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Normal Anatomy and Pathomorphology of Adrenal Glands in Newborns with Respiratory Distress Syndrome

Zubtiyev Sardor Uktamovich-Assistant of the Department of Pathological Anatomy, Tashkent State Medical University, Eurasian Multidisciplinary University, Republican Center of Pathological Anatomy (Tashkent, Uzbekistan).
sardoruktamovich@gmail.com
https://orcid.org/0009-0003-3628-9723
Nafisa Ernazarovna Khadjiboeva – Senior Lecturer, Department of General Specialized Disciplines, Bekobod Abu Ali Ibn Sino Public Health Technical School, Uzbekistan.
E-mail: khadjibayevanafisa1973@gmail.com
Nigora Sabirjanovna Khalikberdiyeva – Highest Category Teacher, Department of General Specialized Disciplines, Bekobod Abu Ali Ibn Sino Public Health Technical School, Uzbekistan.
E-mail: xalikberdiyenigora@gmail.com

Abstract

Background: Respiratory Distress Syndrome (RDS) remains a primary driver of morbidity and mortality in neonates, particularly preterm infants. Under conditions of severe systemic hypoxia and hemodynamic instability, the adrenal glands undergo profound morphological adaptations and pathological transformations that reflect the overall stress response of the newborn. **Objective:** This study aims to evaluate the normal anatomical features of neonatal adrenal glands and characterize the key pathomorphological changes that occur during RDS. **Methods:** A comprehensive literature review and retrospective pathomorphological analysis of neonatal autopsy specimens were performed. Tissue sections were stained with hematoxylin and eosin (H&E) to assess vascular changes, zonal architecture, and cell viability. **Results:** Key pathological findings in neonates with RDS include profound microvascular congestion, extensive lipid depletion within the cortical zones, focal/confluent

necrosis, micro-hemorrhages, and structural disorganization of the fetal cortex.
Conclusion: These structural alterations indicate severe functional overload of the hypothalamic-pituitary-adrenal (HPA) axis under hypoxic stress. Understanding these pathomorphological markers is crucial for assessing neonatal stress adaptation limits in critical care settings.

Keywords: *Newborns, Respiratory Distress Syndrome, Adrenal Glands, Hypoxia, Pathomorphology, Adrenal Cortex, Hemorrhage.*

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Introduction

Respiratory Distress Syndrome (RDS) in newborns is a life-threatening condition primarily caused by surfactant deficiency, leading to alveolar collapse, progressive atelectasis, and severe systemic hypoxemia. Despite modern neonatological advancements—including synthetic surfactant replacement therapy and advanced ventilation techniques—RDS continues to carry significant mortality risks for extremely low birth weight infants.

The adrenal glands are vital organs of adaptation, mediating the metabolic, cardiovascular, and immunological transitions from intrauterine to extrauterine life. In neonates, the adrenal glands possess unique anatomical and functional profiles that differ drastically from those of adults. At birth, they are exceptionally large relative to body weight, dominated by a highly active embryonic structure known as the fetal zone, which makes up approximately 70%−80%70\% - 80\%70%−80% of the entire cortex.

Under the influence of acute and chronic hypoxia in RDS, the hypothalamic-pituitary-adrenal (HPA) axis is hyperactivated. The resulting hormonal demand triggers structural shifts within the adrenal tissue. Prolonged functional overload eventually crosses the threshold of physiological compensation, leading to degenerative, ischemic, and hemorrhagic damage.

Normal Anatomy of Neonatal Adrenal Glands

At term, the combined weight of both adrenal glands ranges from 8 to 12 g (averaging 4−6 g gland). They sit directly superior to the kidneys, encapsulated in adipose tissue.

The neonatal adrenal cortex is divided into three distinct functional zones:

1. **Glomerulosa Zone:** A thin layer located immediately beneath the capsule, responsible for aldosterone synthesis.
2. **Fasciculata Zone (and nascent Reticularis):** Responsible for producing glucocorticoids (primarily cortisol).

