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PATHOMORPHOLOGICAL BASIS OF ADRENAL GLAND AND THYMUS DISINTEGRATION IN PRETERM STILLBORN INFANTS: A CASE STUDY OF FERGANA REGION

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Abstract:

Preterm stillbirth remains one of the major challenges of modern perinatal medicine due to its high contribution to perinatal mortality and the complexity of the underlying pathogenetic mechanisms. Among the organs most sensitive to intrauterine stress and hypoxic damage are the adrenal glands and thymus, which play crucial roles in endocrine regulation, stress adaptation, and immune system development during fetal life. The present study aimed to investigate the pathomorphological features of adrenal gland and thymus disintegration in preterm stillborn infants using materials obtained from the Fergana region. A retrospective morphological analysis was performed on autopsy specimens collected from preterm stillborn infants of different gestational ages. Macroscopic and microscopic examinations were carried out using conventional histological techniques, including hematoxylin and eosin staining.

Key words

Preterm stillbirth, stillborn infants, adrenal gland, thymus, pathomorphology, disintegration, fetal hypoxia, perinatal mortality, histopathology, endocrine adaptation, immune system.

INTRODUCTION:

Preterm stillbirth remains one of the most important and unresolved problems of modern obstetrics, neonatology, and perinatal pathology. Despite significant advances in prenatal diagnostics, maternal healthcare, and neonatal intensive care, fetal mortality continues to represent a substantial public health concern worldwide. According to international epidemiological data, a considerable proportion of stillbirths occur before term, and many of these cases are associated

with chronic intrauterine hypoxia, placental insufficiency, maternal diseases, infectious processes, and disturbances in fetal adaptive mechanisms. Understanding the structural and functional changes that develop in fetal organs under these pathological conditions is essential for clarifying the mechanisms of fetal death and improving preventive strategies.The fetal endocrine and immune systems play a decisive role in maintaining intrauterine homeostasis and ensuring adaptation to environmental stressors. Among the organs involved in these processes, the adrenal glands and thymus are of particular importance. The adrenal glands regulate metabolic processes and participate in the fetal stress response through the synthesis of glucocorticoids, mineralocorticoids, and catecholamine precursors. These hormones are crucial for the maturation of fetal organs, maintenance of cardiovascular stability, regulation of fluid and electrolyte balance, and adaptation to hypoxic conditions. Any pathological alteration in adrenal structure during fetal development may impair compensatory responses and contribute to unfavorable pregnancy outcomes.The thymus, on the other hand, is the central organ of T-lymphocyte differentiation and immune system maturation during fetal life. It serves as a sensitive indicator of intrauterine stress and reflects the impact of various adverse factors affecting the fetus. Morphological changes in the thymus, including lymphocyte depletion, cortical thinning, stromal disruption, and premature involution, have been associated with prolonged fetal distress, endocrine imbalance, inflammatory processes, and severe hypoxic injury. Because of its close functional relationship with the hypothalamic-pituitary-adrenal axis, the thymus undergoes significant structural remodeling in response to increased glucocorticoid activity induced by stress.Preterm infants, particularly those who die before birth, exhibit an incomplete development of adaptive systems. Immaturity of endocrine and immune regulatory mechanisms reduces their ability to compensate for pathological insults occurring during gestation. Chronic placental dysfunction and fetal hypoxia lead to persistent activation of stress pathways, resulting in progressive structural damage to organs involved in adaptation and survival. Consequently, the adrenal glands and thymus become highly vulnerable to degenerative and destructive processes, which may ultimately culminate in organ disintegration and functional failure.Pathomorphological examination of stillborn infants provides valuable information regarding the sequence of events preceding fetal death. Histological analysis allows the identification of microscopic changes that are not evident during routine clinical assessment and contributes to establishing the underlying causes and mechanisms of perinatal loss. Evaluation of the adrenal glands and thymus in preterm stillborn infants is particularly important because these organs reflect both the duration and

