Review Article

Pathophysiological Interactions between Bronchial Asthma, Connective Tissue Dysplasia, and Pubertal Development: A Narrative Review

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Abstract

Pubertal development is a complex neuroendocrine process regulated by activation of the hypothalamic–pituitary–gonadal (HPG) axis and influenced by genetic, inflammatory, metabolic, and nutritional factors. Bronchial asthma (BA), one of the most prevalent chronic inflammatory diseases in adolescence, has been associated with alterations in growth velocity and pubertal timing, particularly in individuals with moderate-to-severe or poorly controlled disease. However, variability in pubertal outcomes among affected adolescents suggests the presence of additional biological modifiers.

Undifferentiated connective tissue dysplasia (UCTD) is a genetically determined condition characterized by abnormalities of collagen synthesis and extracellular matrix organization, resulting in multisystem involvement. Its high prevalence among adolescents with BA indicates a potential role as a structural and biological modifier of endocrine development.

Current evidence suggests that the coexistence of BA and UCTD may amplify inflammatory burden and hypoxic stress. It may also contribute to extracellular matrix instability and micronutrient deficiencies, including vitamin D, zinc, and magnesium. Together, these interacting mechanisms may disrupt hormonal regulation of the HPG axis and contribute to pubertal delay or disharmonious pubertal development.

Recognition of this combined pathology underscores the importance of multidisciplinary monitoring and early identification of endocrine vulnerability in order to improve long-term reproductive outcomes.

Keywords: Bronchial asthma, Connective tissue dysplasia, Puberty, Adolescents, Endocrine regulation, Inflammation.

Introduction

Pubertal development is a tightly regulated biological process driven by activation and maturation of the hypothalamic-pituitary-gonadal (HPG) axis [1–5]. The timing and tempo of puberty are influenced not only by genetic determinants but also by chronic disease burden, nutritional status,

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systemic inflammation, metabolic factors, and tissue responsiveness to hormonal signaling [3–5]. Disruption of any component of this complex regulatory network during adolescence may result in delayed, accelerated, or disharmonious pubertal progression [1,2,4].

Bronchial asthma affects approximately 10–14% of adolescents worldwide, according to data from the Global Asthma Network and the International Study of Asthma and Allergies in Childhood (ISAAC) Phase III, making it one of the most prevalent chronic inflammatory diseases in this age group [6,7]. Accumulating epidemiological and longitudinal evidence indicates that chronic inflammatory conditions, including asthma, may influence growth velocity and pubertal timing, particularly in adolescents with moderate-to-severe or poorly controlled disease [9–11].

Current explanatory models primarily attribute altered pubertal trajectories in asthma to systemic inflammation, recurrent hypoxia, and prolonged glucocorticoid exposure, all of which may disrupt hypothalamic–pituitary regulation and gonadal steroidogenesis during critical developmental windows [12,13]. However, these inflammation-centered models do not fully account for the heterogeneity of pubertal outcomes observed in clinical practice. Not all adolescents with comparable asthma severity exhibit similar endocrine or pubertal alterations, suggesting that additional biological modifiers may influence individual vulnerability.

One potentially underrecognized modifier is undifferentiated connective tissue dysplasia (UCTD). UCTD is highly prevalent in pediatric populations, with reported frequencies ranging from 30% to 65%, depending on diagnostic criteria and regional characteristics, particularly in Eastern Europe and the Commonwealth of Independent States [20,21]. It is characterized by genetically determined abnormalities in collagen synthesis and extracellular matrix organization, leading to multisystem involvement affecting the musculoskeletal, cardiovascular, respiratory, and autonomic systems [20,22].

Importantly, connective tissue provides the structural and functional framework for endocrine organs, vascular supply, and receptor anchoring within target tissues. Therefore, abnormalities of the extracellular matrix may influence hormonal bioavailability, receptor stability, tissue elasticity, and cellular responsiveness to endocrine signaling. In adolescents with asthma, the coexistence of chronic inflammation and connective tissue dysplasia may create a compounded biological burden that extends beyond inflammation alone.

