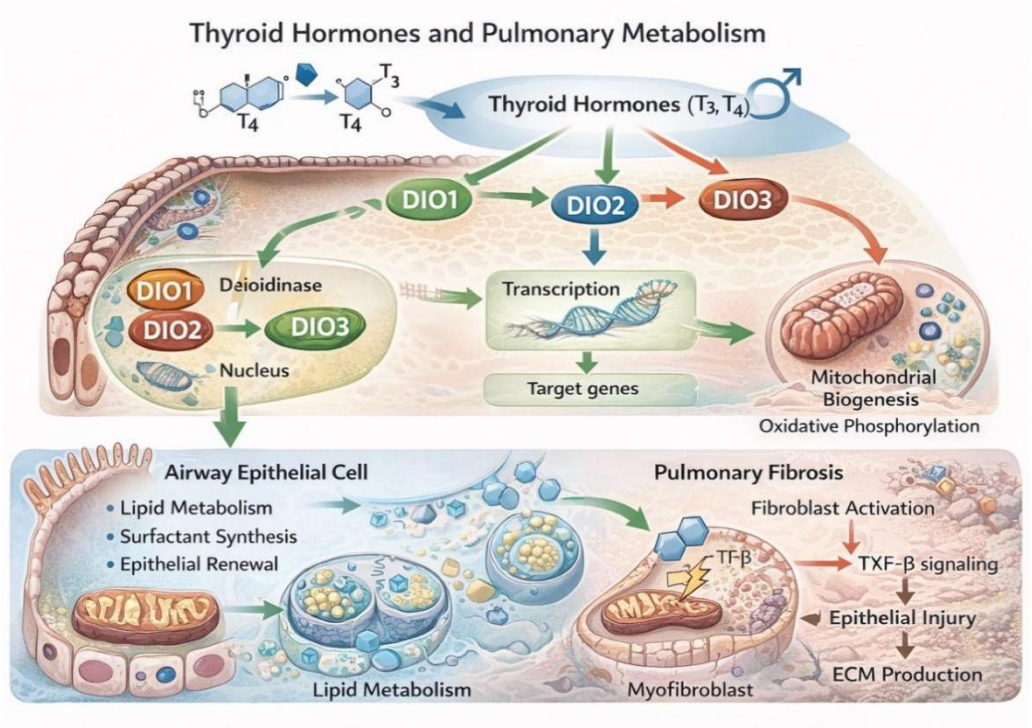


Figure 2. Thyroid hormones in pulmonary metabolism and repair.

T4 and T3 regulate pulmonary metabolism through local deiodinase activity (DIO1, DIO2, DIO3), controlling hormone activation and signaling in epithelial and mesenchymal cells. Active T3 promotes transcription of genes driving mitochondrial biogenesis, oxidative phosphorylation, and surfactant lipid synthesis, supporting epithelial renewal and gas exchange. Dysregulated thyroid signaling contributes to fibroblast activation, ECM deposition, and fibrosis via altered TGF-β pathways, whereas balanced thyroid activity sustains lung repair and metabolic homeostasis.

Adipose tissue is increasingly recognized as an active endocrine organ that influences respiratory physiology through the secretion of adipokines, particularly leptin and adiponectin. Beyond their established roles in energy homeostasis and metabolism, these hormones exert important effects on lung development, immune regulation, and pulmonary tissue remodeling [42,43]. Leptin receptors are expressed in multiple pulmonary cell populations, including alveolar epithelial cells, airway epithelial cells, and immune cells. Experimental studies have demonstrated that leptin contributes to alveolar maturation, surfactant production, and normal lung development while also promoting pro-inflammatory immune responses through activation of macrophages, neutrophils, and T lymphocytes.

In contrast, adiponectin generally exhibits anti-inflammatory and tissue-protective properties within the respiratory system [44,45]. Adiponectin signaling suppresses inflammatory cytokine production, reduces oxidative stress, and may attenuate airway remodeling. Dysregulation of the leptin-adiponectin axis, particularly in obesity, has been implicated in airway inflammation, airway hyperresponsiveness, and altered pulmonary function [18]. Elevated circulating leptin levels coupled with reduced adiponectin concentrations are frequently associated with the obesity-asthma phenotype and may contribute to disease heterogeneity and variable therapeutic responses. These findings highlight adipokines as important mediators of endocrine-respiratory crosstalk and suggest their potential utility as biomarkers and therapeutic targets in precision respiratory medicine.