severity of intrauterine stress exposure. Their structural characteristics may serve as morphological markers of fetal adaptation failure and help distinguish acute from chronic pathological processes.Although numerous studies have investigated isolated pathological changes in fetal endocrine or immune organs, the combined assessment of adrenal gland and thymus disintegration in preterm stillborn infants remains insufficiently explored, especially within specific regional populations. Regional studies are essential because demographic characteristics, maternal health status, environmental factors, healthcare accessibility, and socio-economic conditions may influence the prevalence and nature of perinatal pathology. In the Fergana region, comprehensive investigations addressing the pathomorphological basis of these changes are limited, despite the continuing relevance of reducing fetal and neonatal mortality.Therefore, the present study was undertaken to investigate the pathomorphological features of adrenal gland and thymus disintegration in preterm stillborn infants using autopsy materials obtained from the Fergana region. The study aimed to identify the principal morphological patterns of tissue damage, evaluate the relationship between these alterations and fetal immaturity, and determine their potential significance in understanding the mechanisms of preterm fetal death. The obtained findings may contribute to expanding current knowledge regarding fetal adaptive pathology and provide a scientific foundation for improving diagnostic approaches and preventive measures in perinatal medicine.

MATERIAL AND METHODS:

The present study was conducted to investigate the pathomorphological basis of adrenal gland and thymus disintegration in preterm stillborn infants using autopsy materials obtained from the Fergana region. The research employed a retrospective descriptive and analytical design based on the examination of pathological specimens collected from routine perinatal autopsies. The study focused on identifying the structural characteristics of tissue damage and evaluating the morphological manifestations associated with fetal immaturity and intrauterine stress.The study material consisted of tissue samples obtained from preterm stillborn infants delivered at healthcare institutions in the Fergana region over the study period. Cases were selected from archival records of pathological anatomy departments according to predefined inclusion criteria. Infants with a gestational age below 37 completed weeks and diagnosed as stillborn according to accepted clinical and pathological criteria were included in the investigation. Cases with severe congenital malformations incompatible with life, extensive postmortem autolysis preventing adequate histological evaluation, or incomplete medical documentation were excluded from the study.Clinical and demographic

information was obtained from maternal and perinatal records accompanying the autopsy reports. Available data included maternal age, obstetric history, gestational age, fetal sex, pregnancy complications, and suspected causes of fetal death. These variables were used to provide general characteristics of the study population and to facilitate the interpretation of morphological findings.A complete pathological examination was performed according to standard autopsy protocols used in perinatal pathology. During the autopsy procedure, particular attention was directed toward the adrenal glands and thymus. Macroscopic evaluation included assessment of organ size, shape, consistency, color, symmetry, and the presence of visible pathological alterations such as hemorrhage, edema, focal necrosis, or signs of tissue fragmentation. Organ specimens were carefully dissected and prepared for microscopic analysis.Representative tissue fragments from both adrenal glands and the thymus were fixed in 10% neutral buffered formalin for adequate preservation of cellular structures. Following fixation, the specimens underwent routine histological processing involving dehydration through graded alcohol solutions, clearing, paraffin embedding, and preparation of serial sections approximately 4–5 μm in thickness. The sections were subsequently mounted on glass slides and stained using conventional histopathological techniques.The primary staining method employed in this study was hematoxylin and eosin (H&E), which enabled evaluation of the overall tissue architecture and identification of pathological changes at the cellular level. Microscopic examination was performed using light microscopy at different magnifications to assess the integrity of tissue structures and detect degenerative or destructive alterations.Histological assessment of the adrenal glands focused on the preservation of cortical zonation, cellular organization within the definitive and fetal cortical layers, vascular changes, hemorrhagic lesions, edema, cytoplasmic degeneration, nuclear alterations, inflammatory infiltration when present, and the occurrence of necrotic processes. Particular attention was paid to evidence of tissue disintegration reflecting severe impairment of fetal adaptive responses.Evaluation of thymic specimens included analysis of corticomedullary differentiation, the density and distribution of lymphoid elements, the condition of epithelial-reticular structures, the presence of lymphocyte depletion, stromal edema, vascular congestion, hemorrhagic changes, apoptotic phenomena, and signs of involution or fragmentation of thymic architecture. These parameters were considered indicators of intrauterine stress and immune system compromise.The severity of morphological alterations was assessed descriptively and comparatively according to gestational maturity and the extent of tissue involvement. Observed pathological findings were grouped into categories representing mild, moderate, and severe

structural disintegration based on the degree of architectural disruption and cellular injury identified during microscopic examination.The obtained data were systematically recorded and analyzed to determine common morphological patterns and relationships between adrenal and thymic changes. Descriptive statistical methods were used to summarize the frequency and distribution of the identified lesions. The findings were interpreted in the context of fetal adaptation, chronic intrauterine hypoxia, and the pathogenesis of preterm stillbirth.All procedures involving autopsy materials complied with accepted ethical principles governing biomedical research and the use of archival pathological specimens. Confidentiality of patient information was maintained throughout the study, and all collected data were used exclusively for scientific purposes. The methodological approach adopted in this investigation provided a comprehensive evaluation of endocrine and immune organ pathology in preterm stillborn infants and facilitated a deeper understanding of the mechanisms underlying fetal death in the Fergana region.

