Pregledni članak

TIMOČKI MEDICINSKI GLASNIK

Vol. 51 (2026) br. 1

UDK 616.43-008.6-053.2:612.661
COBISS.SR-ID 191803913

SAVREMENI PRISTUP DIJAGNOSTICI I LEČENJU PREVREMENOG PUBERTETA KOD DECE: PREGLED LITERATURE

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Sažetak: Uvod: Prevremeni pubertet (PP) definiše se kao pojava sekundarnih polnih karakteristika pre 8. godine života kod devojčica i 9. godine kod dečaka. Ključni klinički izazov je razlikovanje centralnog prevremenog puberteta (CPP), uzrokovanog prevremenom aktivacijom hipotalamo-hipofizno-gonadne ose, od perifernog puberteta (PPP) i benignih varijanti. Cilj rada: Sistematizacija savremenih dijagnostičkih stavova, evaluacija efikasnosti terapijskih protokola i precizno diferenciranje patoloških stanja od benignih oblika razvoja. Dijagnostika: Dijagnostički algoritam primarno se oslanja na antropometriju (skok rasta > 7 cm/god) i radiološku procenu koštane zrelosti, gde je uznapredovalost koštane starosti ≥ 2 SD ključni indikator progresije. Dopunski kriterijumi obuhvataju ultrazvuk male karlice (volumen uterusa > 1,8 ml). Zlatni standard dijagnostike ostaje gonadotropin-oslobađajući hormon (GnRH) stimulacioni test sa graničnom vrednošću vršnog LH > 5 IU/L za potvrdu CPP. Poseban fokus rada je na diferencijalnoj dijagnostici progresivnih stanja u odnosu na benigne varijante (izolovana telarha i adrenarha), čime se sprečava nepotrebna terapijska intervencija. Lečenje: Savremena terapija CPP podrazumeva primenu agonista GnRH (triptorelin, leuprolid) u depo formulacijama, koji desenzitizacijom receptora hipofize zaustavljaju pubertetsku progresiju. Zaključak: Pravovremena dijagnostika i uvođenje terapije rezultiraju značajnim dobitkom u finalnoj visini (prosečno 0,63 SDS). Uspešno zbrinjavanje pacijenata zahteva interprofesionalni pristup i jasnu razliku između varijanti normalnog razvoja i patoloških entiteta.

Ključne reči: Centralni prevremeni pubertet, GnRH test, GnRH agonisti, koštana starost, Tannerovi stadijumi.

UVOD: NEUROENDOKRINA KONTROLA I FIZIOLOGIJA

1. Hipotalamus-hipofiza-gonadna (HPG) osa

Pubertet je rezultat reaktivacije hipotalamo-hipofizno-gonadne (HPG) ose [1]. Ovaj složeni proces odvija se kroz tri ključne faze:

Fetalna aktivacija: HPG osa postaje aktivna između 12. i 14. nedelje gestacije, ali je pred kraj trudnoće potiskuju placentarni hormoni [1].

Mini-pubertet: Kratkotrajna reaktivacija ose neposredno nakon rođenja usled uklanjanja placentne inhibicije. Traje do 6 meseci kod dečaka, dok kod devojčica nivoi estradiola mogu fluktuirati do 2-4. godine, izazivajući prolazno uvećanje dojki [1,2].

Pravi pubertet: Nastaje kada neuroendokrini mehanizmi (Kisspeptin sistem i leptin) uklone inhibiciju centralnog nervnog sistema (CNS) sa GnRH neurona. To pokreće pulsirajuće lučenje GnRH, koji stimuliše hipofizu na lučenje luteinizirajućeg (LH) i folikulostimulišućeg hormona (FSH), pokrećući sazrevanje gonada [1,3,4,5,6]. Osnovne komponente ovog regulatornog sistema i njihove funkcije sumirane su u Tabeli 1.

Tabela 1. Komponente i regulacija HPG ose. *Izvor: Prilagođeno prema Sharma L, Daley SF. [1]*

Nivo regulacije	Hormon / Signal	Funkcija i dejstvo
Hipotalamus	GnRH (pulsirajuće)	Stimulacija prednjeg režnja hipofize.
Hipofiza	LH i FSH	Stimulacija gonada na produkciju steroida i gameta.
Gonade	Estrogen / Testosteron	Razvoj sekundarnih polnih karakteristika.
Povratna sprega	Negativna/Pozitivna	Kontrola lučenja na nivou hipotalamusa i hipofize.

