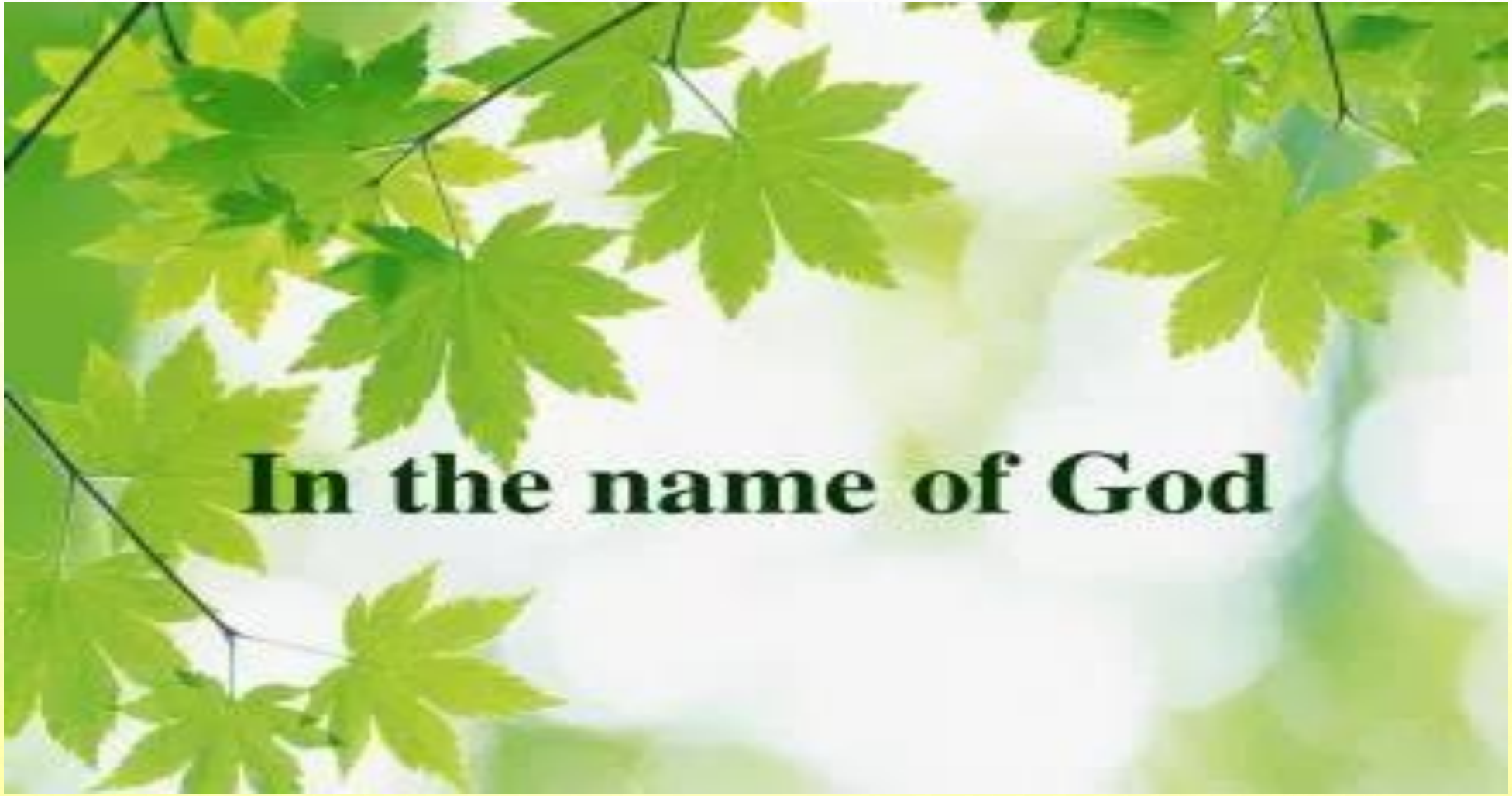

In the name of God

Central precocious puberty

Endocrine society clinical practice guideline

The journal of clinical endocrinology & metabolism, 2026

Dr Niloufar Amini

How the guideline was built

- The guideline development panel (GDP) included 15 members: pediatric endocrinologists, a pharmacist, a general pediatrician, a patient-parent representative, and two methodologists.