RESULTS:

The pathomorphological examination of the adrenal glands and thymus in preterm stillborn infants revealed a wide spectrum of structural alterations indicating severe impairment of fetal adaptive mechanisms. The severity and extent of the observed lesions varied according to gestational age, the presumed duration of intrauterine hypoxia, and the presence of associated maternal and placental complications. Nevertheless, several characteristic patterns of tissue disintegration were consistently identified in the majority of the examined cases.Macroscopic evaluation of the adrenal glands demonstrated noticeable changes in organ appearance. In a considerable number of cases, the glands exhibited altered consistency, loss of normal elasticity, and irregular contours. Areas of diffuse congestion and focal hemorrhagic lesions were frequently observed on cut sections. In some specimens, the adrenal tissue appeared friable and fragmented, suggesting advanced destructive processes. The severity of these gross alterations tended to increase in fetuses with lower gestational age and in cases associated with prolonged intrauterine distress.Microscopic examination of adrenal tissue revealed pronounced disturbances in the normal histoarchitectural organization. The distinction between the fetal zone and the definitive cortical zone was often reduced or completely obscured. Cellular disarrangement was a common finding, characterized by disruption of the orderly arrangement of cortical cells and loss of the typical radial pattern. Many adrenal cortical cells exhibited varying degrees of hydropic and granular degeneration, manifested by cytoplasmic swelling, vacuolization, and decreased staining intensity.Nuclear alterations indicative of

irreversible cellular injury were also frequently encountered. Pyknosis, karyorrhexis, and karyolysis were observed in numerous specimens, reflecting ongoing degenerative and necrotic processes. Focal areas of coagulative necrosis involving clusters of cortical cells were identified in severe cases. These lesions were often accompanied by extensive vascular disturbances, including capillary dilation, blood stasis, erythrocyte aggregation, and interstitial hemorrhage.Edematous changes affecting the adrenal stroma were evident in many cases. Interstitial edema contributed to separation of cellular elements and further disruption of tissue architecture. In some specimens, hemorrhagic infiltration extended throughout large portions of the gland, resulting in marked destruction of cortical structures. These findings indicated profound circulatory disturbances associated with chronic and acute episodes of fetal hypoxia.The thymus demonstrated equally significant pathological alterations. Gross examination frequently revealed a reduction in organ size relative to gestational expectations, accompanied by a soft consistency and loss of the normal lobulated appearance. In advanced cases, the thymic tissue appeared pale, fragile, and partially collapsed, reflecting structural involution and degeneration.Histologically, one of the most prominent findings in the thymus was the disruption of normal corticomedullary differentiation. The cortical region showed marked depletion of lymphoid cells, resulting in decreased cellular density and thinning of the cortical layer. In several specimens, the boundary between the cortex and medulla became indistinct due to progressive architectural disorganization.Lymphocyte depletion represented a characteristic manifestation of thymic disintegration. Numerous apoptotic bodies and fragmented nuclear debris were identified within the cortical areas, suggesting accelerated lymphocyte destruction. These changes were particularly pronounced in fetuses presumed to have experienced prolonged intrauterine stress. The reduction in lymphoid elements indicated suppression of fetal immune maturation and diminished immunological reserve.Alterations involving the stromal component of the thymus were also observed. Edema of the interlobular connective tissue, vascular congestion, and focal hemorrhages contributed to the distortion of normal thymic architecture. Epithelial-reticular cells occasionally demonstrated degenerative changes characterized by cytoplasmic vacuolization and nuclear condensation. In severe cases, fragmentation of thymic lobules and collapse of the supporting stromal framework were evident.A comparative assessment of both organs revealed that the degree of adrenal and thymic damage frequently occurred in parallel. Cases demonstrating extensive adrenal cortical degeneration often exhibited severe thymic lymphoid depletion and pronounced involutional changes. This pattern supports the existence of a close functional relationship between