3. **Fetal Zone (Inner Cortex):** A massive, temporary embryonic structure that synthesizes dehydroepiandrosterone sulfate (DHEA-S), a vital precursor for placental estrogen synthesis.

The medulla is relatively underdeveloped at birth, consisting of small nests of chromaffin cells interspersed along venous sinuses.

Table 1: Architectural and Functional Zoning of the Normal Neonatal Adrenal Gland.

Adrenal Region	**Relative Volume in Newborn**	**Cellular Morphology**	**Primary Secretory Product**	**Main Physiological Function**
Zona Glomerulosa	<10%	Small, densely packed cells arranged in clusters beneath the capsule	Aldosterone (Mineralocorticoids)	Regulation of electrolyte and fluid balance (Na^+/K^+ homeostasis)
Zona Fasciculata	10–15%	Polyhedral cells arranged in parallel cords; contains lipid droplets	Cortisol (Glucocorticoids)	Glucose metabolism, stress response, and metabolic regulation
Fetal Zone	70–80%	Large eosinophilic cells with abundant cytoplasm	Dehydroepiandrosterone sulfate (DHEA-S)	Precursor for placental estrogen synthesis; supports fetal growth and maturation
Adrenal Medulla	<5%	Immature chromaffin cell	Catecholamines (Adrenaline, Noradrenaline)	Sympathetic "fight-or-flight"

		aggregates surrounding central veins		response and cardiovascular adaptation after birth

Pathomorphological Changes in Adrenal Glands during RDS

When a newborn suffers from RDS, the structural integrity of the adrenal gland deteriorates rapidly due to severe hypoxia and poor tissue perfusion.

3.1 Macroscopic Changes

Upon autopsy, the adrenal glands of infants deceased from RDS frequently appear enlarged, swollen, and dark purple or cherry-red. The fibrous capsule is typically tense. Sectioning the organ reveals severe congestion, blurring of the normal yellow-brown cortical boundary, and diffuse or focal dark-red hemorrhagic areas.

Massive, catastrophic subcapsular or intra-adrenal hemorrhages are frequently detected. Interestingly, these hemorrhages are more common in the **right adrenal gland**, which is attributed to its venous drainage directly into the inferior vena cava (which experiences severe pressure changes during mechanical ventilation and respiratory failure), whereas the left adrenal vein drains into the left renal vein.

3.2 Microscopic (Histological) Changes

Microscopic evaluation of H&E stained slides reveals structural breakdown at multiple levels:

- **Vascular Alterations:** Extreme dilation and congestion of sinusoidal capillaries, especially in the transition area between the fetal zone and the medulla. Blood stasis, thrombosis, and perivascular edema are prominent.
- **Parenchymal Dystrophy:** The steroid-producing cells of the fasciculata and fetal zones show severe vacuolar (hydropic) degeneration.
- **Lipid Depletion:** There is a rapid loss of cytoplasmic lipid droplets (which hold steroid hormone precursors). This clearing of the cytoplasm makes cells appear pale, empty, or collapsed—a hallmark of functional exhaustion.
- **Necrosis and Karyorrhexis:** Severe hypoxia causes focal or confluent cell death. Nuclear changes such as pyknosis (shrinkage), karyorrhexis (fragmentation), and karyolysis (dissolution) are widely observed in the fetal cortex.