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Rad primljen: 06.03.2026. Rad prihvaćen: 05.04.2026.. Elektronska verzija objavljena: 22.04.2026.

Vol. 51 (2026) No. 1 TIMOK MEDICAL GAZETTE Review article

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. Ključni termini i fiziološki procesi

Razumevanje pubertetskih poremećaja zahteva jasno razlikovanje dva nezavisna procesa:

- Gonadarhe: Aktivacija polnih žlezda pod uticajem HPG ose. Kod devojčica dovodi do rasta jajnika i razvoja dojki (estradiol), a kod dečaka do rasta testisa i spermatogeneze (testosteron) [2,7].
- Adrenarhe: Povećana proizvodnja nadbubrežnih androgena (DHEA i DHEA-S). Javlja se nezavisno od HPG ose, oko 7-8. godine, i odgovorna je za pojavu stidnih dlaka (pubarhe), akni i mirisa tela.

Hormonske i fizičke promene normalnog razvoja: Fizičke promene puberteta su rezultat proizvodnje polnih hormona gonadama, čiji početak (gonadarhe) ukazuje na početak puberteta. Gonadarhe se pokreće pulsirajućim oslobađanjem hormona koji oslobađa gonadotropin, što aktivira HPG osu [1,2,3]. Adrenarhe (tj. proizvodnja nadbubrežnih androgena koja dovodi do stidnih i aksilarnih dlaka, telesnog mirisa i blagih akni) je odvojen, ali obično istovremen proces i sam po sebi ne ukazuje na pravi početak puberteta kod dečaka ili devojčica [8].

Kod devojčica, povećana sekrecija estradiola u jajnicima uzrokuje razvoj dojki u prosečnom uzrastu od 10 godina (raspon: od osam do 12 godina). Menarha obično sledi 2,5 godine nakon početka razvoja dojki, u prosečnom uzrastu od 12,5 godina (raspon: od devet do 15 godina) [1,2,3,7,9]. Kod dečaka, uvećanje testisa na najmanje 4 ml zapremine ili 2,5 cm dužine je prvi znak pravog puberteta i javlja se u prosečnom uzrastu od 11,5 godina (raspon: od 9,5 do 14 godina) [8, 10]. Maksimalna brzina rasta (PHV) je rani događaj tokom puberteta kod devojčica i relativno kasni kod dečaka, pri čemu je razlika između polova u proseku oko dve godine [11]. Sa početkom menarhe dostignuto je 95,3% (SD 1,7) visine odrasle osobe; odgovarajući preostali dobitak visine je u proseku 7,8 cm (SD 2,8) [12].

3. Klinička progresija (Tannerovi stadijumi)

Progresija puberteta prati predvidljiv niz fizioloških promena koji se u kliničkoj praksi procenjuje korišćenjem standardizovanih Tannerovih stadijuma (I–V) [1,13]. Detaljni kriterijumi za procenu razvoja dojki i pubične kosmatosti kod devojčica sistematizovani su u Tabeli 2, dok su parametri za procenu genitalnog razvoja i kosmatosti kod dečaka prikazani u Tabeli 3.

Tabela 2. Tannerova klasifikacija razvoja kod devojčica

Stadijum	Razvoj dojki (B - Breast)	Pubična kosmatost (P - Pubic hair)
1	Prepubertetski: samo elevacija papile.	Odsustvo pigmentisanih terminalnih dlaka.
2	"Pupljenje" (thelarche): žlezdano tkivo se palpira.	Retke, svetle dlake, uglavnom duž labija.
3	Dalja elevacija dojke bez razdvajanja kontura.	Tamnije, grublje dlake iznad simfize.
4	Sekundarni brežuljak: areola se izdiže iznad dojke.	Adultni tip dlaka, ali manja površina.
5	Adultni stadijum: areola u nivou konture dojke.	Adultna distribucija (širenje na butine).

