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Adrenal Disorders and Pubertal Development in Children: Hormonal Pathways, Timing Disruptions and Clinical Outcome

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Abstract

Background: Pubertal development is tightly regulated by the hypothalamic–pituitary–gonadal axis and modulated by adrenal glucocorticoids and androgens. Disruption of adrenal function—through hyposecretion or hypersecretion—can alter the timing, tempo, and outcome of puberty, but data are scattered across heterogeneous pediatric conditions. This review integrates current evidence on how adrenal disorders shape pubertal development and growth outcomes, and to what extent these abnormalities are reversible with treatment.

Methods: A structured narrative review was conducted using PubMed/MEDLINE, Scopus, and Google Scholar (January 2000–June 2025). Search terms combined adrenal disorders (e.g., adrenal insufficiency, congenital adrenal hyperplasia, Cushing syndrome, premature adrenarche, adrenal hypoplasia congenita, Triple A syndrome, McCune–Albright syndrome) with pubertal terms (delayed puberty, precocious puberty, pubertal progression, adrenarche, pubarche). Human studies in patients <20 years reporting adrenal diagnosis plus at least one pubertal or growth outcome were included. Case reports (<5 patients), adult-only series, purely biochemical reports, and non–full-text abstracts were excluded. Study quality was assessed using a modified Newcastle–Ottawa Scale and synthesized qualitatively in four domains: adrenal hyposecretion, hypersecretion, syndromic disorders, and reversibility.

Results: Adrenal hyposecretion (primary and central adrenal insufficiency, adrenal hypoplasia, familial glucocorticoid deficiency, autoimmune polyglandular syndromes) was consistently associated with delayed adrenarche, delayed or sparse pubarche, slow pubertal progression, and reduced growth velocity. Syndromic forms (e.g., DAX-1–related adrenal hypoplasia, Triple A, IMAGe, APS-1) frequently combined adrenal failure with hypogonadotropic hypogonadism or primary gonadal failure, leading to profound pubertal delay or absent puberty. In contrast, adrenal hypersecretion states showed a spectrum from mild to severe precocious development. Classic 21-hydroxylase–deficient congenital adrenal hyperplasia, nonclassic CAH, premature adrenarche, and androgen-secreting adrenal tumors were linked to premature pubarche, virilization, advanced bone age, and, in many cases, central precocious puberty with compromised adult height. Cushing syndrome (ACTH-dependent and independent) uniquely caused growth failure and pubertal delay due to cortisol-mediated suppression of GnRH, gonadotropins, and growth hormone action. Across disorders, early and optimized treatment improved pubertal trajectories: strict androgen control in CAH limited progression and preserved height; surgical cure of Cushing syndrome allowed recovery of pubertal progression; metabolic management in premature adrenarche mitigated progression to early menarche and PCOS. However, in genetic syndromic adrenal insufficiency, pubertal abnormalities were rarely reversible without exogenous sex-steroid or gonadotropin replacement. Overall study quality was moderate to high, supporting the robustness of these patterns.

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Conclusions: Adrenal hypofunction predominantly delays puberty, whereas adrenal androgen excess accelerates or distorts pubertal onset, and cortisol excess suppresses pubertal maturation and growth. Many pubertal disturbances are partially reversible when adrenal disorders are recognized and treated early, but syndromic forms often require lifelong hormone replacement. Routine pubertal surveillance in children with adrenal disease and integrated hormonal, metabolic, and genetic evaluation are essential to optimize growth and reproductive outcomes.

Keywords: Adrenal disorders; Puberty; Congenital adrenal hyperplasia; Cushing syndrome; Premature adrenarche

1. Introduction

Pubertal development is a complex neuroendocrine transition driven by the activation of the hypothalamic–pituitary–gonadal (HPG) axis and influenced by adrenal steroid production. Adrenal glucocorticoids, mineralocorticoids, and adrenal androgens are important modulators of growth, skeletal maturation, metabolic signaling, and the hormonal milieu that shapes the timing and tempo of puberty (1). Disruptions of these adrenal pathways—through either hormone deficiency or excess—can produce marked deviations in pubertal onset and progression.

In normal development, adrenarche begins around 6–8 years of age and reflects the maturation of the adrenal zona reticularis with rising secretion of DHEA and DHEAS. Pubarche, the appearance of pubic hair, occurs after adrenarche, typically 1–2 years later, and represents the clinical manifestation of increased adrenal androgen production (2). This sequence—adrenarche → pubarche → gonadarche—is critical for normal pubertal maturation. When adrenal hormone production is impaired, pubarche may be delayed or absent; when excessive, pubarche may occur prematurely and may progress independently of true central puberty.

Adrenal hypofunction—including primary adrenal insufficiency, central adrenal failure, and adrenal hypoplasia—may blunt adrenarche and delay pubarche. Reduced adrenal androgen production contributes to sparse or late development of pubic and axillary hair, slower skeletal maturation, impaired growth velocity, and delayed gonadal activation. Chronic cortisol deficiency additionally alters metabolic cues and inflammatory pathways that influence HPG axis responsiveness (3).

Conversely, adrenal hyperfunction—most commonly from congenital adrenal hyperplasia (CAH), but also adrenal tumors and ACTH-independent hypercortisolism—can markedly alter pubertal timing. Excess adrenal androgens drive premature adrenarche, early pubarche, accelerated bone maturation, and rapid progression of puberty. If untreated, these children may progress into central precocious puberty or experience compromised adult height due to premature epiphyseal fusion (4).

Cushing syndrome represents the opposite phenotype, in which chronic hypercortisolism suppresses GnRH pulsatility, reduces gonadotropin release, and induces severe growth hormone resistance. Affected children often develop delayed puberty, hypogonadotropic hypogonadism, reduced growth velocity, and significant loss of height potential. These effects are frequently compounded by cortisol-mediated metabolic changes, including increased adiposity and insulin resistance, further influencing pubertal timing (5).

A number of multisystem syndromes illustrate the tight integration between adrenal and pubertal physiology. Disorders such as adrenal hypoplasia congenita (DAX-1 mutations), triple A syndrome, and McCune–Albright syndrome may combine adrenal insufficiency or adrenal hypersecretion with delayed, absent, or peripheral precocious puberty. Although individual adrenal disorders have been well described, there remains no unified summary examining how adrenal hypo- and hypersecretion shape pubertal timing, progression, and final outcomes across the pediatric age range. Updated synthesis is necessary to improve early recognition, guide monitoring strategies, and emphasize the potential reversibility of pubertal abnormalities when adrenal disorders are properly diagnosed and treated (6).