5. Sex Hormones and Lung Immune Responses

Sex hormones exert profound influences on lung physiology and immunity, contributing to the striking sex differences observed in the prevalence, severity, and clinical trajectory of respiratory diseases [46]. The lung functions as a hormonally responsive organ, equipped with receptors for estrogens, progesterone, and androgens that are expressed across airway epithelial cells, fibroblasts, endothelial cells, smooth muscle, and resident immune populations. These endocrine signals regulate not only airway tone and vascular function but also cytokine production, immune cell recruitment, and epithelial barrier integrity. As a result, the pulmonary immune landscape exhibits marked sexual dimorphism, with females generally displaying heightened immune reactivity and males tending toward immunosuppression [47,48]. These patterns vary dynamically across the lifespan, particularly during periods of major endocrine remodeling such as puberty, pregnancy, and aging. Understanding how sex hormones orchestrate these immune dynamics provides a mechanistic foundation for the observed differences in respiratory disease susceptibility and response to therapy between men and women.

5.1 Estrogen and Progesterone

Estrogen plays a multifaceted role in shaping pulmonary immunity and airway physiology. Acting through estrogen receptor subtypes ERα and ERβ, which are abundantly expressed in airway epithelial, endothelial, and immune cells, estrogen enhances both innate and adaptive immune processes [48]. At the innate level, estrogen upregulates nitric oxide synthase, antimicrobial peptide expression, and the activation of macrophages and dendritic cells, leading to increased cytokine production, including interleukin (IL)-6, IL-8, and IL-10 [26,49]. In adaptive immunity, estrogen promotes B cell maturation and antibody production, while directing T helper cell differentiation toward Th2 and T follicular helper phenotypes that secrete IL-4 and IL-13 [50,51]. These actions amplify mucosal immunity and improve antimicrobial defense but can also potentiate airway hyperreactivity, mucus hypersecretion, and allergic inflammation. Such estrogen-driven immune enhancement likely contributes to the higher prevalence and severity of asthma and autoimmune airway diseases among women, especially during estrogen-dominant phases of the menstrual cycle or pregnancy [18].

Progesterone, in contrast, functions primarily as an immune-modulating and tolerance-inducing hormone. Through nuclear and membrane progesterone receptors, it dampens inflammatory responses and promotes immune homeostasis. Progesterone facilitates regulatory T cell differentiation and suppresses pro-inflammatory Th1 and Th17 pathways, while increasing the production of anti-inflammatory cytokines such as IL-10 and transforming growth factor beta (TGF-β) [52,53]. It also reduces airway smooth muscle contractility and neurogenic inflammation, contributing to bronchodilation and respiratory stability. Beyond its local immunomodulatory actions, progesterone influences central respiratory control by enhancing the ventilatory drive and sensitivity to carbon dioxide, a mechanism that becomes particularly relevant during pregnancy, when oxygen demand rises (Figure 3) [54,55]. The interplay between estrogen and progesterone thus creates cyclical fluctuations in pulmonary immune responsiveness. During the follicular phase, when estrogen dominates, immune activation is heightened, whereas in the luteal phase, progesterone-mediated tolerance prevails. These hormonal oscillations account for menstrual cycle-associated variations in asthma symptoms, with disease exacerbation often occurring during phases of high estrogen and low progesterone activity [56].