Tabela 3. Tannerova klasifikacija razvoja kod dečaka

Stadijum	Razvoj genitalija (G - Genitals)	Pubična kosmatost (P - Pubic hair)
1	Prepubertetski: testisi < 4 ml.	Odsustvo terminalnih dlaka.
2	Uvećanje skrotuma i testisa (≥ 4 ml).	Retke, duge dlake pri korenu penisa.
3	Porast penisa, prvenstveno u dužinu.	Tamnije i grublje dlake, kovrdžave.
4	Dalji rast penisa u širinu; razvoj glansa.	Guste dlake adultnog tipa, manja površina.
5	Genitalije adultnog oblika i veličine.	Adultna distribucija.

ETIOLOGIJA I KLASIFIKACIJA

Prevremeni pubertet se definiše kao pojava sekundarnih polnih karakteristika pre 9 godina kod dečaka (ili pre 8 kod devojčica), u hronološkom uzrastu 2–2,5 standardne devijacije pre prosečne starosti početka puberteta za belu populaciju [13,14]. Njegova incidencija je između 1:5000 i 1:10.000, a njegova prevalencija raste širom sveta [15].

Na osnovu osnovnog patološkog procesa, prevremeni pubertet se može klasifikovati na sledeći način:

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].

Centralni prevremeni pubertet (CPP): (zavisan od gonadotropina) zbog ranog sazrevanja HPG ose. Nastaje usled prevremene aktivacije ose (GnRH zavisan) [16,2]. Uzroci obuhvataju kongenitalne promene (hamartom, ciste), stečene lezije (tumori, trauma) i genetske mutacije (MKRN3). Kod devojčica je do 90% slučajeva idiopatske prirode [2,9].

Periferni prevremeni pubertet (PPP): (nezavisan od gonadotropina), uzrokovan prekomernim lučenjem polnih hormona iz gonada ili nadbubrežnih žlezda, egzogenim izvorima polnih steroida ili ektopičnom proizvodnjom gonadotropina iz tumora germinativnih ćelija.

Benigne pubertalne varijante: uključujući neprogresivni ili intermitentno progresirajući CPP ili izolovane androgenima posredovane seksualne karakteristike kod dečaka koje su rezultat rane aktivacije hipotalamus-hipofizno-nadbubrežne ose (prevremena adrenarha). Oba ova poremećaja mogu biti varijanta normalnog puberteta [13,14].

Diferencijalne karakteristike između centralnog i perifernog puberteta sumirane su u Tabeli 4.

Tabela 4. Diferencijalna dijagnoza centralnog (CPP) i perifernog (PPP) puberteta

Karakteristika	Centralni (CPP)	Periferni (PPP)
HPG osa	Aktivirana (GnRH zavisan)	Miruje (GnRH nezavisan)
Gonadotropini (LH/FSH)	Povišeni	Potisnuti (niski)
Tok razvoja	Prati biološki pol deteta	Može biti suprotan polu
Najčešći uzrok	Idiopatski (kod devojčica)	Ciste jajnika, KAH, egzogeni unos

Detaljnije o perifernom prevremenom pubertetu (PPP):

Periferni prevremeni pubertet (PPP) je uzrokovan prekomernom proizvodnjom polnih hormona u gonadama ili nadbubrežnim žlezdama, tumorima koji luče b-hCG ili izlaganjem egzogenim polnim hormonima. Etiologije uključuju Mekjun-Olbrajtov sindrom (MAS), funkcionalne ciste jajnika (FC), tumore Lajdigovih ćelija ili porodični muški prevremeni pubertet. Adrenalno poreklo viška androgena uzrokovano je tumorima ili kongenitalnom adrenalnom hiperplazijom [17]. PPP je mnogo ređi od CPP.

Neklasična kongenitalna adrenalna hiperplazija (NKAH): usled nedostatka 21-hidroksilaze (gen CYP21A2) je čest autozomno recesivni poremećaj. Kliničke karakteristike odražavaju višak androgena (stidne dlake, miris tela, akne pre 8/9 godine). Dodatne karakteristike uključuju visok rast u detinjstvu i ubrzano sazrevanje skeleta koje dovodi do niskog rasta u odraslom dobu [18,19,20]. Za preciznu dijagnostiku NKAH koristi se korelacija nivoa 17-OHP prikazana u Tabeli 5.