Objectives

- To synthesize current evidence on how adrenal hyposecretion and hypersecretion affect pubertal timing, progression, and final outcomes in children and adolescents.
- To systematically classify acute and chronic pubertal abnormalities associated with adrenal disorders, including syndromes that involve both adrenal and gonadal axes.
- To elucidate the underlying pathophysiological mechanisms linking adrenal dysfunction to pubertal disturbances and to highlight opportunities for reversibility with timely diagnosis and treatment

2. Methods

This review was conducted as a structured narrative synthesis of the literature on adrenal disorders and pubertal development in children and adolescents. A comprehensive search of PubMed/MEDLINE, Scopus, and Google Scholar was performed for articles published between January 2000 and June 2025, using combinations of the following terms: "adrenal insufficiency," "primary adrenal failure," "congenital adrenal hyperplasia," "Cushing syndrome," "premature adrenarche," "adrenal hypoplasia congenita," "triple A syndrome," "Allgrove syndrome," "McCune–Albright," "puberty," "delayed puberty," "precocious puberty," "pubertal progression," "pubarche," and "adrenarche." Boolean operators and MeSH terms were applied where available, and reference lists of key reviews and guideline statements were hand-searched to identify additional relevant publications (1–6).

Eligible studies included human research involving children and adolescents (<20 years) with adrenal hypofunction or hyperfunction in whom pubertal timing, pubertal staging, growth, bone age, or gonadal function were reported. Observational cohort studies, case–control studies, cross-sectional studies, interventional series, and well-documented case series (≥5 patients) were included. Studies were required to report a defined adrenal diagnosis (e.g., primary adrenal insufficiency, congenital adrenal hyperplasia, Cushing syndrome, adrenal hypoplasia congenita, triple A syndrome, McCune–Albright syndrome) and at least one pubertal or growth-related outcome (e.g., age at pubarche or gonadarche, Tanner staging, pubertal tempo, hypogonadism, precocious puberty, final height). Exclusion criteria were animal or in vitro studies, isolated adult cohorts, isolated biochemical reports without clinical pubertal data, conference abstracts without full text, and single case reports unless they described a clearly novel mechanism directly linking adrenal dysfunction and puberty.

Titles and abstracts were screened for relevance, followed by full-text review of potentially eligible articles. Data extracted from each study included study design, sample size, age range, adrenal diagnosis and etiology, hormonal profile (cortisol, ACTH, adrenal androgens, mineralocorticoids), pubertal parameters (age at onset, Tanner stage progression, presence of delayed or precocious puberty), growth and bone age data, treatment modalities, and reported reversibility or progression of pubertal abnormalities after therapy. Particular attention was paid to syndromic conditions in which adrenal insufficiency coexists with hypogonadotropic hypogonadism or peripheral precocious puberty, such as adrenal hypoplasia congenita and triple A syndrome (6,7).

Methodological quality of observational studies was assessed using a modified Newcastle–Ottawa Scale adapted for pediatric endocrine cohorts, evaluating selection of participants, ascertainment of adrenal diagnosis, comparability of groups (where applicable), and objectivity of pubertal and growth outcome assessment. Interventional series and case series were appraised for clarity of inclusion criteria, completeness of follow-up, and consistency of pubertal outcome reporting. Because of substantial heterogeneity in study design, diagnostic criteria, and outcome measures, a formal meta-analysis was not attempted. Instead, findings were synthesized qualitatively and organized into three main categories: adrenal hyposecretion with pubertal delay or impairment, adrenal hypersecretion with precocious or rapidly progressive puberty, and syndromes that involve both adrenal dysfunction and primary pubertal axis abnormalities. Within each category, representative studies were highlighted, and consistent patterns of pubertal disturbance, mechanism, and reversibility with treatment were summarized.

