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CONTEMPORARY APPROACH TO THE DIAGNOSIS AND TREATMENT OF PRECOCIOUS PUBERTY IN CHILDREN: A LITERATURE REVIEW

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Summary: Introduction: Precocious puberty (PP) is defined as the onset of secondary sexual characteristics before the age of 8 years in girls and before 9 years in boys. The main clinical challenge is the differentiation between central precocious puberty (CPP), caused by premature activation of the hypothalamic–pituitary–gonadal axis, peripheral precocious puberty (PPP), and benign variants of pubertal development. Aim: To systematize current diagnostic approaches, evaluate the effectiveness of therapeutic protocols, and accurately differentiate pathological conditions from benign developmental variants. Diagnostics: The diagnostic algorithm is primarily based on anthropometric assessment (growth velocity > 7 cm/year) and radiological evaluation of bone maturation, where advanced bone age ≥ 2 SD represents a key indicator of progression. Additional criteria include pelvic ultrasound findings, with uterine volume > 1.8 ml suggestive of pubertal activation. The gold standard for diagnosis remains the gonadotropin-releasing hormone (GnRH) stimulation test, with a peak LH value > 5 IU/L confirming CPP. A special focus is placed on differentiating progressive forms from benign variants such as isolated thelarche and adrenarche, in order to avoid unnecessary therapeutic intervention. Treatment: Modern management of CPP involves the use of GnRH agonists (triptorelin, leuprolide) in depot formulations, which suppress pubertal progression by desensitizing pituitary GnRH receptors. Conclusion: Early diagnosis and timely initiation of therapy result in a significant improvement in final adult height (average gain of 0.63 SDS). Effective management requires an interprofessional approach and clear differentiation between normal developmental variants and pathological entities.

Keywords: Central precocious puberty, GnRH test, GnRH agonists, bone age, Tanner stages.

INTRODUCTION: NEUROENDOCRINE CONTROL AND PHYSIOLOGY

1. Hypothalamic–Pituitary–Gonadal (HPG) Axis

Puberty is the result of reactivation of the hypothalamic–pituitary–gonadal (HPG) axis [1]. This complex process occurs through three key phases:

Fetal activation:

The HPG axis becomes active between the 12th and 14th week of gestation, but is suppressed toward the end of pregnancy by placental hormones [1].

Mini-puberty:

A short-term reactivation of the axis occurs immediately after birth due to the removal of placental inhibition. It lasts up to 6 months in boys, while in girls estradiol levels may fluctuate up to 2–4 years of age, leading to transient breast enlargement [1,2].

True puberty:

Occurs when neuroendocrine mechanisms (primarily the kisspeptin system and leptin) remove central nervous system (CNS) inhibition of GnRH neurons. This triggers pulsatile secretion of gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thereby initiating gonadal maturation [1,3–6].

The main components of this regulatory system and their functions are summarized in Table 1..

Table 1. Components and Regulation of the HPG Axis. Source: Adapted from Sharma L, Daley SF [1]

Regulatory level	Hormone / Signal	Function and effect
Hypothalamus	GnRH (pulsatile)	Stimulates the anterior pituitary gland
Pituitary gland	LH and FSH	Stimulate the gonads to produce sex steroids and gametes
Gonads	Estrogen / Testosterone	Development of secondary sexual characteristics
Feedback loop	Negative / Positive	Regulation of hormone secretion at the hypothalamic and pituitary levels

2. Key Terms and Physiological Processes

Understanding pubertal disorders requires a clear distinction between two independent processes:

- Gonadarche:

Activation of the gonads under the influence of the HPG axis. In girls, it leads to ovarian growth and breast development (via estradiol), while in boys it leads to testicular enlargement and spermatogenesis (via testosterone) [2,7].

- Adrenarche:

Increased production of adrenal androgens (DHEA and DHEA-S). It occurs independently of the HPG axis, around 7–8 years of age, and is responsible for the development of pubic hair (pubarche), acne, and body odor.

Hormonal and physical changes in normal development

Physical changes of puberty result from sex steroid production by the gonads, and the onset of gonadarche indicates the beginning of puberty. Gonadarche is initiated by pulsatile secretion of gonadotropin-releasing hormone (GnRH), which activates the HPG axis [1–3].