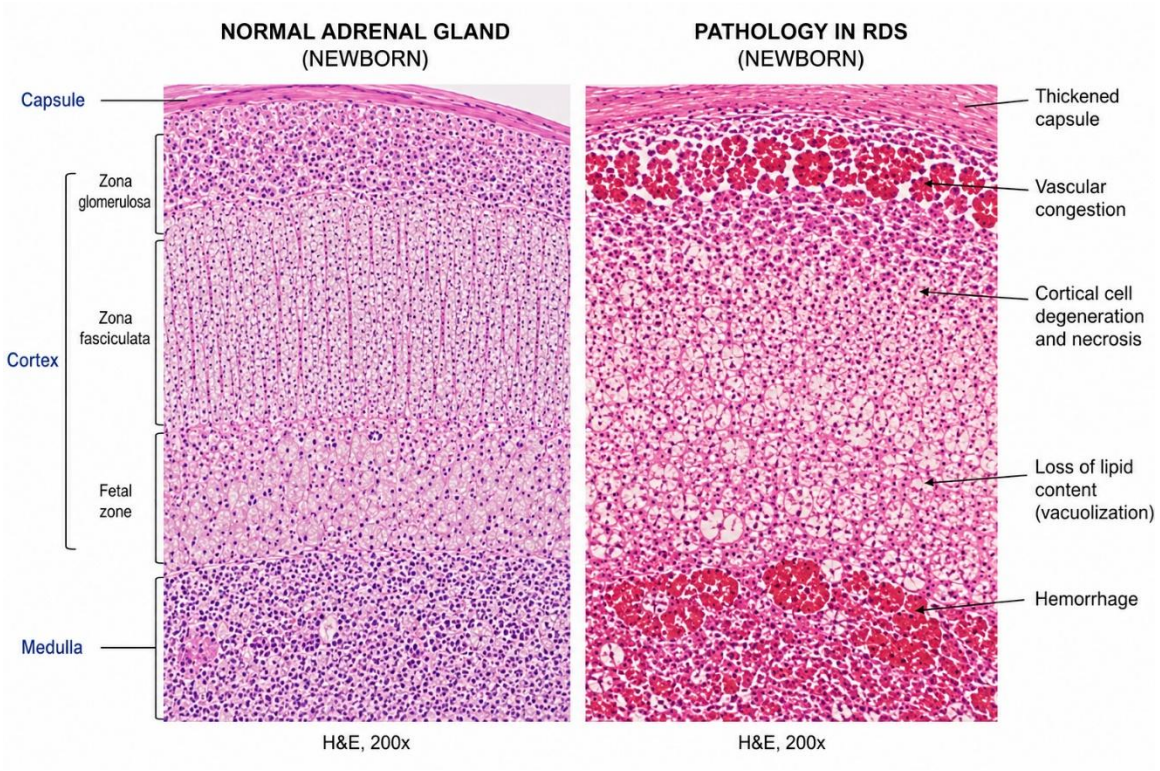

Figure 1. Comparative histological appearance of the adrenal gland in a normal newborn and a newborn with respiratory distress syndrome (RDS) (H&E stain, ×200).

The left panel demonstrates the normal histological architecture of the neonatal adrenal gland. The cortex is clearly differentiated into the zona glomerulosa, zona fasciculata, and the prominent fetal zone, which occupies approximately 70–80% of the cortical volume. Cortical cells exhibit preserved morphology with abundant cytoplasm and normal lipid content. The adrenal medulla is composed of immature chromaffin cell aggregates with intact structural organization.

The right panel illustrates pathological changes observed in the adrenal gland of a newborn with respiratory distress syndrome (RDS). Marked vascular congestion, sinusoidal dilatation, and extensive hemorrhage are evident. Cortical cells show severe vacuolar degeneration, depletion of intracellular lipid reserves, and focal necrotic changes. The normal zonal architecture is disrupted, with evidence of corticocyte degeneration and structural disorganization. The medulla demonstrates congestion and hemorrhagic injury. These findings reflect severe hypoxic-ischemic damage and excessive activation of the hypothalamic–pituitary–adrenal stress response associated with neonatal RDS.