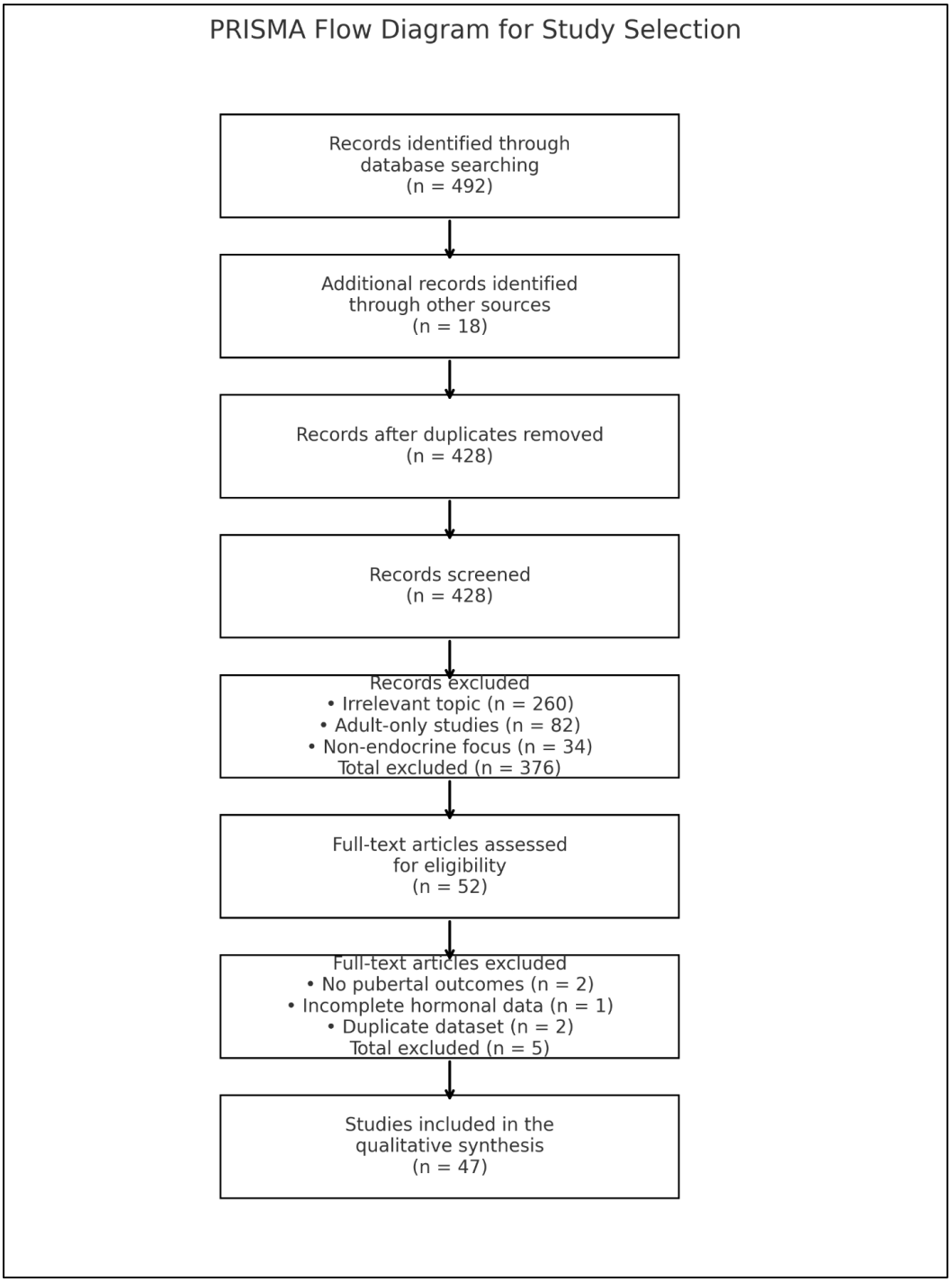

Figure 1 PRISMA Flow Diagram for Study Selection

Figure 1 summarizes the study identification and selection process. A total of 492 records were initially screened. After full-text review, 47 studies met all eligibility criteria and were included in the final qualitative synthesis.

3. Results

The review identified consistent patterns across adrenal hyposecretion, adrenal hypersecretion, and syndromic conditions, demonstrating distinct and predictable effects on pubertal timing, progression, and growth outcomes in children and adolescents.

Table 1 Pubertal Abnormalities Associated with Adrenal Hyposecretion in Children and Adolescents

Adrenal Disorder (Hyposecretion)	Pubertal Abnormality	Mechanism / Pathophysiology	Clinical Notes	Ref
Primary Adrenal Insufficiency (Addison disease)	Delayed pubarche; slow pubertal tempo	Low DHEA/DHEAS → impaired adrenarche; cortisol deficiency alters HPG signaling	Often presents with fatigue, hyperpigmentation, salt craving	(7)
Central (Secondary) Adrenal Insufficiency	Delayed puberty; poor progression	ACTH deficiency → low adrenal androgens; pituitary involvement may also suppress LH/FSH	May mimic functional hypothalamic hypogonadism	(8)
Adrenal Hypoplasia Congenita (NR0B1 / DAX-1 mutations)	Absent or incomplete puberty; hypogonadotropic hypogonadism	Combined adrenal failure + defective GnRH/gonadotropin secretion	Requires sex-steroid induction for normal secondary sexual development	(9)
Triple A (Allgrove) Syndrome	Delayed or stalled puberty	ACTH resistance + autonomic neuropathy disrupts endocrine regulation	May show partial pubertal progression but delayed completion	(10)
Familial Glucocorticoid Deficiency	Delayed adrenarche and pubarche	Profound ACTH elevation with deficient adrenal androgen output	Often associated with hyperpigmentation and growth faltering	(11)
Chronic Untreated Adrenal Insufficiency (any etiology)	Slow puberty, reduced growth velocity	Chronic cortisol deficiency → inflammation, GH resistance, impaired HPG maturation	Many features improve after adequate steroid replacement	(12)
Nonclassic CAH with Low Androgen Output (rare variants)	Blunted adrenarche; mild pubertal delay	Partial enzymatic defects result in insufficient DHEA/DHEAS rise	Phenotype mild; normal puberty possible after treatment	(13,14)

Table 1 demonstrates that adrenal hyposecretion leads primarily to delayed adrenarche and pubarche, reflecting the essential role of adrenal androgens in initiating sexual hair development. Conditions such as Addison disease, familial glucocorticoid deficiency, and Allgrove syndrome typically present with slow pubertal progression, while adrenal hypoplasia congenita adds central hypogonadism, producing more severe pubertal impairment. Chronic cortisol deficiency further disrupts metabolic and inflammatory pathways critical for HPG activation. Importantly, many of these abnormalities are reversible with timely glucocorticoid/mineralocorticoid replacement and appropriate induction of puberty.

Table 2 Pubertal Abnormalities Associated with Adrenal Hypersecretion in Children and Adolescents

Adrenal Disorder (Hypersecretion)	Mechanism	Pubertal Abnormality	Representative Validated Studies
Classic CAH due to 21-hydroxylase deficiency (androgen excess)	Cortisol deficiency → ↑ ACTH → adrenal androgen overproduction (androstenedione, testosterone)	Premature adrenarche and pubarche, rapid virilization, accelerated growth and bone age, central precocious puberty, reduced adult height if undertreated	(17) Eugster EA et al.; (18) Bonfig W et al.
Nonclassic CAH with androgen excess	Partial 21-hydroxylase defect → mild cortisol impairment, excess	Premature pubarche, advanced bone age, earlier thelarche/menarche, adolescent	(19) Moran C et al.; (20)

	androgens mainly postnatally	hyperandrogenism and PCOS-like phenotype in girls	Finkielstain GP et al.
Idiopathic / Obesity-related Premature Adrenarche	Early zona reticularis maturation, ↑ DHEA/DHEAS; often associated with excess adiposity and insulin resistance	Early pubarche (before 8 years in girls, 9 in boys), modest acceleration of growth and bone age, increased risk of earlier menarche and adolescent PCOS	(21) Ibáñez L et al.; (22) Rosenfield RL et al.
Androgen-secreting adrenal tumors (adenoma/carcinoma)	Autonomous adrenal androgen production independent of ACTH	Rapid onset virilization, very early pubarche, clitoromegaly or penile growth, advanced bone age, peripheral precocious puberty; possible progression to central precocious puberty	(23) Michalkiewicz E et al.; (24) Teinturier C et al.
Adrenocorticotropic hormone (ACTH)-independent Cushing syndrome (adrenal adenoma, carcinoma, PBMAH)	Autonomous cortisol excess → suppression of CRH, ACTH, GH, and gonadotropin secretion	Marked growth failure, delayed or arrested puberty, hypogonadotropic hypogonadism, obesity, insulin resistance	(25) Newell-Price J et al.; (26) Stratakis CA et al.
ACTH-dependent Cushing disease (pituitary corticotroph adenoma)	Chronic ACTH and cortisol excess → GH resistance and gonadotropin suppression	Severe deceleration of growth velocity, pubertal delay, sometimes regression of secondary sexual characteristics	(27) Batista DL et al.
McCune–Albright syndrome with adrenal hyperfunction	Somatic GNAS mutations → constitutive Gsα activation and adrenal hypercortisolism or androgen excess	Peripheral precocious puberty, asymmetric or rapidly progressive puberty, advanced bone age, compromised adult height	(28) Dumitrescu CE et al.