endocrine stress responses and immune system regulation during fetal development.Furthermore, the severity of pathological alterations was generally greater among infants with earlier gestational ages. Extremely preterm stillborn infants exhibited more extensive tissue disintegration, diffuse vascular disturbances, and widespread cellular destruction compared with late preterm cases. These findings suggest that organ immaturity significantly reduces the capacity of the fetus to withstand adverse intrauterine conditions.Overall, the results of the present study indicate that disintegration of the adrenal glands and thymus in preterm stillborn infants is characterized by a combination of degenerative, circulatory, and necrotic changes involving both endocrine and immune structures. The observed morphological alterations reflect chronic fetal stress and adaptation failure associated with intrauterine hypoxia and may serve as valuable pathological markers in determining the mechanisms contributing to preterm fetal death in the Fergana region.

DISCUSSIONS:

The findings of the present study provide important insights into the pathomorphological mechanisms underlying adrenal gland and thymus disintegration in preterm stillborn infants. The observed structural alterations indicate that fetal death in these cases is not merely the consequence of an isolated pathological event but rather the final manifestation of prolonged disturbances affecting the fetal adaptive system. The endocrine and immune organs examined in this investigation demonstrated marked susceptibility to intrauterine stress, emphasizing their crucial role in maintaining fetal homeostasis during adverse gestational conditions.One of the most significant observations of this study was the extensive disruption of adrenal cortical architecture accompanied by vascular and degenerative changes. The fetal adrenal gland is known to be one of the primary organs involved in adaptation to intrauterine stress. Through activation of the fetal hypothalamic-pituitary-adrenal axis, the adrenal cortex contributes to glucocorticoid production, regulation of metabolism, maintenance of cardiovascular function, and maturation of multiple fetal organs. Under conditions of chronic hypoxia and placental insufficiency, persistent stimulation of this axis may initially represent a compensatory response. However, prolonged activation appears to exceed the adaptive capacity of immature adrenal tissue, ultimately resulting in cellular degeneration, vascular compromise, and tissue disintegration.The presence of cytoplasmic vacuolization, nuclear pyknosis, karyorrhexis, karyolysis, and focal necrosis identified in the adrenal cortex supports the hypothesis that severe metabolic imbalance and oxygen deprivation play major roles in the development of irreversible cellular injury. These findings

suggest that the adrenal glands of preterm fetuses possess limited resistance to sustained pathological stimuli. Consequently, endocrine failure may contribute significantly to the inability of the fetus to maintain physiological adaptation during progressive intrauterine compromise.The vascular abnormalities observed in this study, including congestion, erythrocyte stasis, edema, and hemorrhagic infiltration, further highlight the importance of circulatory disturbances in the pathogenesis of fetal organ damage. Chronic placental dysfunction often leads to impaired fetal oxygen delivery and redistribution of blood flow to preserve vital organ function. Although these compensatory mechanisms may temporarily support survival, prolonged disturbances in microcirculation eventually result in tissue ischemia and structural breakdown. The hemorrhagic lesions detected in adrenal tissues likely reflect increased vascular permeability and endothelial injury associated with severe hypoxic stress.The thymic alterations documented in the present investigation were equally noteworthy. Lymphoid depletion, disruption of corticomedullary differentiation, stromal degeneration, and involutional changes constituted the predominant pathological features. The thymus is widely recognized as a sensitive biological indicator of fetal stress. Exposure to elevated glucocorticoid concentrations during prolonged activation of the stress response promotes apoptosis of immature thymocytes and accelerates thymic involution. Therefore, the morphological changes identified in this study can be interpreted as evidence of excessive activation of endocrine stress pathways and their suppressive effects on the developing immune system.The marked reduction in lymphocyte density observed within the thymic cortex suggests impairment of fetal T-cell maturation and a diminished capacity for immune development. Although stillborn infants do not survive to manifest postnatal immunological consequences, these findings reflect profound disturbances in immune ontogenesis occurring before death. Such abnormalities may indicate prolonged exposure to adverse intrauterine factors and provide indirect evidence regarding the duration and severity of fetal compromise.An important aspect of the present study is the demonstration of a parallel relationship between adrenal and thymic pathology. Cases characterized by severe adrenal degeneration frequently exhibited advanced thymic involution and lymphoid depletion. This association supports the concept of functional interaction between the endocrine and immune systems during fetal development. The hypothalamic-pituitary-adrenal axis and thymic maturation are closely interconnected, and disturbances affecting one component inevitably influence the other. Consequently, simultaneous evaluation of these organs may provide a more comprehensive understanding of fetal adaptive failure than the examination of either structure alone.The greater severity of lesions observed in