Table 2: Comparison of Normal Neonatal Adrenal Morphology vs. RDS Pathology

Feature	**Normal Neonatal Adrenals**	**Pathological Adrenals in Respiratory Distress Syndrome (RDS)**
Organ Weight and Size	4–6 g per gland; normal firm consistency	Enlarged and edematous (>7–8 g); soft and friable texture
Capsule and Gross Appearance	Thin, intact capsule; golden-yellow cortical surface	Stretched capsule; congested dark-red to purple parenchyma
Lipid Content	Abundant intracellular lipid droplets, particularly in zona fasciculata	Marked lipid depletion; cytoplasmic vacuolization and exhaustion of corticocytes
Vascular Network	Well-organized physiological microcirculation	Severe vascular congestion, sinusoidal dilatation, microthrombi formation, and extensive hemorrhage
Cortical Architecture	Well-defined cortical zones; orderly fascicular arrangement; prominent fetal zone	Disorganization of cortical cords, focal necrosis, karyopyknosis, karyorrhexis, and cellular degeneration
Fetal Zone	Occupies approximately 70–80% of cortical volume; composed of large eosinophilic cells	Cellular swelling, degeneration, focal necrosis, and reduction of functional activity
Medullary Status	Intact chromaffin cell nests with preserved architecture	Medullary congestion, focal hemorrhages, edema, and chromaffin cell disintegration
Microcirculation	Normal capillary density and endothelial integrity	Endothelial injury, capillary collapse,

		perivascular edema, and impaired perfusion
Histological Appearance	Preserved zonal differentiation and cellular morphology	Diffuse dystrophic changes, hemorrhagic foci, necrosis, and loss of zonal organization
Functional State	Adequate corticosteroid and catecholamine synthesis	Functional exhaustion associated with severe hypoxia and stress response

Pathogenetic Mechanisms of Adrenal Injury in RDS

The pathomorphological changes in the adrenal glands are not random but follow a defined sequence of systemic stress responses and ischemic cascades:

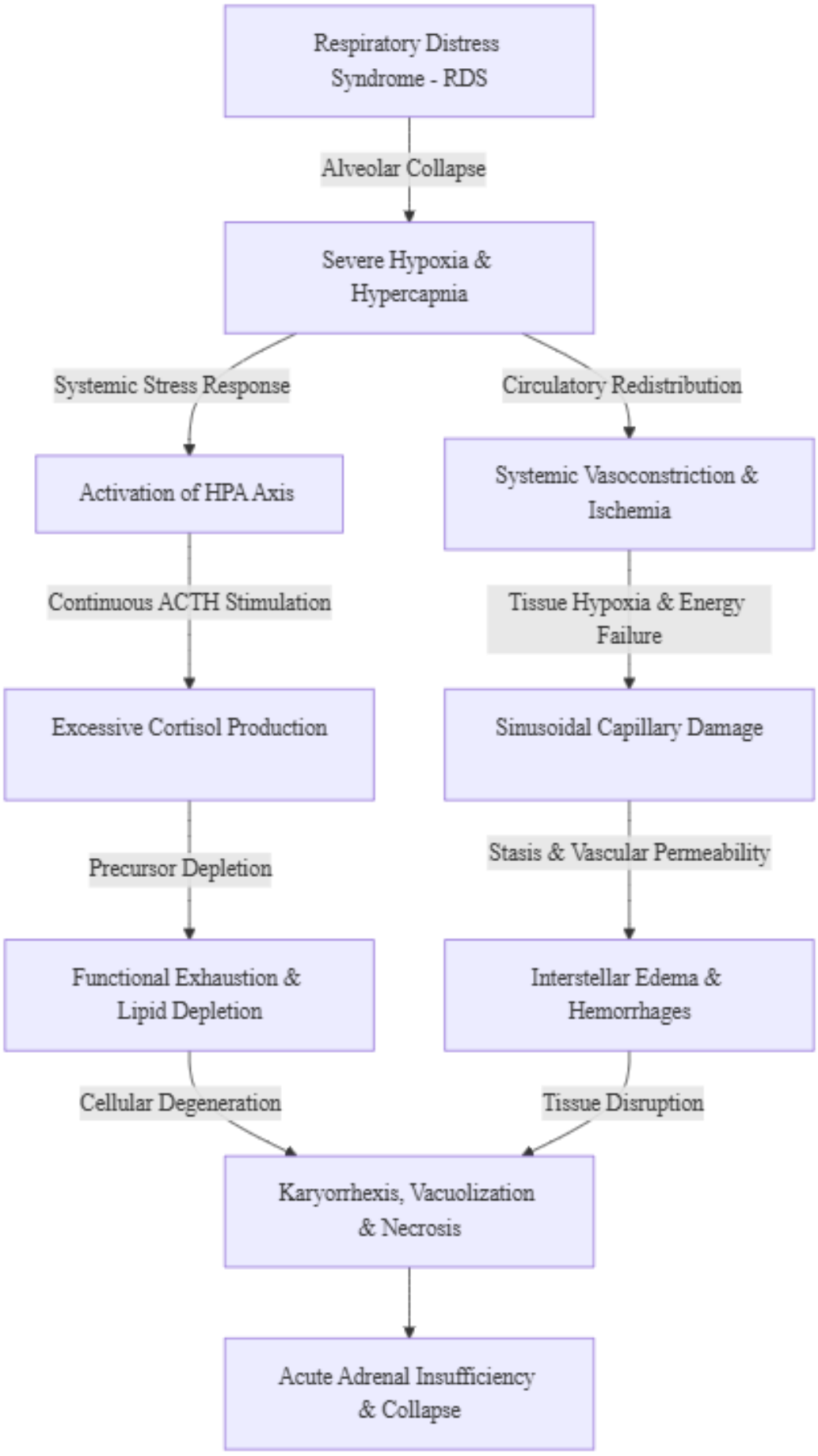
Respiratory Distress Syndrome - RDS
Alveolar Collapse
Severe Hypoxia & Hypercapnia
Systemic Stress Response
Circulatory Redistribution
Activation of HPA Axis
Systemic Vasoconstriction & Ischemia
Continuous ACTH Stimulation
Tissue Hypoxia & Energy Failure
Excessive Cortisol Production
Sinusoidal Capillary Damage
Precursor Depletion
Stasis & Vascular Permeability
Functional Exhaustion & Lipid Depletion
Interstellar Edema & Hemorrhages
Cellular Degeneration
Tissue Disruption
Karyorrhexis, Vacuolization & Necrosis
Acute Adrenal Insufficiency & Collapse