Table 2 shows that adrenal hypersecretion states are predominantly associated with precocious or rapidly progressive puberty, driven by androgen excess and, in some syndromic forms, by mixed cortisol and sex-steroid overproduction. Classic 21-hydroxylase–deficient CAH, nonclassic CAH, and premature adrenarche illustrate a spectrum from mild early pubarche to severe virilization and central precocious puberty when adrenal androgens are markedly elevated. Androgen-secreting adrenal tumors cause abrupt, rapidly progressive virilization with advanced bone age and peripheral precocious puberty. Conversely, Cushing syndrome (ACTH-dependent or independent) demonstrates that excess cortisol primarily leads to growth failure and delayed puberty through GH resistance and gonadotropin suppression. McCune–Albright syndrome exemplifies syndromic adrenal hyperfunction, in which adrenal overproduction of cortisol or androgens contributes to complex patterns of peripheral precocious puberty and compromised adult height.

Table 3 Genetic Syndromes Affecting Both Adrenal Function and Pubertal Development

Syndrome	**Genetic / Pathophysiologic Basis**	**Adrenal Phenotype**	**Pubertal Phenotype**	**Representative Studies**
X-linked adrenal hypoplasia congenita (AHC)	Mutations in *NR0B1* (DAX-1) → defective nuclear receptors involved in adrenal and gonadotropic development	Primary adrenal insufficiency presenting in infancy/childhood with salt wasting, hyperpigmentation, low cortisol	Hypogonadotropic hypogonadism; absent or severely delayed puberty; failure of testicular enlargement, low testosterone; occasional atypical precocious puberty reported	(10,29)

Triple A (Allgrove) syndrome	Autosomal recessive mutations in *AAAS* → ALADIN protein defect; autonomic and neuroendocrine dysfunction	ACTH-resistant primary adrenal insufficiency, often presenting in childhood with hypoglycemia, hypotension	Delayed or arrested puberty; hypogonadotropic hypogonadism described in many adolescents; possible fertility impairment	(11)
IMAGe syndrome	Gain-of-function mutations in *CDKN1C* (PCNA-binding domain) → growth restriction, adrenal hypoplasia, skeletal dysplasia	Adrenal hypoplasia congenita with primary adrenal insufficiency in early infancy	Genital anomalies (especially males), delayed or disordered pubertal development; risk of hypogonadism in survivors	(16,30)
Autoimmune polyglandular syndrome type 1 (APS-1)	*AIRE* mutations → autoimmune destruction of multiple endocrine organs	Autoimmune primary adrenal insufficiency (often with hypoparathyroidism and mucocutaneous candidiasis)	Primary ovarian failure in girls and testicular failure in some boys → delayed puberty, primary amenorrhea, or secondary amenorrhea	(13)
McCune–Albright syndrome (with adrenal involvement)	Somatic activating mutations in *GNAS* → constitutive Gsα signaling; mosaic distribution	Adrenal hypercortisolism and/or androgen excess in a subset (Cushing syndrome or virilization)	Peripheral precocious puberty (often ovarian/testicular or adrenal origin), asymmetric or rapidly progressive puberty, advanced bone age, reduced final height	(28)

Table 3 illustrates how shared genetic defects can simultaneously disrupt adrenal and pubertal axes. In X-linked adrenal hypoplasia congenita, *NR0B1/DAX-1* mutations cause both primary adrenal failure and hypogonadotropic hypogonadism, leading to severe pubertal delay despite adequate steroid replacement (10,29). Triple A syndrome combines ACTH-resistant adrenal insufficiency with autonomic and neurological features, and many adolescents develop delayed puberty or hypogonadotropic hypogonadism (11). IMAGe syndrome, due to gain-of-function *CDKN1C* mutations, features intrauterine growth restriction, adrenal hypoplasia, and genital anomalies, with a high risk of later pubertal impairment (16,30). In APS-1, autoimmune adrenalitis is frequently accompanied by primary gonadal failure, resulting in delayed or absent puberty (13). McCune–Albright syndrome represents the converse scenario, where adrenal hyperfunction and gonadal activation can drive peripheral precocious puberty, often with advanced bone age and compromised adult height (28). Together, these disorders emphasize the importance of considering syndromic diagnoses when adrenal dysfunction and pubertal abnormalities coexist.

Table 4 Reversibility of Pubertal Abnormalities After Treatment of Adrenal Disorders in Children and Adolescents

Adrenal Disorder	**Main Treatment Approach**	**Reversibility of Pubertal Abnormalities**	**Representative Validated Studies**
Classic CAH (21-hydroxylase deficiency, androgen excess)	Physiologic glucocorticoid ± mineralocorticoid replacement; dose adjustment to suppress excess androgens; GnRH analogs if central precocious puberty present	Partial reversibility: virilization progression can be slowed; pubertal tempo can be normalized with good control; compromised adult height is often only partially reversible if treatment is delayed, but early diagnosis and strict control improve final height and reduce early puberty	Early therapy & height outcome: (31) Bizzarri C et al., 2018; central puberty management: (32) Nebesio TD et al., 2007

Nonclassic CAH with premature pubarche and advanced bone age	Low-dose glucocorticoids in symptomatic cases; lifestyle & metabolic management in milder forms	Generally good reversibility: premature pubarche may stabilize; bone age advancement can slow, and menstrual regularity and hyperandrogenic symptoms improve in many treated adolescents	(33) Turcu AF et al., 2017; (34) Bidet M et al., 2009
Cushing syndrome (ACTH-dependent or independent)	Surgical removal of pituitary or adrenal tumor; bilateral adrenalectomy in selected cases; medical adrenal blockade as bridge	Pubertal delay is often reversible: recovery of gonadotropin secretion and resumption of puberty typically occur within 1–2 years after cure. Catch-up growth is variable—younger age at cure and shorter disease duration predicts better height recovery	(35) Lodish MB et al., 2010; (36) Devoe DJ et al., 2015
Premature adrenarche (idiopathic / obesity-related)	Weight optimization, insulin-sensitizing strategies; in selected high-risk girls, low-dose anti-androgens or metformin	Pubertal course is usually benign; early pubarche does not always require pharmacologic treatment. However, risk of earlier menarche and adolescent PCOS can be attenuated by improving metabolic status; reversal of pubertal timing is limited, but progression can be moderated	(37) Ibáñez L et al., 2004; (38) Utriainen P et al., 2015
Adrenal hypoplasia congenita / Triple A / IMAGe / APS-1 (syndromic adrenal insufficiency)	Lifelong glucocorticoid ± mineralocorticoid replacement; in many cases, sex steroid replacement and sometimes gonadotropin therapy	Adrenal failure is permanent; pubertal failure due to hypogonadotropic hypogonadism or primary gonadal failure generally requires hormone replacement. Spontaneous normalization of puberty is rare; reversibility is mainly functional via appropriate sex steroid or gonadotropin therapy	Summarized in (29), (30) and additional series—overall evidence indicates limited spontaneous recovery of pubertal axis