Adrenarche (i.e., adrenal androgen production leading to pubic and axillary hair, body odor, and mild acne) is a separate but usually concurrent process and, by itself, does not indicate true pubertal onset in either boys or girls [8].

In girls, increased ovarian estradiol secretion leads to breast development at an average age of 10 years (range: 8–12 years). Menarche typically follows approximately 2.5 years after the onset of breast development, at an average age of 12.5 years (range: 9–15 years) [1,2,3,7,9].

In boys, testicular enlargement to at least 4 mL in volume or 2.5 cm in length is the first sign of true puberty and occurs at an average age of 11.5 years (range: 9.5–14 years) [8,10].

Peak height velocity (PHV) occurs earlier in puberty in girls and later in boys, with an average sex difference of approximately two years [11].

At the onset of menarche, approximately 95.3% (SD 1.7) of adult height has already been achieved; the remaining height gain averages 7.8 cm (SD 2.8) [12].

3. Clinical Progression (Tanner Stages)

Pubertal progression follows a predictable sequence of physiological changes that are clinically assessed using the standardized Tanner staging system (I–V) [1,13].

Detailed criteria for assessing breast development and pubic hair in girls are systematized in Table 2, while parameters for evaluating genital development and pubic hair in boys are presented in Table 3..

Table 2. Tanner Classification of Development in Girls

Stage	Breast development (B – Breast)	Pubic hair (P – Pubic hair)
1	Prepubertal: only papilla elevation	No pigmented terminal hair
2	"Breast budding" (thelarche): glandular tissue palpable	Sparse, lightly pigmented hair, mainly along labia
3	Further breast elevation without separation of contours	Darker, coarser hair over the pubic symphysis
4	Secondary mound: areola elevated above breast contour	Adult-type hair, but limited distribution
5	Adult stage: areola flush with breast contour	Adult distribution extending to medial thighs

Table 3. Tanner Classification of Development in Boys

Stage	Genital development (G – Genitals)	Pubic hair (P – Pubic hair)
1	Prepubertal: testicular volume < 4 mL	No terminal hair
2	Enlargement of scrotum and testes (≥ 4 mL)	Sparse, long hair at base of penis
3	Increase in penile length	Darker, coarser, curlier hair
4	Further penile growth in width; glans development	Dense adult-type hair with limited distribution
5	Adult genital size and morphology	Adult distribution pattern

ETIOLOGY AND CLASSIFICATION

Precocious puberty is defined as the appearance of secondary sexual characteristics before the age of 9 years in boys (or before 8 years in girls), corresponding to a chronological age approximately 2–2.5 standard deviations earlier than the average age of pubertal onset in the White population [13,14]. Its incidence ranges between 1:5,000 and 1:10,000, while its prevalence is increasing worldwide [15].

Based on the underlying pathological mechanism, precocious puberty can be classified as follows:

Central Precocious Puberty (CPP)

(Gonadotropin-dependent) – caused by early maturation of the HPG axis. It results from premature activation of the axis (GnRH-dependent) [16,2]. Etiologies include congenital abnormalities (hamartoma, cysts), acquired lesions (tumors, trauma), and genetic mutations (e.g., MKRN3). In girls, up to 90% of cases are idiopathic [2,9].

Peripheral Precocious Puberty (PPP)

(Gonadotropin-independent) – caused by excessive secretion of sex steroids from the gonads or adrenal glands, exogenous exposure to sex steroids, or ectopic production of gonadotropins from germ cell tumors.

Benign Pubertal Variants

These include non-progressive or intermittently progressive forms of CPP, as well as isolated androgen-mediated sexual characteristics in boys resulting from early activation of the hypothalamic–pituitary–adrenal axis (premature adrenarche). Both conditions may represent normal variants of pubertal development [13,14].

Differential characteristics between central and peripheral precocious puberty are summarized in Table 4.