Figure 2. Pathogenetic Mechanisms of Adrenal Gland Injury in Neonatal Respiratory Distress Syndrome (RDS)

This schematic diagram illustrates the major pathogenic pathways leading to adrenal gland damage in newborns with respiratory distress syndrome (RDS).

RDS initially results in alveolar collapse, causing severe impairment of pulmonary gas exchange. Consequently, systemic hypoxia and hypercapnia develop, triggering two parallel pathological mechanisms.

The first pathway involves activation of the hypothalamic–pituitary–adrenal (HPA) axis as part of the systemic stress response. Persistent stimulation by adrenocorticotropic hormone (ACTH) leads to excessive cortisol production. Continuous steroidogenesis gradually depletes intracellular lipid reserves and steroid precursors within cortical cells, resulting in functional exhaustion, lipid depletion, and progressive cellular degeneration.

The second pathway is associated with circulatory redistribution and systemic vasoconstriction, which occur in response to severe hypoxia. Reduced tissue perfusion causes ischemia and energy deficiency within the adrenal gland. Subsequent endothelial injury and sinusoidal capillary damage increase vascular permeability, leading to blood stasis, interstitial edema, and hemorrhage. These vascular disturbances disrupt the normal adrenal architecture and further aggravate cellular injury.

Both mechanisms ultimately converge, producing characteristic histopathological alterations including vacuolar degeneration, lipid depletion, karyorrhexis, focal necrosis, and hemorrhagic lesions. Progressive destruction of adrenal cortical and medullary tissues may culminate in acute adrenal insufficiency, contributing to circulatory collapse and worsening clinical outcomes in critically ill newborns with RDS.