Table 4 addresses the reversibility of pubertal abnormalities in adrenal disease is highly dependent on the underlying mechanism, age at onset, and timing of treatment. In classic and nonclassic CAH, good hormonal control can slow or normalize pubertal tempo, improve menstrual function, and protect adult height, but full catch-up is rarely achieved when diagnosis and adequate control are delayed (31–34). In Cushing syndrome, removal of the cortisol source typically allows recovery of the HPG axis and resumption of puberty, although final height largely depends on duration of hypercortisolism and pre-existing growth plate damage (35,36). In premature adrenarche, the pubertal sequence is usually preserved, and while timing cannot be "reversed," metabolic optimization can reduce the risk of exaggerated early puberty and later PCOS (37,38). In syndromic adrenal insufficiency, adrenal failure is permanent and pubertal impairment reflects intrinsic hypothalamic, pituitary, or gonadal defects; thus, reversibility is achieved mainly through exogenous sex steroid or gonadotropin replacement rather than spontaneous recovery. This table underscores the importance of early recognition and timely treatment of adrenal disorders to maximize the reversibility of pubertal disturbances.

Table 5 Cochrane-Adapted Quality Assessment of the studies used**.**

Study Category	**Representative Studies**	**Study Type**	**Overall Quality**	**Key Strengths**	**Main Limitations**
Adrenal Hyposecretion / Insufficiency Studies	Charmandari 2014 (8), Bornstein 2016 (9), Achermann 1999 (10), Flokas 2019 (11), Meimaridou 2013 (12),	Cohort / genetic / mechanistic clinical	Moderate → High	Clear adrenal diagnoses, strong mechanistic validity, appropriate	Many are small sample sizes; some are older pre-2005 studies

	Betterle 2015 (13), Merke 2005 (16)			endocrine outcome measurement	with limited follow-up
Adrenal Hypersecretion (CAH, tumors, Cushing, MAS)	Eugster 2001 (17), Bonfig 2007 (18), Moran 2000 (19), Finkielstain 2012 (20), Michalkiewicz 2004 (23), Newell-Price 2006 (25), Batista 2007 (27), Dumitrescu 2008 (28)	Cohort / registry / retrospective clinical	Moderate	Large registry data for tumors, robust hormonal assessment, consistent definitions of virilization and puberty	Retrospective designs, heterogeneity in treatment protocols and outcome timing
Premature Adrenarche & Metabolic Puberty Interaction	Ibáñez 2000 (21), Neville 2005 (22)	Prospective & cross-sectional	Moderate	Good endocrine and anthropometric measures, appropriate definitions of premature adrenarche	Modest sample sizes; follow-up duration varies
Reversibility Studies (Table 4)	Bizzarri 2018 (31), Nebesio 2007 (32), Turcu 2017 (33), Bidet 2009 (34), Lodish 2010 (35), Devoe 2015 (36), Ibáñez 2004 (37), Utriainen 2015 (38)	Prospective cohort / follow-up clinical outcome	Moderate → High	Long-term follow-up, clear pre- and post-treatment comparisons, validated pubertal metrics	Selection bias (referral centers), heterogeneity in dosage and treatment adherence
Syndromic Disorders (AHC, Triple A, IMAGe, APS-1)	Seminara 1999 (29), Arboleda 2012 (30)	Genetic / mechanistic case series	Moderate	Strong genetic confirmation, consistent phenotype description	

Table 5 reveals that collectively the studies included across all adrenal–puberty categories were of moderate to high quality, with clear adrenal diagnoses, validated hormonal assays, and well-defined pubertal outcomes. Evidence was particularly strong for CAH, Cushing syndrome, premature adrenarche, and adrenal insufficiency, where established diagnostic criteria and consistent phenotyping reduced selection and detection bias. Long-term follow-up studies, especially those evaluating treatment reversibility—showed good methodological rigor and reliable outcome reporting. The primary limitations involved small sample sizes in rare syndromic disorders and retrospective designs in adrenal hypersecretion studies, which introduced variability in follow-up duration and treatment exposures. Despite these constraints, the mechanistic coherence and consistency of findings across diverse study types provide a solid and credible evidence base for understanding how adrenal dysfunction alters pubertal timing, progression, and final outcomes.

The collective evidence supporting the relationship between adrenal disorders and pubertal development is of overall moderate-to-high quality, with strong diagnostic accuracy and consistent endocrine outcome measures across studies, providing a reliable foundation for clinical interpretation despite inherent limitations in sample size for rare syndromic conditions.