Table 4. Differential diagnosis of central (CPP) and peripheral (PPP) puberty

Characteristic	Central puberty (CPP)	Peripheral puberty (PPP)
HPG axis	Activated (GnRH-dependent process)	Suppressed (GnRH-independent process)
Gonadotropins (LH/FSH)	Elevated or pubertal response to GnRH stimulation	Low or suppressed
Response to GnRH test	Pubertal LH response (positive pubertal pattern)	No significant LH increase
Development pattern	Progressive, consistent with biological sex	May be asynchronous, sometimes discordant with sex
Secondary sexual characteristics	Consistent with HPG axis activation	Dependent on hormone source (gonads, adrenal glands, exogenous hormones)
Most common cause	Idiopathic (especially in girls), CNS lesions, genetic mutations (e.g., MKRN3)	Ovarian/testicular cysts or tumors, congenital adrenal hyperplasia (CAH), exogenous steroid exposure, hCG-secreting tumors

Detailed description of peripheral precocious puberty (PPP):

Peripheral precocious puberty (PPP) is caused by excessive production of sex steroids from the gonads or adrenal glands, secretion of β-hCG–producing tumors, or exposure to exogenous sex hormones. Etiological causes include McCune–Albright syndrome (MAS), functional ovarian cysts (FC), Leydig cell tumors, or familial male-limited precocious puberty. Adrenal sources of androgen excess are most commonly due to adrenal tumors or congenital adrenal hyperplasia [17]. PPP is significantly less common than central precocious puberty (CPP).

Non-classic congenital adrenal hyperplasia (NCAH), most commonly due to 21-hydroxylase deficiency (CYP21A2 gene mutation), is an autosomal recessive disorder. Clinical manifestations reflect androgen excess, including premature pubic hair (pubarche), body odor, and acne before the age of 8 in girls or 9 in boys. Additional features may include accelerated linear growth during childhood and advanced bone maturation, which can ultimately result in reduced adult height due to premature epiphyseal closure [18,19,20].

MFor accurate diagnosis of NCAH, assessment of 17-hydroxyprogesterone (17-OHP) levels—often including basal and ACTH-stimulated values—is essential, as they correlate with disease severity and are used for diagnostic confirmation (see Table 5.

Table 5. Differential diagnosis of NCCAH based on 17-OHP levels. Source: Adapted from White PC, Speiser PW [21]

Category	Basal 17-OHP (ng/dL)	Stimulated 17-OHP (ng/dL)
Healthy children	< 200	< 1000
Heterozygous carriers	< 200	1000 – 3500
NCCAH (non-classic congenital adrenal hyperplasia)	> 200	> 1000 (often > 3500)

BENIGN VARIANTS (PARTIAL PRECOCIOUS PUBERTY)

Benign variants of precocious puberty include premature thelarche, premature adrenarche, and isolated premature menarche. These conditions are characterized by the appearance of isolated pubertal signs without full activation of the hypothalamic–pituitary–gonadal (HPG) axis. Importantly, bone age, growth velocity, and biochemical findings are usually within normal limits [1,8]. Sharma L and Daley SF emphasize the importance of distinguishing these conditions to reduce unnecessary diagnostic procedures [1].

Premature thelarche (PT)

The most common benign variant. It presents as unilateral or bilateral breast development in girls, typically occurring between 0–24 months of age or again around 6–8 years. No other pubertal changes are present. Clinical follow-up is recommended to monitor for progression to central puberty [1,22,23,24].

Premature adrenarche (PA)

Characterized by early adrenal androgen production, leading to pubic or axillary hair, acne, and body odor before the age of 8 years. There is no breast development or testicular enlargement. Exogenous androgen exposure, tumors, and late-onset congenital adrenal hyperplasia (CAH) must be excluded [1,24].

Isolated premature menarche

Defined as vaginal bleeding in girls younger than 8 years in the absence of other pubertal signs. It generally does not affect final adult height. Differential diagnosis must exclude sexual abuse, foreign bodies, genital tract tumors, and infections [1,24].)

Table 6. Differential diagnosis of benign variants

Condition	Main symptom	Hormonal findings	Recommendation
Premature thelarche (PT)	Isolated breast development (glandular tissue)	Estradiol normal or mildly elevated	Clinical follow-up every 3–6 months
Premature adrenarche (PA)	Pubic and/or axillary hair development	Elevated DHEA-S	Exclude NCAH and androgen-secreting tumors
Isolated premature menarche	Vaginal bleeding	Prepubertal hormone levels	Exclude local causes (infection, trauma, foreign body, tumors)
Lipomastia	Excess adipose breast tissue (no glandular proliferation)	Prepubertal hormone levels	Weight reduction and clinical observation

CLINICAL ASSESSMENT AND DIAGNOSTIC APPROACH

1. Medical history and anthropometry

A detailed clinical history is essential to distinguish true precocious puberty (PP) from benign variants. Progressive pubertal development, rapid linear growth, and advanced bone age are characteristic of true PP [1,25].