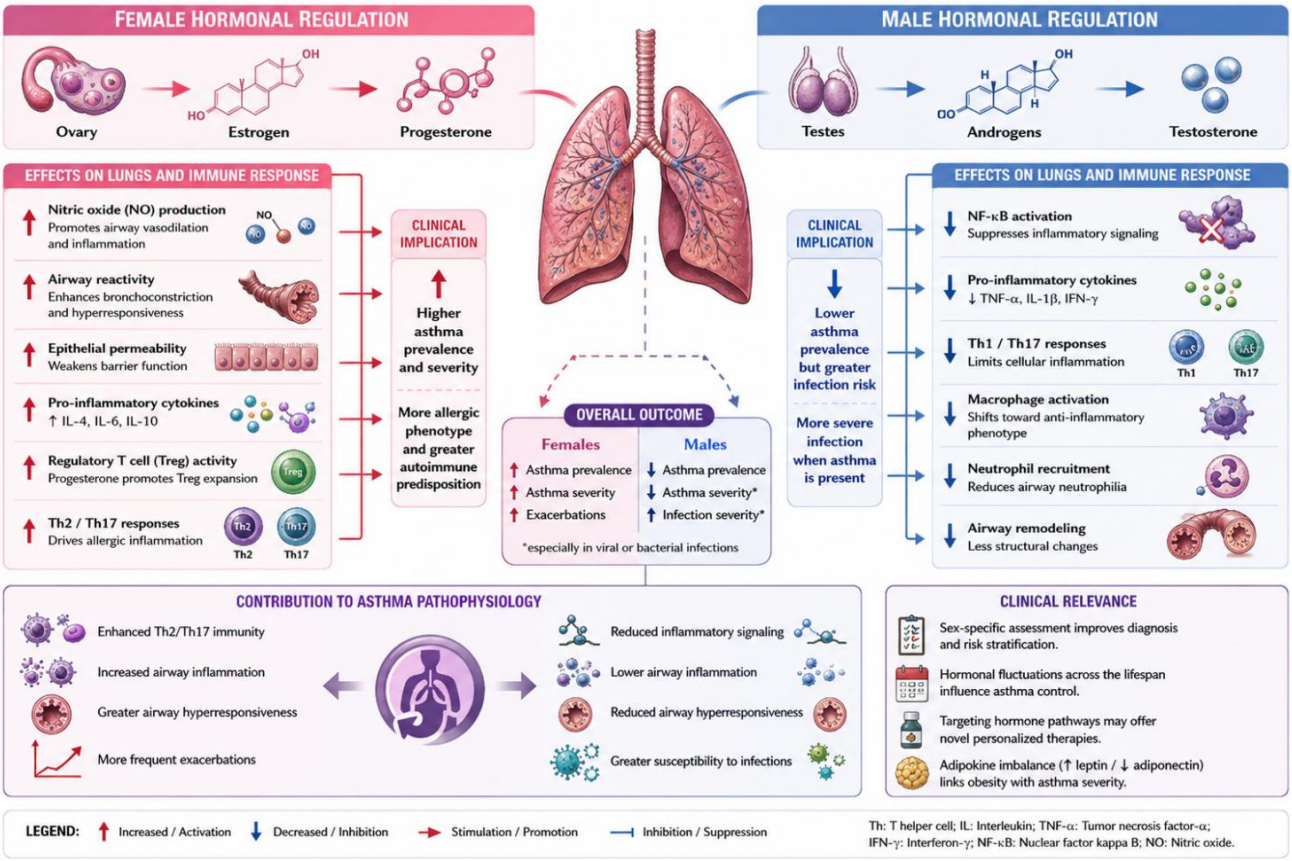


Figure 3. Sex hormones and lung immune responses. This figure illustrates how sex hormones estrogen, progesterone, and androgens modulate immune responses in the lung, shaping distinct respiratory phenotypes in females and males. The diagram integrates hormonal sources, receptor pathways, immune effects, and disease implications across both sexes.

5.2 Androgens

Androgens, primarily testosterone and its more potent derivative dihydrotestosterone, exert broadly immunosuppressive and anti-inflammatory effects within the respiratory system. Acting through androgen receptors expressed on airway epithelial cells, alveolar macrophages, and lymphocytes, androgens suppress pro-inflammatory transcriptional programs such as nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 1 (STAT1). This leads to reduced secretion of cytokines including tumor necrosis factor alpha (TNF-α), IL-1β, and interferon gamma (IFN-γ), as well as diminished macrophage activation and neutrophil recruitment [57,58]. In adaptive immunity, testosterone restrains T helper 1 (Th1) and Th17 cell differentiation, while modestly enhancing regulatory T cell activity [59], thereby establishing a tolerogenic environment that limits tissue inflammation. Furthermore, androgen signaling downregulates antigen presentation and cytotoxic T cell proliferation, reducing immune-mediated tissue injury but also attenuating host defense mechanisms against infections.