Tabela 5. Diferencijalna dijagnostika NCCAH (na osnovu 17-OHP nivoa). *Izvor: Prilagođeno prema White PC, Speiser PW [21]*

Kategorija	Bazalni 17-OHP (ng/dl)	Stimulisani 17-OHP (ng/dl)
Zdrava deca	< 200	< 1000
Heterozigoti	< 200	1000 – 3500
NCCAH	> 200	> 1000 (često > 3500)

BENIGNE VARIJANTE (PARCIJALNI PREVREMENI PUBERTET)

Benigne varijante prevremenog puberteta su: Prevremena telarhea, Prevremena adrenarhea i Izolovana prevremena menarha. Ova stanja karakteriše pojava izolovanih pubertetskih znakova bez pune aktivacije HPG ose. Ključno je da su koštana starost, brzina rasta i biohemijski nalazi obično normalni [1,8]. Sharma L, Daley SF naglašavaju značaj razlikovanja ovih stanja radi smanjenja obima dijagnostičkog postupka [1].

Prevremena telarhea (P. Telarha): Najčešća benigna varijanta. Jednostrani ili bilateralni razvoj dojki kod devojčica (obično 0-24 meseca ili 6-8 godina). Nema drugih povezanih pubertetskih promena. Potrebno je kliničko praćenje [1,22,23,24].

Prevremena adrenarhea (P. Adrenarha): Rana proizvodnja nadbubrežnih androgena (stidne/aksilarne dlake, akne, miris tela pre 8.

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)

godine). Nema razvoja dojki niti uvećanja testisa. Moraju se isključiti egzogeni izvori androgena, tumori i kasno nastala KAH [1,24].

Izolovana prevremena menarha (P. Menarha): Vaginalno krvarenje kod devojčica < 8 godina bez drugih znakova puberteta. Obično nema uticaja na konačnu visinu. Moraju se isključiti seksualno zlostavljanje, strana tela, tumori genitalnog trakta i infekcije [1,24].

Lipomastija: Višak masnog tkiva u dojkama kod gojaznih devojčica, ponekad se meša sa prevremenom telarhom [1]. (Tabela 6)

Tabela 6. Diferencijalna dijagnoza benignih varijanti

Stanje	Glavni simptom	Hormonski nalaz	Preporuka
P. Telarha	Izolovan razvoj dojki (žlezdano tkivo)	Estradiol (norm. / blago ↑)	Kliničko praćenje na 3-6 meseci
P. Adrenarha	Pubična / aksilarna dlakavost	Povišen DHEA-S	Isključiti NKAH i tumore
P. Menarha	Vaginalno krvarenje	Prepubertalni nivoi	Isključiti lokalne uzroke
Lipomastija	Višak masnog tkiva (bez žlezda)	Prepubertalni nivoi	Redukcija telesne mase i praćenje

KLINIČKA PROCENA I DIJAGNOSTIČKI PUT

1. Anamneza i antropometrija

Značajna je detaljna anamneza za razlikovanje pravog PP od benignih varijanti. Progresivni razvoj, brz linearni rast i uznapredovala koštana starost karakterišu pravi PP [1,25].

Ispitivanje treba da obuhvati: Neurološke simptome (glavobolje, napadi, epizode neprimerenog smeha - hamartom), prethodne traume glave, lečenje tumora mozga ili infekcije CNS-a.

Fizički pregled: Procena stidnih i aksilarnih dlaka, znaka virilizacije (klitoromegalija, uvećanje penisa, akne). Sveobuhvatni neurološki pregled.

Inspekcija kože: Makule "kafe sa mlekom" (Neurofibromatoza tip 1 ili Mekjun-Olbrajtov sindrom).

Nagli skok rasta: Skok > 7 cm/godišnje uz uvećanje testisa ili dojki zahteva hitnu evaluaciju [24].

2. Laboratorijska i Radiološka dijagnostika

Koštana starost (KZ): Kada je KZ uznapredovala više od 2 standardne devijacije (SD) u poređenju sa hronološkim uzrastom (HU), sprovodi se dalje testiranje [1,14].

Hormonsko testiranje: Merenje ultrasenzitivnim testovima (ICMA ili ECLIA). Koncentracije serumskog **LH > 0,2 do 0,3 IU/L** mogu ukazivati na pubertetski razvoj [1].

GnRH stimulacioni test (Zlatni standard): Aktivacija pubertetske HPG ose se potvrđuje ako je vršni **LH > 5 IU/L**. Odnos LH/FSH manji od 0,43 ukazuje na prepubertetski status, dok odnos veći od 0,66 u stimulaciji razlikuje progresivne od neprogresivnih varijanti [1].