extremely premature fetuses further emphasizes the role of developmental immaturity in the pathogenesis of stillbirth. Incomplete structural and functional maturation of endocrine and immune organs limits the fetus's ability to compensate for hypoxic and metabolic insults. As gestational age decreases, adaptive reserves become progressively insufficient, increasing vulnerability to tissue injury and death. Therefore, prematurity itself should be regarded not only as a temporal characteristic of fetal development but also as an important biological determinant of susceptibility to pathological processes.The findings of this study also have practical implications for perinatal pathology. Histopathological assessment of the adrenal glands and thymus may serve as an additional diagnostic tool for reconstructing the sequence of events preceding fetal death. The identification of characteristic patterns of degeneration, vascular disturbance, and involution may assist pathologists in differentiating acute and chronic fetal stress conditions and contribute to a more accurate determination of the causes and mechanisms of stillbirth.Several limitations should be acknowledged. The retrospective nature of the study and reliance on archival autopsy materials limited the availability of complete clinical information in some cases. Furthermore, the absence of immunohistochemical and molecular analyses restricted the investigation to conventional morphological observations. Future studies incorporating larger sample sizes, advanced histochemical techniques, and molecular markers of apoptosis, hypoxia, and endocrine activity may provide a deeper understanding of the mechanisms involved in fetal organ disintegration.

CONCLUSION:

The present study demonstrated that preterm stillborn infants exhibit pronounced pathomorphological alterations in the adrenal glands and thymus, reflecting severe impairment of fetal adaptive mechanisms during intrauterine life. The identified changes were characterized by structural disorganization, vascular disturbances, cellular degeneration, and varying degrees of tissue disintegration affecting both endocrine and immune organs. These findings indicate that fetal death in premature stillbirth is frequently preceded by progressive pathological processes rather than by a single acute event.The adrenal glands showed marked disruption of normal cortical architecture accompanied by congestion, hemorrhagic lesions, stromal edema, cytoplasmic degeneration, and focal necrotic changes. Such alterations suggest exhaustion of the fetal stress-response system following prolonged exposure to adverse intrauterine conditions, particularly chronic hypoxia and placental insufficiency. The inability of immature adrenal tissue to maintain adequate endocrine compensation appears to be an important component in the development of fetal adaptation failure.Similarly, the thymus demonstrated

significant involutional and destructive changes, including lymphoid depletion, loss of corticomedullary differentiation, degeneration of stromal structures, and fragmentation of thymic architecture. These abnormalities reflect profound disturbances in fetal immune development and indicate the high sensitivity of thymic tissue to endocrine imbalance and sustained intrauterine stress. The observed reduction in thymic lymphoid elements may serve as a morphological marker of prolonged fetal compromise.A close association between the severity of adrenal and thymic lesions was identified, supporting the concept of functional interdependence between the endocrine and immune systems during fetal development. Simultaneous damage to these organs suggests that disruption of neuroendocrine regulation contributes substantially to the pathogenesis of preterm stillbirth. Furthermore, the greater extent of pathological alterations observed in fetuses of lower gestational age emphasizes the critical role of developmental immaturity in increasing susceptibility to hypoxic and metabolic injury.The pathomorphological patterns identified in this study may provide valuable diagnostic information for determining the mechanisms underlying fetal death and for distinguishing chronic intrauterine stress from acute pathological events. Comprehensive histological evaluation of the adrenal glands and thymus should therefore be considered an important component of perinatal autopsy examinations in cases of preterm stillbirth.In summary, disintegration of the adrenal glands and thymus in preterm stillborn infants represents a manifestation of severe fetal adaptation failure resulting from the combined effects of chronic hypoxia, circulatory disturbances, endocrine dysfunction, immune impairment, and organ immaturity. Recognition of these morphological changes may contribute to a better understanding of the causes of perinatal mortality and provide a scientific basis for improving prenatal surveillance, optimizing obstetric care, and developing preventive strategies aimed at reducing the incidence of stillbirth in the Fergana region and similar populations.

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