Despite its systemic nature and high prevalence, UCTD has not been adequately integrated into existing models of pubertal or endocrine risk assessment in adolescents with chronic inflammatory diseases. This gap limits a comprehensive understanding of endocrine vulnerability in this population.

This review therefore evaluates undifferentiated connective tissue dysplasia as a potential structural and biological modifier of pubertal and hormonal development in adolescents with bronchial asthma. By synthesizing evidence from epidemiological cohorts, longitudinal clinical studies, and regional investigations, it aims to expand current pathogenetic models beyond inflammation-centered paradigms and to support more individualized approaches to adolescent endocrine assessment and care [20–23].

Methodology

This study was conducted as an evidence-based narrative review examining undifferentiated connective tissue dysplasia (UCTD) as a potential modifier of pubertal and hormonal development in adolescents with bronchial asthma (BA). A narrative review design was selected because the objective was to integrate heterogeneous evidence from epidemiological, clinical, endocrine, and pathophysiological studies that differ substantially in methodology, populations, and outcome measures. Given the conceptual and mechanistic focus of this review, a systematic review with meta-analysis was not feasible due to variability in study designs, definitions of UCTD, and reported endocrine endpoints.

A structured literature search was performed using PubMed/MEDLINE, Scopus, and Web of

Science to identify relevant studies published between January 2000 and March 2025, with emphasis on recent publications. Search terms included combinations of the following keywords: "bronchial asthma," "puberty," "hypothalamic–pituitary–gonadal axis," "connective tissue dysplasia," "undifferentiated connective tissue dysplasia," "vitamin D," "micronutrients," and "prolactin." Reference lists of relevant articles were also screened to identify additional studies.

Eligible studies included longitudinal cohort studies, randomized controlled trials, meta-analyses, and large observational studies involving adolescents aged 10–19 years. Studies were included if they reported data on pubertal timing, hormonal parameters, endocrine function, micronutrient status, or connective tissue characteristics relevant to the proposed mechanistic framework. Publications in English were included. Regional studies, particularly from Eastern Europe and the Commonwealth of Independent States, were considered when they provided clinically relevant data on UCTD prevalence or phenotype. Case reports and small case series were excluded unless they contributed unique mechanistic insights.

Data were synthesized using a pathophysiological framework integrating inflammatory, hypoxic, extracellular matrix, micronutrient, and endocrine mechanisms. In cases of conflicting findings, greater weight was given to large-scale longitudinal studies, meta-analyses, and studies with clearly defined endocrine outcomes. Divergent results were analyzed in the context of differences in asthma severity, treatment exposure (including glucocorticoids), nutritional status, and diagnostic criteria for UCTD. Rather than excluding discordant data, inconsistencies were examined to identify potential effect modifiers and sources of heterogeneity.

As this review was based exclusively on previously published data, ethical approval was not required.

Results

Synthesis of longitudinal cohort studies, meta-analyses, and regional endocrine investigations demonstrates a general pattern of endocrine vulnerability among adolescents with bronchial asthma (BA) [9–12]. However, the magnitude and clinical significance of these alterations vary across studies, partly reflecting differences in asthma severity classification, treatment exposure, and outcome assessment methods.

Large international cohorts primarily report modest alterations in pubertal timing, particularly in males with moderate-to-severe or poorly controlled disease [9–12]. These changes include delayed pubertal growth acceleration, transient suppression of gonadotropin secretion, and slight reductions in sex steroid concentrations relative to chronological age. Importantly, many of these findings are derived from observational designs and rely on indirect endocrine markers (e.g., single-timepoint hormone measurements rather than pulsatility assessments), which may underestimate dynamic hypothalamic–pituitary–gonadal (HPG) axis variability.

In contrast, regional studies-particularly from Eastern Europe and the Commonwealth of Independent States-describe a more pronounced and complex phenotype in adolescents with combined BA and undifferentiated connective tissue dysplasia (UCTD) [20–23]. In these cohorts, pubertal progression is frequently described as disharmonious, with discordance between chronological age, Tanner stage, and hormonal profile. Gonadotropin secretion patterns are often unstable, suggesting functional hypothalamic suppression rather than primary gonadal insufficiency [13–15]. Circulating sex steroid levels are reported to be lower relative to pubertal stage, implying reduced endocrine responsiveness [9–12,20–23].