The evaluation should include:

Neurological symptoms (headache, seizures, episodes of inappropriate laughter – suggestive of hypothalamic hamartoma)

Previous head trauma, brain tumor treatment, or central nervous system (CNS) infections

Physical examination: assessment of pubic and axillary hair, signs of virilization (clitoromegaly, penile enlargement, acne), and full neurological examination

Skin examination: café-au-lait macules (suggestive of Neurofibromatosis type 1 or McCune–Albright syndrome)

Growth velocity: a growth spurt >7 cm/year with breast or testicular enlargement requires urgent evaluation [24]

2. Laboratory and radiological evaluation

Bone age (BA):

Advanced bone age >2 standard deviations (SD) compared to chronological age (CA) requires further diagnostic work-up [1,14].

Hormonal testing:

Measured using ultrasensitive assays (ICMA or ECLIA). Basal serum LH levels >0.2–0.3 IU/L may indicate pubertal activation [1].

GnRH stimulation test (gold standard):

Activation of the pubertal HPG axis is confirmed if peak LH >5 IU/L. An LH/FSH ratio <0.43 suggests a prepubertal state, while a stimulated ratio >0.66 helps differentiate progressive from non-progressive variants [1].

In girls:

Serum estradiol (E2) levels after 24-hour GnRH agonist stimulation (peak >50 pg/mL) improve diagnostic sensitivity [16,22].

In boys:

Measurement of testosterone, DHEA-S, 17-OHP, and early-morning hCG is recommended when PPP is suspected. Certain tumors may secrete hCG, which activates LH receptors and mimics central puberty [1].

Reference tables:

Reference hormone and steroid levels are presented in Table 7 and Table 8

Pelvic ultrasound criteria in girls are shown in Table 8

Differential diagnostic criteria (CPP vs benign variants) are presented in Table 9.

Table 7. Reference serum concentrations of gonadotropins and steroids. Source: Neely EK et al. [26]

Parameter	Prepubertal (Tanner stage I)	Pubertal (Tanner stage II)
LH (basal)	0.03 ± 0.03 IU/L	0.71 ± 1.04 IU/L
Estradiol	< 1.0 ng/dL	1.6 ± 0.7 ng/dL
Testosterone	< 10 ng/dL	42 ± 15 ng/dL

Table 8. Pelvic ultrasound criteria in girls

Parameter	Threshold value	Clinical significance
Uterine volume	> 1.8 mL	Sensitive marker of early CPP
Uterine length	> 3.4 cm	Indicates estrogen exposure
Ovarian volume	> 1.2 mL	Suggests gonadal activation

Table 9. Differential diagnostic criteria (CPP vs benign variants)

Parameter	Central precocious puberty (CPP)	Isolated thelarche	Isolated adrenarche
Bone age	Advanced ≥ 2 SD	Normal	Normal / mildly increased
Growth velocity	Accelerated (> 7 cm/year)	Normal	Normal
Peak LH (GnRH test)	> 5 IU/L	< 4.5 IU/L	< 4.5 IU/L

DIAGNOSTIC ALGORITHMS

ALGORITHM 1. DIAGNOSTIC APPROACH IN GIRLS WITH THELARCHE (Adapted from: Root AW. Pediatr Rev. 2000 [27])

Normal growth velocity and bone age (BA ≈ CA):

Bone age corresponds to chronological age.

Diagnosis: Isolated premature thelarche

Management: Clinical follow-up; no treatment usually required

Accelerated growth velocity and advanced bone age (BA > CA):

Bone age is advanced compared to chronological age.

Indicated test: GnRH stimulation test

Peak LH > 5 IU/L (pubertal response):

Diagnosis: Central precocious puberty (CPP)

Next step: Brain MRI to exclude CNS pathology

Low LH (prepubertal response) with ovarian cysts present:

Suspicion: McCune–Albright syndrome (MAS) or other forms of peripheral puberty

In boys, differential diagnosis requires a systematic approach presented in Algorithm 2.