These androgenic effects help explain why men exhibit lower rates of autoimmune airway diseases and asthma compared to women. However, the same immunosuppressive properties can contribute to an increased susceptibility to severe respiratory infections, including influenza, bacterial pneumonia, and viral diseases such as COVID-19 [60]. Androgens also influence structural and metabolic aspects of lung biology, modulating fibroblast proliferation, deposition, and smooth muscle contractility. Through these mechanisms, they shape the course of chronic lung diseases such as COPD and pulmonary fibrosis [61,62]. Declining testosterone levels with age—a phenomenon termed androgen deficiency or late-onset hypogonadism—further compromise these protective effects, leading to impaired tissue repair, heightened oxidative stress, and chronic low-grade inflammation in the aging lung.

Together, the actions of estrogen, progesterone, and androgens demonstrate that hormonal regulation of pulmonary immunity is not merely a secondary effect of systemic physiology but a central determinant of lung homeostasis [63-65]. Estrogen and progesterone create a dynamic balance between immune activation and tolerance that enhances defense and repair capacity, albeit at the cost of greater inflammatory risk. Androgens maintain immune restraint and tissue stability but reduce responsiveness to infection and regenerative stimuli. This endocrine-immune interplay provides a unifying explanation for sex-specific patterns in respiratory health and disease [64,66-68]. Incorporating hormonal profiling into respiratory research and clinical practice may thus pave the way for precision medicine strategies that align treatment approaches with sex, age, and hormonal status. From a clinical perspective, growing recognition of the endocrine-respiratory axis may have important implications for patient management and therapeutic decision-making. Endocrine disorders such as diabetes mellitus, thyroid dysfunction, obesity, adrenal abnormalities, and sex hormone

imbalances can influence respiratory symptoms, disease severity, and treatment outcomes. Incorporating endocrine assessment into respiratory evaluation may therefore improve risk stratification and facilitate more individualized management strategies. Furthermore, emerging evidence suggests that hormonal biomarkers and endocrine-related molecular signatures may help identify patient subgroups with distinct disease phenotypes or therapeutic responses. As hormone-targeted therapies and precision medicine approaches continue to evolve, integration of endocrine factors into respiratory practice may offer new opportunities for improving diagnosis, prognosis, and treatment optimization across a range of pulmonary diseases.

6. Pregnancy, Aging, and Hormone-Driven Lung Repair

Physiological states such as pregnancy and aging represent natural models of profound endocrine remodeling, during which systemic hormonal shifts exert strong influence on pulmonary structure, immunity, and regenerative capacity. These life stages reveal how the endocrine-respiratory axis dynamically adapts lung function to meet changing metabolic, immunological, and oxygenation demands. Understanding these adaptations provides critical insight into hormone-driven mechanisms of lung resilience, vulnerability, and repair [69].

During pregnancy, the maternal respiratory system undergoes extensive functional and immunological reprogramming to accommodate increased oxygen consumption and to maintain immune tolerance toward the fetus. Elevated levels of progesterone, estrogen, cortisol, and placental hormones collectively reshape pulmonary physiology. Progesterone enhances central respiratory drive by increasing sensitivity to carbon dioxide, leading to physiological hyperventilation that improves oxygen delivery [7]. Simultaneously, estrogen promotes vascular remodeling and angiogenesis within the pulmonary circulation, supporting increased blood flow and gas exchange efficiency. At the immune level, pregnancy induces a finely tuned balance between immune tolerance and antimicrobial defense [70]. Hormonal modulation skews immune responses toward a Th2-dominant and regulatory phenotype, reducing excessive inflammation while preserving barrier immunity. This endocrine-mediated immune recalibration helps explain why certain inflammatory lung diseases, such as asthma, may improve, worsen, or remain unchanged during pregnancy, depending on individual hormonal responsiveness and immune baseline.

Table 2. Endocrine regulation of lung function and repair during pregnancy and aging [71].