Hypoxia-Induced Tissue Damage: Under severe hypoxemia, the high metabolic demand of the neonatal adrenal cortex cannot be met. The resulting lack of ATP causes cell membrane pump failures, leading to intracellular sodium accumulation, cellular swelling, and vacuolar degeneration.

HPA Axis Hyperactivation: The infant's body attempts to survive the respiratory crisis by pumping out cortisol. Under persistent ACTH stimulation, the cells consume their stored cholesterol (lipids) rapidly. Once these resources are depleted, the cells undergo structural atrophy.

Vascular Vulnerability of the Fetal Zone: The fetal zone is highly vascularized with thin-walled, fragile sinusoidal capillaries. Systemic acidosis, hypercapnia, and hemodynamic fluctuations (common in mechanically ventilated

babies) cause these weak vessel walls to rupture, causing localized or massive intra-adrenal hemorrhages.

Conclusion

The neonatal adrenal gland is a highly specialized endocrine organ that plays a fundamental role in maintaining physiological adaptation during the transition from intrauterine to extrauterine life. Owing to its unique structural organization, particularly the presence of a prominent fetal zone and an actively developing cortical compartment, the adrenal gland is exceptionally sensitive to systemic disturbances associated with respiratory distress syndrome [1-5].

The present analysis demonstrates that severe hypoxia, hypercapnia, metabolic acidosis, and hemodynamic instability characteristic of RDS initiate a complex cascade of neuroendocrine and microvascular alterations within the adrenal gland. Persistent activation of the hypothalamic–pituitary–adrenal (HPA) axis results in excessive stimulation of steroidogenesis, leading to progressive depletion of intracellular lipid reserves and functional exhaustion of cortical cells. Simultaneously, impaired tissue perfusion and endothelial injury promote vascular congestion, sinusoidal dilatation, hemorrhage, interstitial edema, and focal ischemic damage [6-8].

The most characteristic pathological findings observed in adrenal glands affected by RDS include severe vascular congestion, extensive hemorrhagic lesions, lipid depletion of corticocytes, vacuolar degeneration, disruption of normal cortical architecture, and focal areas of necrosis. These changes are particularly pronounced within the fetal and fascicular zones, reflecting their high metabolic activity and vulnerability to oxygen deprivation. Histologically, the combination of vascular injury, cellular degeneration, karyopyknosis, karyorrhexis, and necrosis constitutes a distinctive morphological pattern associated with severe neonatal respiratory failure [9-12].

Importantly, the identified pathomorphological triad—vascular congestion and hemorrhage, lipid depletion, and focal cortical necrosis—may serve as a valuable structural indicator of acute adrenal stress and HPA-axis exhaustion in critically ill newborns. The severity of these alterations appears to correlate with the degree of respiratory insufficiency, duration of hypoxia, and overall systemic compromise, suggesting their potential prognostic significance [13-16].

From a clinical perspective, understanding adrenal involvement in neonatal RDS expands current knowledge of the systemic consequences of respiratory failure beyond pulmonary pathology alone. Recognition of adrenal injury may

contribute to improved diagnostic assessment of disease severity and provide a morphological basis for individualized therapeutic strategies, including corticosteroid supplementation, optimization of hemodynamic support, and prevention of adrenal insufficiency-related complications[17-20].

Further investigations integrating histopathological, immunohistochemical, morphometric, and molecular approaches are warranted to clarify the mechanisms underlying adrenal dysfunction in neonatal RDS. Such studies may facilitate the identification of novel biomarkers of adrenal injury and contribute to the development of targeted interventions aimed at reducing mortality, preventing acute adrenal crises, and improving outcomes in vulnerable newborn populations [21-24].

In summary, respiratory distress syndrome induces profound structural and functional alterations in the neonatal adrenal gland. These changes reflect the combined effects of systemic hypoxia, neuroendocrine overstimulation, and microcirculatory failure, ultimately compromising adrenal adaptive capacity and contributing to the progression of critical illness in newborns.

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