However, interpretation of these findings requires caution. Diagnostic criteria for UCTD are not standardized internationally, and definitions vary substantially between studies. Some investigations rely on phenotypic scoring systems, whereas others use broader clinical descriptions of connective tissue features. This heterogeneity complicates direct comparison across cohorts and may partially account for the stronger associations reported in regional studies.

Hyperprolactinemia appears more frequently in adolescents with combined BA and UCTD, particularly in the presence of persistent inflammatory activity and vitamin D deficiency [14,15,32]. Nevertheless, most data are derived from cross-sectional analyses, limiting causal inference. Similarly, micronutrient disturbances-including reduced zinc and magnesium statusare more commonly reported in adolescents with both asthma and connective tissue manifestations [16-19,24-27]. While correlations with asthma severity and pubertal delay are described, these associations remain largely observational and may be influenced by dietary, socioeconomic, or treatment-related confounders.

Respiratory instability, increased exacerbation frequency, and greater cumulative exposure to corticosteroid therapy are more frequently observed in adolescents with BA + UCTD, potentially intensifying systemic endocrine stress [9-12,22,23]. However, disentangling the independent contribution of UCTD from asthma severity itself remains challenging, as few studies employ stratified or multivariate modeling to isolate connective tissue status as an independent modifier.

Overall, although the direction of findings across studies is relatively consistent—suggesting amplified endocrine vulnerability in adolescents with combined BA and UCTD—the strength of evidence is moderated by heterogeneity in UCTD diagnostic approaches, reliance on observational designs, limited longitudinal endocrine tracking, and variation in regional research methodologies. These limitations highlight the need for standardized diagnostic criteria and prospective mechanistic studies incorporating dynamic hormonal assessment.

The integrated mechanistic framework presented in Table 1. synthesizes inflammatory, hypoxic, extracellular matrix, micronutrient, and neuroendocrine pathways into a unified model of pubertal vulnerability. Rather than acting independently, these mechanisms appear to interact synergistically, with connective tissue dysplasia potentially lowering the threshold for endocrine dysregulation in the context of chronic asthma. This model helps explain the observed heterogeneity in pubertal outcomes across clinical populations.

Table 1. Integrated Mechanistic Model of Endocrine Disruption in Adolescents with Bronchial Asthma and UCTD

Pathogenic Mechanism	Bronchial Asthma (BA)	Contribution of UCTD	Endocrine Consequence	Clinical Manifestation
Chronic systemic inflammation	Persistent cytokine activation (IL-6, TNF-α)	Increased inflammatory persistence due to structural airway instability	Suppression of GnRH pulsatility and reduced LH/FSH secretion	Delayed pubertal onset
Recurrent hypoxia	Episodic oxygen desaturation during exacerbations	Enhanced bronchial collapsibility and impaired ventilation mechanics	Activation of HPA axis → Elevated cortisol → Inhibition of HPG axis	Slowed Tanner progression
Extracellular matrix remodeling	Airway wall thickening and fibrosis	Collagen disorganization and receptor anchoring instability	Reduced tissue responsiveness to sex steroids	Disharmonious pubertal development

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Corticosteroid exposure	Anti-inflammatory therapy (inhaled/ systemic)	Greater cumulative exposure due to severe disease	Transient suppression of steroidogenesis	Delayed growth acceleration
Vitamin D deficiency	Common in chronic inflammatory disease	Impaired collagen synthesis and immune modulation	Altered steroidogenic enzyme activity; prolactin elevation	Menstrual irregularities
Zinc deficiency	Associated with chronic disease	Impaired collagen cross-linking	Reduced androgen receptor function	Delayed virilization in boys
Magnesium insufficiency	Suboptimal intake common	Reduced vitamin D activation	Decreased anabolic hormonal signaling	Reduced pubertal growth velocity
Autonomic dysregulation	Present in some asthma phenotypes	Frequent in connective tissue dysplasia	Neuroendocrine instability	Irregular menstrual cycles