Physiological State	Dominant Hormonal Changes	Key Pulmonary Targets	Effects on Lung Structure and Function	Implications for Lung Repair and Disease Susceptibility
Pregnancy	↑ Progesterone, ↑ Estrogen, ↑ Glucocorticoids, placental hormones (hCG, placental lactogen)	Respiratory control centers, alveolar epithelium, pulmonary vasculature, immune cells	Enhanced respiratory drive and ventilation; increased pulmonary blood flow and angiogenesis; maintained epithelial integrity	Improved oxygen delivery; balanced immune tolerance; variable modulation of inflammatory lung diseases (e.g., asthma)
Pregnancy-associated immune remodeling	Hormone-driven Th2 and regulatory immune bias	Alveolar macrophages, dendritic cells, airway epithelium	Reduced pro-inflammatory responses; preserved antimicrobial defense; controlled inflammation	Efficient resolution of lung inflammation; protection against excessive immune-mediated tissue damage
Hormone-mediated lung repair during pregnancy	↑ Estrogen and glucocorticoid signaling	Epithelial progenitor cells, macrophages, ECM	Enhanced epithelial survival; promotion of reparative macrophage phenotypes; accelerated tissue regeneration	Improved recovery from lung injury or infection; vulnerability in cases of endocrine dysregulation
Aging (endocrine senescence)	↓ Estrogens/androgens, altered cortisol rhythms, ↓ thyroid hormone responsiveness	Alveolar epithelium, stem/progenitor cells, mitochondria, immune cells	Reduced epithelial regeneration; impaired surfactant production; loss of elastic recoil; metabolic inflexibility	Increased susceptibility to chronic lung diseases and impaired post-injury repair
Age-related glucocorticoid dysfunction	Preserved or ↑ cortisol with ↓ receptor sensitivity	Inflammatory signaling pathways, immune cells	Ineffective inflammation control; chronic low-grade inflammation ("inflammaging")	Accelerated tissue damage; increased fibrosis risk
Age-related thyroid hormone decline	↓ Thyroid hormone signaling efficiency	Mitochondria, epithelial cells	Reduced mitochondrial biogenesis and antioxidant capacity	Delayed epithelial repair; increased vulnerability to fibrotic remodeling
Endocrine-immune-metabolic crosstalk	Coordinated action of sex hormones, glucocorticoids, thyroid hormones	Wnt/β-catenin, STAT signaling, macrophage polarization	Regulation of progenitor cell activation, angiogenesis, and ECM remodeling	Determines balance between regeneration and chronic inflammation/fibrosis across the lifespan

Hormones also play a critical role in lung repair during pregnancy-associated injury or infection. Elevated glucocorticoids and estrogens enhance epithelial cell survival, stimulate progenitor cell activity, and modulate macrophage polarization toward reparative phenotypes [7]. These mechanisms promote efficient resolution of inflammation and restoration of epithelial integrity. However, dysregulation of these hormonal pathways, as seen in gestational endocrine disorders or severe infections, may impair repair processes and increase susceptibility to respiratory complications [72]. In contrast to pregnancy, aging is characterized by a gradual decline in endocrine signaling efficiency, often referred to as endocrine senescence. Reduced levels of sex hormones, altered cortisol rhythms, and diminished thyroid hormone responsiveness collectively contribute to age-associated pulmonary decline. The aging lung exhibits impaired epithelial regeneration, reduced surfactant production, decreased elastic recoil, and blunted immune responses [18]. These changes are compounded by immunosenescence, a state in which immune cells display diminished responsiveness, altered cytokine production, and reduced capacity for pathogen clearance [73]. Hormonal decline exacerbates these processes by weakening endocrine support for mitochondrial function, antioxidant defense, and stem cell maintenance within lung tissue (Table 2) [66].

Age-related alterations in glucocorticoid signaling further disrupt lung homeostasis. While basal cortisol levels may remain normal or elevated, receptor sensitivity and downstream signaling efficiency decline, leading to ineffective control of inflammation. This phenomenon contributes to chronic low-grade inflammation, often termed "inflammaging," which accelerates tissue damage and fibrosis [74]. Similarly, declining thyroid hormone activity reduces mitochondrial biogenesis and metabolic flexibility, impairing epithelial repair after injury and increasing vulnerability to fibrotic remodeling. These endocrine-driven deficits help explain the increased incidence and severity of chronic lung diseases, such as idiopathic pulmonary fibrosis, COPD, and severe viral pneumonia, in older populations [75] (Figure 4).