Kod devojčica: Nivoi serumskog E2 nakon 24 sata stimulacije agonistom GnRH (pik > 50 pg/ml) povećavaju osetljivost testa [16,22].

Kod dečaka: Merenje testosterona, DHEA-S, 17-OHP i **hCG** (humani horionski gonadotropin) rano ujutru kod sumnje na PPP. Određeni tumori luče hCG koji stimuliše LH receptore [1].

Referentne vrednosti koncentracije gonadotropina i steroida u serumu date su u Tabeli 7, Tabela 8. a Ultrasonografski kriterijumi za devojčice (Karlični UZ) u Tabeli 8. Diferencijalno-dijagnostički kriterijumi (CPP vs. Benigne varijante) date su u Tabeli 9.

Tabela 7. Referentne vrednosti koncentracije gonadotropina i steroida u serumu. *Izvor: Neely EK, et al [26]*

Parametar	Prepubertetski (Stadijum I)	Pubertetski (Stadijum II)
LH (bazalni)	0,03 ± 0,03 IU/L	0,71 ± 1,04 IU/L
Estradiol	< 1,0 ng/dL	1,6 ± 0,7 ng/dL
Testosteron	< 10 ng/dL	42 ± 15 ng/dL
Legenda: ICMA metoda.		

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:

Tabela 8. Ultrasonografski kriterijumi za devojčice (Karlični UZ)

Parametar	Granična vrednost	Značaj
Volumen uterusa	> 1,8 ml	Senzitivnost za rani CPP
Dužina materice	> 3,4 cm	Estrogenska ekspozicija
Volumen ovarijuma	> 1,2 ml	Aktivacija gonada

Tabela 9. Diferencijalno-dijagnostički kriterijumi (CPP vs. Benigne varijante)

Parametar	Centralni PP (CPP)	Izolovana telarha	Izolovana adrenarha
Koštana starost	Uznapredovala ≥ 2 SD	Normalna	Normalna / blago ↑
Brzina rasta	Ubrzana (> 7 cm/god)	Normalna	Normalna
Vršni LH (test)	> 5 IU/L	< 4,5 IU/L	< 4,5 IU/L

DIJAGNOSTIČKI ALGORITMI

ALGORITAM 1. DIJAGNOSTIČKI PUT KOD DEVOJČICA SA TELARHOM.*(Prema: Root AW. Pediatr Rev. 2000 [27])*

Normalna brzina rasta i KZ ≈ HU (Koštana zrelost odgovara hronološkom uzrastu):
Dijagnoza: **Izolovana prevremena telarha**.
Postupak: Kliničko praćenje; obično nije potrebna terapijska intervencija.
Ubrzana brzina rasta i KZ > HU (Uznapredovala koštana zrelost):
Indikovan: **GnRH stimulacioni test**.
Vršni LH > 5 IU/L (Pubertetski odgovor):
Dijagnoza: **Centralni prevremeni pubertet (CPP)**.
Sledeći korak: **Magnetna rezonanca(MRI) mozga** radi isključenja patoloških procesa.
LH nizak (Prepubertetski odgovor) uz prisustvo cista na jajnicima:
Sumnja na: **Mekjun-Olbrajtov sindrom (MAS)** ili druge oblike perifernog puberteta.
Kod dečaka, diferencijalna dijagnoza zahteva sistematičan pristup prikazan u **Algoritmu 2**.

ALGORITAM 2. DIJAGNOSTIČKA EVALUACIJA DEČAKA SA PREVREMENIM PUBERTETOM
(Sistematizovano prema: Root AW. Pediatr Rev. 2000 [27])