Pathophysiological Domain	**Healthy Adolescents**	**Bronchial Asthma**	**Asthma + UCTD**	**Key References**
Systemic inflammation	Physiological baseline	Chronic airway inflammation	Amplified and persistent systemic inflammation	[9–13,22]
Hypoxic exposure	Absent	Episodic during exacerbations	More frequent and prolonged	[9–12]
HPG axis regulation	Stable pulsatility	Mild cytokine-mediated suppression	Greater instability and delayed activation	[13–15]
Sex steroid dynamics	Age-appropriate rise	Slight pubertal delay	Relative insufficiency for stage	[9–12,20–23]
Prolactin levels	Normal	Mild elevation in severe cases	Higher prevalence of hyperprolactinemia	[14,15,32]
Extracellular matrix integrity	Normal	Preserved	Structurally compromised	[20–22]
Vitamin D status	Variable	Frequently deficient	Markedly deficient	[16–19]
Zinc/Magnesium status	Within reference	Suboptimal in some	Frequently reduced	[24–27]

Note: The relative contributions described in this model are derived from heterogeneous observational and regional data; causal relationships remain to be confirmed in prospective mechanistic studies.

Discussion

The integrated analysis indicates that undiffer entiated connective tissue dysplasia functions as

a biological modifier of endocrine vulnerability in adolescents with bronchial asthma [20–23]. Asthma-related inflammation alone can delay pubertal timing through cytokine-mediated suppression of hypothalamic gonadotropin-releasing hormone pulsatility [13–15], findings consistently demonstrated in large longitudinal cohorts [9–12]. These alterations are typically functional and reversible.

However, the coexistence of connective tissue dysplasia introduces an additional structural dimension. Collagen disorganization and extracellular matrix instability alter bronchial mechanics and increase susceptibility to exacerbations, thereby intensifying inflammatory and hypoxic stress [20–23]. Recurrent hypoxia activates the hypothalamic–pituitary–adrenal axis, elevating cortisol levels and further suppressing gonadotropic signaling [9–13].

Moreover, extracellular matrix dysfunction may impair endocrine target organ responsiveness. Proper steroid hormone signaling depends on receptor stabilization and intracellular matrix organization; structural abnormalities may compromise these processes and produce functional hormone resistance despite near-normal circulating levels [20–22].

Micronutrient deficiencies further compound this vulnerability. Vitamin D deficiency contributes to immune dysregulation and altered prolactin secretion [16–19,32]. Zinc deficiency affects androgen receptor integrity and testosterone synthesis [24,25], while magnesium insufficiency interferes with vitamin D activation and anabolic hormone metabolism [26,27]. The convergence of inflammatory, structural, and metabolic stressors during a critical developmental window creates cumulative suppression of the hypothalamic–pituitary–gonadal axis.

Sex-specific patterns are also evident. Boys appear more susceptible to delayed testosterone rise and slowed pubertal activation under inflammatory stress [9–12], whereas girls more frequently exhibit menstrual irregularities and PCOS-like phenotypes [30,31]. Connective tissue instability may intensify these gender-dependent vulnerabilities by modifying tissue-level hormonal responsiveness [20–22].

Conclusion

Undifferentiated connective tissue dysplasia (UCTD) acts as an important biological modifier of pubertal and hormonal development in adolescents with bronchial asthma. While asthma alone may contribute to functional delays in pubertal timing, the coexistence of connective tissue instability appears to amplify inflammatory, hypoxic, and metabolic stress, resulting in greater disruption of hypothalamic–pituitary–gonadal axis regulation.

This combined pathology increases the risk of pubertal delay or disharmonious pubertal progression and endocrine imbalance. Early multidisciplinary monitoringincluding structured endocrine evaluation and assessment of micronutrient statusmay support timely identification of at-risk adolescents and help prevent long-term reproductive consequences.

Future prospective longitudinal studies incorporating standardized UCTD diagnostic criteria and dynamic hormonal assessment are needed to clarify causal mechanisms and refine risk stratification strategies in this population.

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