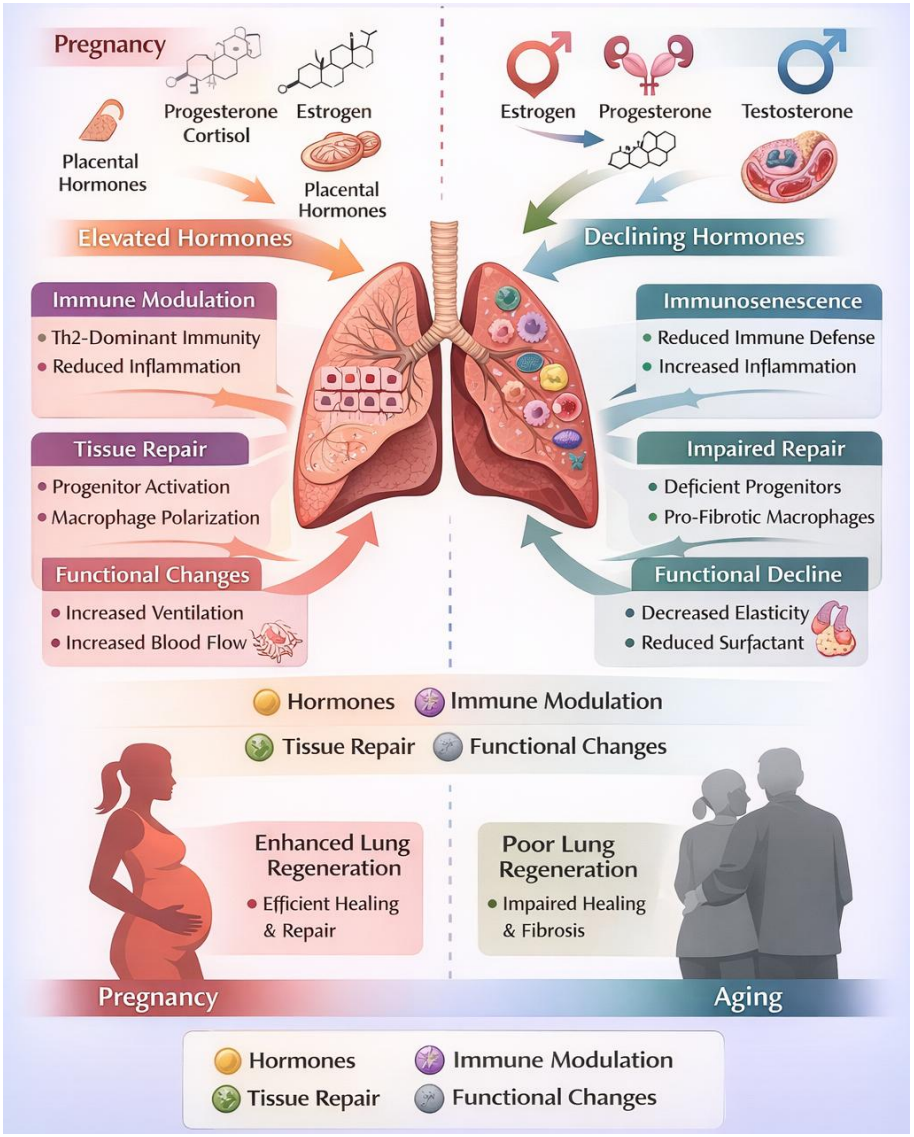


Figure 4. Pregnancy, aging, and hormone-driven lung repair. This schematic illustrates how distinct endocrine environments during pregnancy and aging differentially regulate pulmonary structure, immune balance, and tissue repair through the endocrine-respiratory axis.