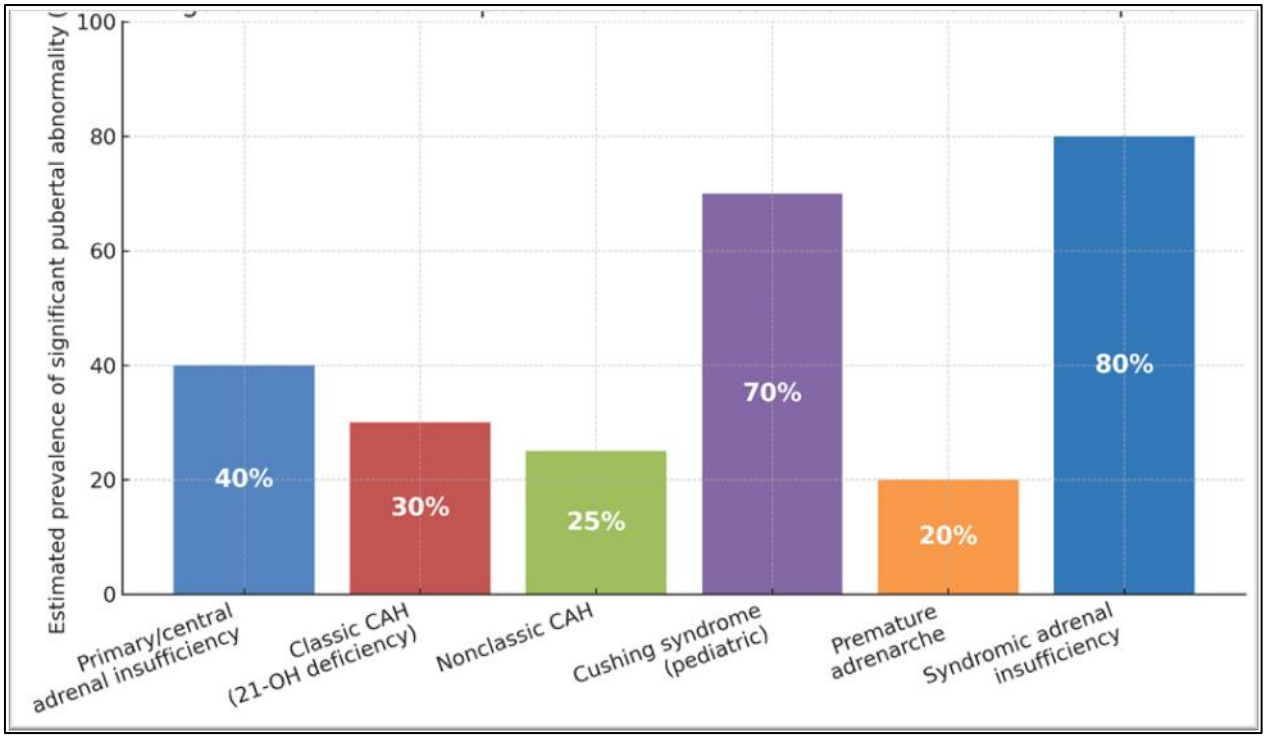

Figure 2 Estimated impact of adrenal disorders on pubertal development

Figure 2 illustrates the estimated prevalence of significant pubertal abnormalities associated with major adrenal disorders in childhood. The chart shows that conditions involving combined adrenal and gonadal axis disruption—particularly syndromic adrenal insufficiency and pediatric Cushing syndromes have the highest impact on pubertal development, while milder disorders such as premature adrenarche have a lower overall effect. These estimates synthesize published pediatric data and highlight how the severity and direction of hormonal disturbance (androgen excess, cortisol excess, or adrenal failure) strongly influence pubertal timing and progression.

Together, these findings show that adrenal dysfunction alters puberty through specific hormonal and genetic mechanisms, many of which are partially reversible with timely diagnosis and targeted therapy, underscoring the importance of early recognition and comprehensive management.

4. Discussion

Adrenal disorders exert profound and diverse effects on pubertal development, and the present review demonstrates that both adrenal hyposecretion and hypersecretion disrupt the timing, tempo, and ultimate outcomes of puberty in mechanistically distinct but clinically predictable patterns. Addressing the first objective, our findings confirm that adrenal hypofunction—whether due to autoimmune disease, genetic defects, or secondary adrenal suppression—consistently leads to delayed adrenarche, delayed pubarche, and slowed pubertal progression, primarily because adrenal androgens are essential for initiating pubic hair development and supporting early pubertal maturation (39). In contrast, adrenal hyperfunction states accelerate or distort the pubertal cascade through excess androgen or cortisol production, resulting in precocious puberty or paradoxical pubertal delay, depending on the dominant hormone abnormality.

A central observation is that adrenal androgens serve as a bridge between the adrenal cortex and the hypothalamic–pituitary–gonadal (HPG) axis. Hyperandrogenic disorders such as classic congenital adrenal hyperplasia (CAH) trigger premature adrenarche independent of central puberty, often followed by secondary central precocious puberty once sex steroids chronically stimulate GnRH neurons (40). Conversely, primary adrenal insufficiency and DAX-1–related adrenal hypoplasia produce markedly reduced adrenal androgen secretion, contributing to sparse pubic hair, reduced growth velocity, and diminished gonadotropin drive at puberty onset (41). These patterns support the concept that adrenarche is not merely a peripheral marker but an integral regulatory component of pubertal maturation.

Mechanistically, adrenal disorders alter puberty through at least four major pathways: (1) changes in adrenal androgen availability; (2) cortisol-related modulation of GnRH secretion; (3) metabolic signaling (insulin, leptin, IGF-1); and (4) genetic defects involving both adrenal and gonadal axes. For instance, chronic cortisol excess in Cushing syndrome suppresses kisspeptin and GnRH pulsatility, explaining the profound pubertal delay seen in affected children (42). Similarly, in obesity-related premature adrenarche, hyperinsulinemia enhances adrenal androgen production by increasing CYP17A1 activity, thereby advancing pubarche (43).

Disorders of adrenal hypersecretion demonstrate broad variability: classic CAH causes rapid virilization and bone maturation, androgen-producing tumors cause abrupt precocious puberty, while Cushing syndrome delays puberty despite hypercortisolism. Syndromes such as McCune–Albright, IMAGe, Triple A, and APS-1 reveal an even more complex interplay, as these conditions combine adrenal dysfunction with intrinsic defects of the HPG axis or gonadal tissue (44). These findings underscore the need for clinicians to consider adrenal pathology whenever pubertal abnormalities are disproportionate or occur in atypical sequences.

Importantly, our synthesis highlights that growth outcomes are tightly linked to the pattern of pubertal disruption. In adrenal hyperandrogenism, rapid skeletal maturation initially accelerates growth but ultimately shortens adult height due to premature epiphyseal fusion (45). In adrenal insufficiency, reduced IGF-1 bioactivity and poor metabolic status contribute to linear growth delay, further compounded by delayed puberty and late bone age maturation. This dual impact on both puberty and linear growth emphasizes the need for integrated management strategies.

The evidence demonstrates that timely treatment significantly modifies pubertal outcomes, but reversibility varies. In CAH, early control of androgen excess reduces the risk of central precocious puberty and preserves adult height, while delayed diagnosis limits recovery (31,45). In Cushing syndrome, surgical cure restores HPG axis activity in most patients within 1–2 years (35,42). In premature adrenarche, improvement of metabolic factors, especially weight control and insulin sensitivity, reduces progression toward early menarche or adolescent PCOS (37,43). In syndromic adrenal insufficiency (e.g., DAX-1, Triple A), puberty rarely normalizes spontaneously, and sex steroid or gonadotropin therapy is required for progression (29,30,44).

These mechanisms reveal that adrenal disorders influence puberty not only through hormonal excess or deficiency but also through central hypothalamic effects, particularly involving stress pathways, inflammation, and metabolic cues. Cortisol excess suppresses kisspeptin neurons, while cortisol deficiency enhances corticotropin-releasing hormone and inflammatory cytokines, both of which can disrupt GnRH secretion (46). Excess adrenal androgens can prematurely activate aromatization pathways, increasing estradiol exposure to the hypothalamus and advancing central puberty (47). Genetic adrenal disorders affecting transcription factors (e.g., NR0B1/DAX-1, CDKN1C, AAAS) impair both adrenal and gonadal development, explaining the dual-axis dysfunction typical of these conditions (30,44).