ALGORITHM 2. DIAGNOSTIC EVALUATION OF BOYS WITH PRECOCIOUS PUBERTY (Adapted from: Root AW. Pediatr Rev. 2000 [27])

I. Clinical triage (growth velocity and bone age assessment)

BA ≈ CA:

Likely isolated premature adrenarche

→ Periodic clinical follow-up recommended

BA > CA:

→ Requires hormonal laboratory evaluation

II. Gonadotropin (LH) assessment

Elevated LH (pubertal response at baseline or after GnRH test):

Diagnosis: Central precocious puberty (CPP)

Mandatory: Brain MRI to exclude hypothalamic hamartoma or CNS tumors

Low LH (suppressed/prepubertal response):

Diagnosis: Peripheral precocious puberty

→ Proceed with etiological work-up

III. Differential diagnosis of peripheral precocious puberty (low LH)

Elevated 17-OHP / DHEA-S:

Suggests congenital adrenal hyperplasia (CAH) or adrenal tumors

Elevated hCG:

Suggests ectopic hCG-secreting tumors (e.g., hepatoblastoma or germ cell tumors)

High testosterone with suppressed gonadotropins and enlarged testes:

Suggests testotoxicosis (familial male-limited precocious puberty, FMPP) or Leydig cell tumor

THERAPY AND MANAGEMENT

1. Central precocious puberty (CPP)

Gold standard treatment: GnRH agonists (GnRHa) [7,24]

Goals: Maximize final adult height and reduce psychosocial stress

Early onset (<6–7 years) with rapid progression → standard indication for treatment

Formulations:

Monthly depot injections (3.75 mg)

Long-acting depot preparations (every 4–12 weeks)

Monitoring:
Clinical evaluation every 3–6 months
Bone age every 6–12 months
Target stimulated LH suppression: <2.5–4.5 IU/L
Discontinuation:
Usually around chronological age 11 years
Or when bone age reaches ~12.5 years in girls and ~14 years in boys [1,7,28]
Safety:
Therapy is considered safe
Meta-analysis shows average gain in final height of ~0.63 SDS [1]
2. Peripheral precocious puberty (PPP)
Surgery: For gonadal or adrenal tumors
NCCAH: Treated with glucocorticoids
MAS: Aromatase inhibitors and selective estrogen receptor modulators
Important note:
Children with PPP may later develop secondary CPP; in such cases, GnRH analogs should be added [1]

CONCLUSION (Practical aspects)

The main clinical sign suggesting precocious puberty is the development of breast tissue in girls and testicular enlargement (> 4 mL) in boys before 8–9 years of age.

Differential diagnosis: The priority is to distinguish benign variants from progressive central precocious puberty (CPP) in order to avoid unnecessary treatment.

Gold standard: The GnRH stimulation test combined with assessment of bone age maturation.

Brain MRI: Recommended in all cases of CPP in boys, and in girls younger than 6 years or in those with neurological symptoms.

Time is a critical factor: The best outcomes are achieved when treatment is initiated before 6 years of age.

Education: A thorough discussion with the family is essential, including explanation of normal pubertal development, treatment goals, and psychosocial aspects (peer interaction, self-esteem, and emotional well-being).

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ABBREVIATIONS:

ACTH – Adrenocorticotropic hormone
BMI – Body mass index
CNS – Central nervous system
CPP – Central precocious puberty
DHEA-S – Dehydroepiandrosterone sulfate
FSH – Follicle-stimulating hormone
GnRH – Gonadotropin-releasing hormone
GnRHa – Gonadotropin-releasing hormone agonists
HPG axis – Hypothalamic–pituitary–gonadal axis
CAH – Congenital adrenal hyperplasia
LH – Luteinizing hormone
MAS – McCune–Albright syndrome
MRI – Magnetic resonance imaging
NCAH – Non-classic congenital adrenal hyperplasia
PPP – Peripheral precocious puberty
SDS – Standard deviation score
TSH – Thyroid-stimulating hormone
BA – Bone age
CA – Chronological age
US – Ultrasound