Emerging evidence highlights that effective lung repair relies on coordinated endocrine-immune-metabolic crosstalk. Hormones regulate key regenerative pathways, including Wnt/β-catenin, STAT signaling, and mitochondrial quality control, which govern epithelial progenitor cell activation and differentiation [3,46,76,77]. Glucocorticoids and thyroid hormones modulate macrophage phenotypes, promoting transitions from pro-inflammatory to pro-resolving states that are essential for tissue repair. Sex hormones further influence ECM remodeling and angiogenesis, shaping the structural restoration of damaged lung tissue. Disruption of these endocrine signals, whether due to aging, endocrine disease, or pharmacological intervention, can tip the balance from regeneration toward chronic inflammation and fibrosis [78,79]. Collectively, pregnancy and aging underscore the dynamic nature of the endocrine-respiratory axis, revealing how hormonal environments dictate lung adaptability across the lifespan. These insights emphasize that lung repair and regeneration are not solely local processes but are deeply embedded within systemic endocrine networks [18,80]. Targeting hormone-responsive pathways therefore represents a promising strategy for enhancing lung regeneration, improving disease outcomes, and developing precision therapies tailored to life stage and hormonal status.

7. Conclusion and Future Perspectives

The emerging concept of the endocrine-respiratory axis fundamentally reshapes our understanding of lung biology by positioning hormones as central regulators of pulmonary development, immune balance, disease susceptibility, and tissue regeneration. Beyond their classical systemic roles, glucocorticoids, thyroid hormones, and sex hormones exert direct and indirect effects on lung-resident epithelial cells, immune populations, and stromal compartments, orchestrating complex responses that determine respiratory health across the lifespan. Disruption of these finely tuned hormonal networks, whether through endocrine disorders, physiological transitions such as pregnancy and aging, or chronic disease states, can profoundly alter pulmonary homeostasis and repair capacity. This review highlights that lung diseases cannot be fully understood in isolation from systemic endocrine regulation. Hormone-driven modulation of immune responses explains sex-specific differences in respiratory disease prevalence, variable asthma trajectories during pregnancy, and increased vulnerability to chronic lung disease in older individuals. Importantly, endocrine signaling also governs mitochondrial metabolism, epithelial progenitor cell activation, and macrophage polarization, processes that are essential for effective lung regeneration following injury. These insights underscore the need to move beyond purely immunological or environmental frameworks and adopt integrated endocrine-immune models of respiratory disease.

Looking forward, endocrine-informed precision medicine represents a promising frontier in pulmonary research and therapy. Stratifying patients based on hormonal status, life stage, and endocrine responsiveness may improve therapeutic outcomes and reduce treatment resistance, particularly in steroid-refractory asthma, fibrotic lung disease, and post-infectious lung injury. Emerging strategies that modulate hormone receptors, downstream signaling pathways, or metabolic targets hold potential to enhance lung repair while minimizing systemic side effects. Furthermore, advances in single-cell transcriptomics, organoid models, and systems biology will enable deeper dissection of hormone-specific effects within distinct lung cell populations. In conclusion, recognizing the lung as an endocrine-responsive organ opens new avenues for understanding respiratory disease mechanisms and developing innovative therapeutic strategies. Integrating endocrine biology into respiratory medicine will be essential for advancing personalized, life-stage-specific interventions that promote lung health, resilience, and regeneration. Despite substantial advances in understanding endocrine influences on lung biology, several important limitations remain. Much of the current mechanistic evidence originates from animal models, *in vitro* systems, or observational human studies, which may not fully capture the complexity of endocrine-respiratory interactions in clinical settings. Furthermore, hormonal effects often vary according to age, sex, physiological state, disease subtype, and environmental exposures, making direct translation of experimental findings challenging. While accumulating evidence supports a role for endocrine signaling in lung development, immune regulation, and tissue repair, the causal contribution of specific hormonal pathways to disease progression and therapeutic response remains incompletely defined. Future longitudinal and interventional studies are needed to establish the clinical relevance of these mechanisms and to identify patient populations most likely to benefit from hormone-targeted approaches.

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Not applicable. This article is a narrative review based on previously published studies and does not involve human participants, animals, or identifiable personal data.

Data Availability Statement

No new datasets were generated or analyzed during the current study. All data discussed are derived from publicly available literature sources.

Author Contributions

All authors contributed to the conceptualization, literature review, analysis, and writing of the manuscript. All authors read and approved the final version of the manuscript.

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