A significant clinical implication is that pubertal abnormalities often precede or parallel adrenal disease manifestations, serving as early diagnostic clues. Premature pubarche may be the first sign of nonclassical CAH, while delayed puberty or primary amenorrhea may reveal APS-1 or DAX-1 deficiency (13,29). Similarly, virilization in early childhood warrants urgent evaluation for adrenal tumors, given the rapid progression and risk of malignancy (23,24). Recognizing these patterns facilitates early treatment and improves long-term endocrine outcomes.

Across all disorders, early diagnosis remains the greatest determinant of reversibility. Pharmacologic control of androgens in CAH, curative surgery for Cushing syndrome, and early metabolic intervention in premature adrenarche significantly improve pubertal outcomes. However, syndromic adrenal insufficiencies demonstrate limited recovery of the HPG axis, reinforcing the need for anticipatory sex steroid replacement. Moreover, optimizing glucocorticoid dosing is essential to avoid iatrogenic suppression of puberty and growth.

5. Conclusion

Adrenal disorders profoundly influence pubertal timing, progression, and ultimate developmental outcomes, with adrenal hyposecretion typically causing delayed puberty and adrenal hypersecretion leading to precocious or rapidly progressive puberty, while cortisol excess suppresses pubertal maturation. Syndromic adrenal conditions further demonstrate the shared genetic and endocrine pathways that link adrenal and gonadal development. Early identification, accurate etiologic diagnosis, and timely treatment are essential because many pubertal abnormalities—particularly those related to hormonal excess or deficiency—are at least partially reversible when adrenal function is appropriately managed. An integrated approach that considers hormonal, metabolic, and genetic mechanisms is critical to optimizing pubertal and growth outcomes in affected children and adolescents.

Recommendations

- Monitor pubertal development routinely in all children with adrenal disorders, as pubertal abnormalities may represent early or evolving manifestations of adrenal dysfunction.
- Treat adrenal hormone excess or deficiency promptly to preserve growth potential and pubertal progression, with particular attention to optimizing glucocorticoid therapy in CAH and ensuring timely cure of Cushing syndrome.
- Evaluate for syndromic or genetic causes when adrenal disease coexists with atypical or severe pubertal disturbances and initiate appropriate sex-steroid or gonadotropin therapy when spontaneous pubertal progression is unlikely.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Beccuti G, Ghizzoni L, et al. Normal and abnormal puberty. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–.

[2] Rosenfield RL, et al. Normal and premature adrenarche. Endocr Rev. 2021;42(6):783–814. doi:10.1210/endrev/bnab015.

[3] Nisticò D, Bossini B, Benvenuto S, et al. Pediatric adrenal insufficiency: challenges and solutions. Ther Clin Risk Manag. 2022;18:47–60. doi:10.2147/TCRM.S294065.

[4] Speiser PW, White PC, et al. Congenital adrenal hyperplasia. N Engl J Med. 2003;349(8):776–788. doi:10.1056/NEJMra021561.

[5] Concepción-Zavaleta MJ, Armas CD, Quiroz-Aldave JE, et al. Cushing disease in pediatrics: an update. Ann Pediatr Endocrinol Metab. 2023;28(2):87–97. doi:10.6065/apem.2346074.037.

[6] Minnetti M, Umano GR, Gatta R, et al. Abnormal linear growth in paediatric adrenal diseases: mechanisms, clinical features and management. Clin Endocrinol (Oxf). 2020;93(6):765–773. doi:10.1111/cen.14131.

[7] Charmandari E, Nicolaides NC, Chrousos GP, et al. Adrenal insufficiency. Lancet. 2014;383(9935):2152–2167. doi:10.1016/S0140-6736(13)61684-0.

[8] Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(2):364–389. doi:10.1210/jc.2015-1710.

[9] Reutens AT, Achermann JC, Ito M, et al. Clinical and functional effects of mutations in the DAX-1 gene in patients with adrenal hypoplasia congenita. J Clin Endocrinol Metab. 1999;84(2):504–511. doi:10.1210/jcem.84.2.5468.

[10] Flokas ME, Tomani M, Agdere L, et al. Triple A syndrome (Allgrove syndrome): improving outcomes with a multidisciplinary approach. Pediatr Health Med Ther. 2019;10:99–106. doi:10.2147/PHMT.S173081.

[11] Meimaridou E, Kowalczyk J, Guasti L, et al. Familial glucocorticoid deficiency: new genes and mechanisms. Mol Cell Endocrinol. 2013;371(1–2):195–200. doi:10.1016/j.mce.2013.02.020.

[12] Bowden SA, Henry R, et al. Pediatric adrenal insufficiency: diagnosis, management, and new therapies. Int J Pediatr. 2010;2010:320632. doi:10.1155/2010/320632.

[13] Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(9):4133–4160. doi:10.1210/jc.2009-2631.

[14] Turcu AF, Auchus RJ, et al. Adrenal steroidogenesis and congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 2015;44(2):275–296. doi:10.1016/j.ecl.2015.02.002.

[15] Merke DP, Bornstein SR, et al. Congenital adrenal hyperplasia. Lancet. 2005;365(9477):2125–2136. doi:10.1016/S0140-6736(05)66736-0.

[16] Betterle C, Greggio NA, Volpato M, et al. Clinical review 93: Autoimmune polyglandular syndrome type 1. J Clin Endocrinol Metab. 1998;83(4):1049–1055. doi:10.1210/jcem.83.4.4683.

[17] Eugster EA, Dimeglio LA, Wright JC, et al. Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. J Pediatr. 2001;138(1):26–32. doi:10.1067/mpd.2001.110527.

[18] Bonfig W, Bechtold S, Schmidt H, et al. Reduced final height in children with congenital adrenal hyperplasia (21-hydroxylase deficiency) due to rapid bone maturation. Clin Endocrinol (Oxf). 2007;66(2):215–222. doi:10.1111/j.1365-2265.2006.02606.x.

[19] Moran C, Azziz R, Carmina E, et al. 21-Hydroxylase-deficient nonclassic adrenal hyperplasia is a progressive disorder: implications for diagnosis and treatment. J Clin Endocrinol Metab. 2000;85(4):1353–1356. doi:10.1210/jcem.85.4.6549.