I. Klinička trijaža (Brzina rasta i procena koštane zrelosti - KZ)
KZ odgovara hronološkom uzrastu (KZ ≈ HU): Verovatna **izolovana prevremena adrenarha**; potrebno periodično kliničko praćenje rasta i razvoja.
KZ značajno naprednija od hronološkog uzrasta (KZ > HU): Neophodna hormonska laboratorijska obrada.
II. Određivanje nivoa gonadotropina (LH)
LH povišen (Pubertetski odgovor na bazalnom nivou ili GnRH testu):
Dijagnoza: **Centralni prevremeni pubertet (CPP)**.
Obavezno: **MRI (Magnetna rezonanca) mozga** radi isključenja hamartoma ili drugih tumora CNS-a.
LH nizak (Potisnut/Prepubertetski odgovor):
Dijagnoza: **Periferni prevremeni pubertet**. Preći na diferencijalnu dijagnozu uzroka.
III. Diferencijalna dijagnoza perifernog oblika (Nizak LH)
Povišen 17-OHP / DHEA-S: Ukazuje na **KAH (Kongenitalnu adrenalnu hiperplaziju)** ili tumore nadbubrežne žlezde.
Povišen hCG (Humani horionski gonadotropin): Ukazuje na ekstrapituitarne tumore koji luče hCG (npr. hepatoblastom ili tumori zametnih ćelija).
Visok testosteron uz niske gonadotropine i uvećane testise: Sumnja na **testotoksikozu** (FMPP) ili tumor Lajdigovih ćelija.

TERAPIJA I MENADŽMENT

1. Centralni prevremeni pubertet (CPP)
Zlatni standard su **agonisti GnRH (GnRHa)** [7,24].
Ciljevi: Maksimiziranje konačne visine i ublažavanje psihosocijalnih stresova. Ako dete ima početak mlađe od 6-7 godina i brz tempo progresije, lečenje je standard nege.
Formulacije: Mesečne depo injekcije (3,75 mg) ili dugodelujući depoi (svake 4 ili 12 nedelja).
Monitoring: Klinički pregled svaka 3–6 meseci. Sazrevanje skeleta svakih 6-12 meseci. Ciljni stimulisani LH < 2,5–4,5 IU/L.
Prekid: Obično između 11. godine (hronološki) ili kada se dostigne KZ od 12,5 godina (devojčice) i 14 godina (dečaci) [1,7,28].
Bezbednost: Terapija je bezbedna. Meta-analiza ukazuje na korist u visini od 0,63 SDS [1].
2. Periferni prevremeni pubertet (PPP)

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)

Hirurgija: Za tumore gonada ili nadbubrežne žlezde.
NKAH: Lečenje glukokortikoidima.
MAS: Inhibitori aromataze i selektivni modulatori estrogenskih receptora.
Napomena: Deca sa PPP imaju rizik od razvoja sekundarnog CPP; tada je neophodno dodati GnRH analoge **[1]**.

ZAKLJUČAK (Praktični aspekti)

Glavni znak sumnje NA PREVREMNI PUBERTET: Razvoj dojki kod devojčica i uvećanje testisa (više od 4 ml) kod dečaka pre 8/9 godine. **Diferencijalna dijagnoza:** Prioritet je razlikovati benigne varijante od progresivnog CPP kako bi se izbeglo nepotrebno lečenje. **Zlatni standard:** GnRH test uz procenu koštane zrelosti. **Magnetna rezonanca mozga (MRI mozga):** Preporučuje se za sve slučajeve CPP kod dečaka i kod devojčica mlađih od 6 godina ili sa neurološkim znacima. **Vreme je faktor:** Najbolji rezultati se postižu započinjanjem terapije pre 6. godine života. **Edukacija:** Temeljan razgovor sa porodicom o normalnom toku puberteta, ciljevima terapije i psihosocijalnim aspektima (interakcija sa vršnjacima, samopoštovanje).

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SKRAĆENICE:

ACTH – Adrenokortikotropni hormon
BMI – Indeks telesne mase
CNS – Centralni nervni sistem
CPP – Centralni prevremeni pubertet
DHEA-S – Dehidroepiandrosteron sulfat
FSH – Folikulostimulišući hormon
GnRH – Gonadotropin-oslobađajući hormon
GnRHa – Agonisti gonadotropin-oslobađajućeg hormona
HPG osa – Hipotalamo-hipofizno-gonadna osa
KAH – Kongenitalna adrenalna hiperplazija
LH – Luteinizirajući hormon
MAS – Mekjun-Olbrajtov sindrom
MRI – Magnetna rezonanca
NKAH – Neklasična kongenitalna adrenalna hiperplazija
PPP – Periferni prevremeni pubertet
SDS – Standardna devijacija
TSH – Tireostimulišući hormon
KZ – Koštana zrelost
HU – Hronološki uzrast
UZ – Ultrazvuk

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