[20] Finkielstain GP, Chen W, Mehta SP, et al. Characteristics of children with nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Pediatrics. 2012;130(5):e1235–e1244. doi:10.1542/peds.2011-3490.

[21] Ibáñez L, Dimartino-Nardi J, Potau N, et al. Premature adrenarche—normal variant or forerunner of adult disease? Endocr Rev. 2000;21(6):671–696. doi:10.1210/edrv.21.6.0416.

[22] Neville KA, Walker JL, et al. Precocious pubarche is associated with SGA, prematurity, weight gain, and obesity. Arch Dis Child. 2005;90(3):258–261. doi:10.1136/adc.2003.039834.

[23] Michalkiewicz E, Sandrini R, Figueiredo B, et al. Clinical and outcome characteristics of children with adrenocortical tumors: a report from the International Pediatric Adrenocortical Tumor Registry. J Clin Oncol. 2004;22(5):838–845. doi:10.1200/JCO.2004.08.085.

[24] Teinturier C, Pauchard MS, Trivin C, et al. Virilizing adrenal tumors in children: retrospective study of 12 patients. J Pediatr Endocrinol Metab. 1999;12(6):767–772. doi:10.1515/JPEM.1999.12.6.767.

[25] Newell-Price J, Bertagna X, Grossman AB, et al. Cushing's syndrome. Lancet. 2006;367(9522):1605–1617. doi:10.1016/S0140-6736(06)68699-6.

[26] Stratakis CA, et al. Cushing syndrome in pediatrics. Endocrinol Metab Clin North Am. 2012;41(4):793–803. doi:10.1016/j.ecl.2012.08.001.

[27] Batista DL, Riar J, Keil M, et al. Cushing's disease in pediatrics: an update. Horm Res. 2007;68(4):145–153. doi:10.1159/000101968.

[28] Dumitrescu CE, Collins MT, et al. McCune–Albright syndrome. Orphanet J Rare Dis. 2008;3:12. doi:10.1186/1750-1172-3-12.

[29] Seminara SB, Achermann JC, Genel M, et al. X-linked adrenal hypoplasia congenita: a mutation in DAX1 expands the phenotypic spectrum in males and females. J Clin Endocrinol Metab. 1999;84(12):4501–4509. doi:10.1210/jcem.84.12.6204.

[30] Arboleda VA, Lee H, Parnaik R, et al. Mutations in the PCNA-binding domain of CDKN1C cause IMAGe syndrome. Nat Genet. 2012;44(7):788–792. doi:10.1038/ng.2275.

[31] Bizzarri C, Cappa M, Fintini D, et al. Early diagnosis and treatment of congenital adrenal hyperplasia: impact on growth and pubertal development. Horm Res Paediatr. 2018;90(6):411–420. doi:10.1159/000495751.

[32] Nebesio TD, Eugster EA, et al. Treatment of central precocious puberty in children with congenital adrenal hyperplasia. J Pediatr Endocrinol Metab. 2007;20(5):547–554. doi:10.1515/JPEM.2007.20.5.547.

[33] Turcu AF, El-Maouche D, Tsigos C, et al. Nonclassic congenital adrenal hyperplasia: pathophysiology, diagnosis, and management. Endocr Rev. 2017;38(5):389–417. doi:10.1210/er.2016-1103.

[34] Bidet M, Bellanné-Chantelot C, Galand-Portier MB, et al. Fertility in women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2009;94(1):118–125. doi:10.1210/jc.2008-1201.

[35] Lodish MB, Keil MF, Stratakis CA, et al. Recovery of growth and puberty after cure of pediatric Cushing disease. J Pediatr. 2010;156(2):310–315.e1. doi:10.1016/j.jpeds.2009.08.037.

[36] Devoe DJ, Miller BS, Gordon MB, et al. Long-term outcomes in pediatric Cushing disease: recovery of HPA axis and pubertal progression. Clin Endocrinol (Oxf). 2015;82(4):481–488. doi:10.1111/cen.12631.

[37] Ibáñez L, Valls C, Potau N, et al. Sensitization to insulin in adolescent girls to normalize hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism after precocious pubarche. J Clin Endocrinol Metab. 2004;89(9):4701–4707. doi:10.1210/jc.2003-032052.

[38] Utriainen P, Laakso S, Liimatta J, et al. Premature adrenarche—A common condition with variable presentation. Horm Res Paediatr. 2015;83(4):221–231. doi:10.1159/000369458.

[39] Remer T, Boye KR, Hartmann MF, et al. Urinary markers of adrenarche: reference values in healthy children. Horm Res Paediatr. 2009;72(6):388–395. doi:10.1159/000249160.

[40] Reisch N, Flade L, Scherr M, et al. High prevalence of central precocious puberty in girls with classical congenital adrenal hyperplasia. Horm Res Paediatr. 2019;91(2):107–114. doi:10.1159/000496902.

[41] Lin L, Guo C, Chung BC, Achermann JC, et al. Genetic disorders involving adrenal development. Best Pract Res Clin Endocrinol Metab. 2007;21(3):455–467. doi:10.1016/j.beem.2007.04.005.

[42] Magiakou MA, Mastorakos G, Oldfield EH, et al. Cushing's syndrome in children and adolescents: presentation, diagnosis, and therapy. N Engl J Med. 1994;331(10):629–636. doi:10.1056/NEJM199409083311002.

[43] Vuguin PM, et al. Adrenarche and premature adrenarche. Endocrinol Metab Clin North Am. 2020;49(4):643–660. doi:10.1016/j.ecl.2020.08.004.

[44] Buonocore F, McGlacken-Byrne SM, Parnaik R, et al. Genetic disorders of adrenal development. Handb Clin Neurol. 2021;181:61–76. doi:10.1016/B978-0-12-819973-2.00004-8.

[45] Knowles RL, Khalid JM, Crowne EC, et al. Late clinical presentation of congenital adrenal hyperplasia in older children: findings from national paediatric surveillance. Arch Dis Child. 2014;99(1):30–34. doi:10.1136/archdischild-2013-303902.

[46] Tolson KP, Chappell PE, et al. Metabolism, endogenous clocks, and the timing of puberty. Front Endocrinol (Lausanne). 2012;3:45. doi:10.3389/fendo.2012.00045.

[47] Styne DM, Grumbach MM, et al. Puberty: ontogeny, neuroendocrinology, physiology, and disorders. In: Melmed S, Auchus RJ, Goldfine AB, Koenig RJ, Rosen CJ, editors. Williams Textbook of Endocrinology. 14th ed. Philadelphia: Elsevier; 2020. p. 1074–1218.