- The GDP used the **GRADE methodology** and **evidence-to-decision** (etd) frameworks to address **10 prioritized clinical questions** on CPP diagnosis and treatment.

- A systematic review was conducted for each question.
- Searches: February 2025, updated January 2026.
- Few RCTs were available.
- Evidence was predominantly observational and/or indirect.
- Recommendation strength is classified as Strong (1) or Conditional (2).
- Most recommendations in this guideline are conditional, reflecting uncertainty and the need for individualized/shared decision-making.

GRADE evidence certainty

⨁⨁⨁⨁ High

High confidence the true estimate falls within the specified range.

⨁⨁⨁◯ Moderate

Moderate confidence; true value may deviate slightly.

⨁⨁◯◯ Low

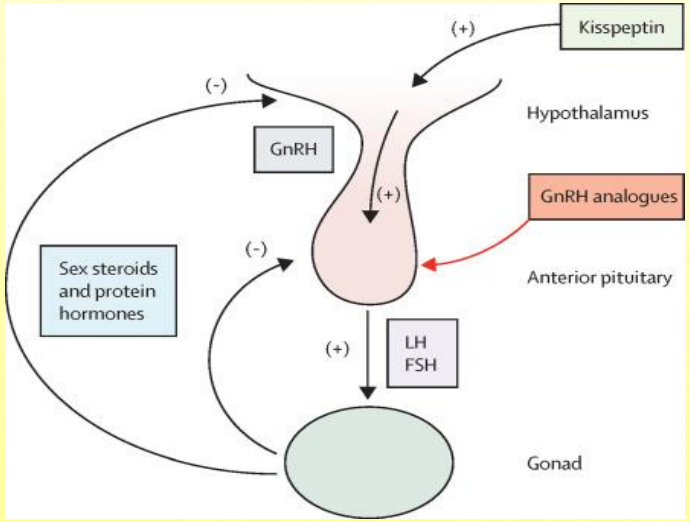
Low confidence; true value likely falls in a different range.

⨁◯◯◯ Very Low

Very low confidence; true value probably deviates significantly. *Most CPP recommendations fall here.*

Central precocious puberty (CPP)

- Premature activation of the hypothalamic-pituitary-gonadal (HPG) axis.
- Early pulsatile gonadotropin-releasing hormone (GnRH) secretion.
- Downstream gonadal sex steroid production.
- Development of associated secondary sexual characteristics.



Central precocious puberty (CPP)

- Before age **8 years** in girls.
- Before age **9 years** in boys.
- Pubertal milestones are being reached **earlier than in prior decades**, raising the possibility that the current CPP definition may be outdated.

Central precocious puberty (CPP)

- **Sex ratio:**

  ~10× more common in girls than boys

- **Incidence:**
- 0.2–26 per 10,000 girls/year
- 0.02–0.9 per 10,000 boys/year

Clinical significance

Reduced Adult Height

Accelerated bone age advancement can compromise final height potential in both sexes.

Psychosocial Outcomes

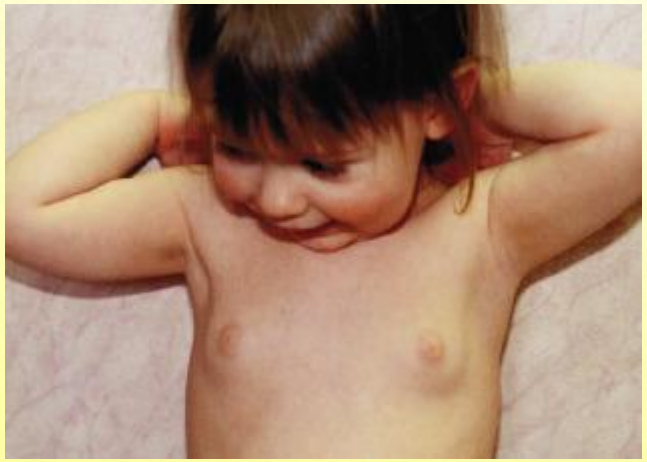
Increased prevalence of psychiatric disorders, including conduct disorder in adolescence and adulthood.

Long-Term Health Risks

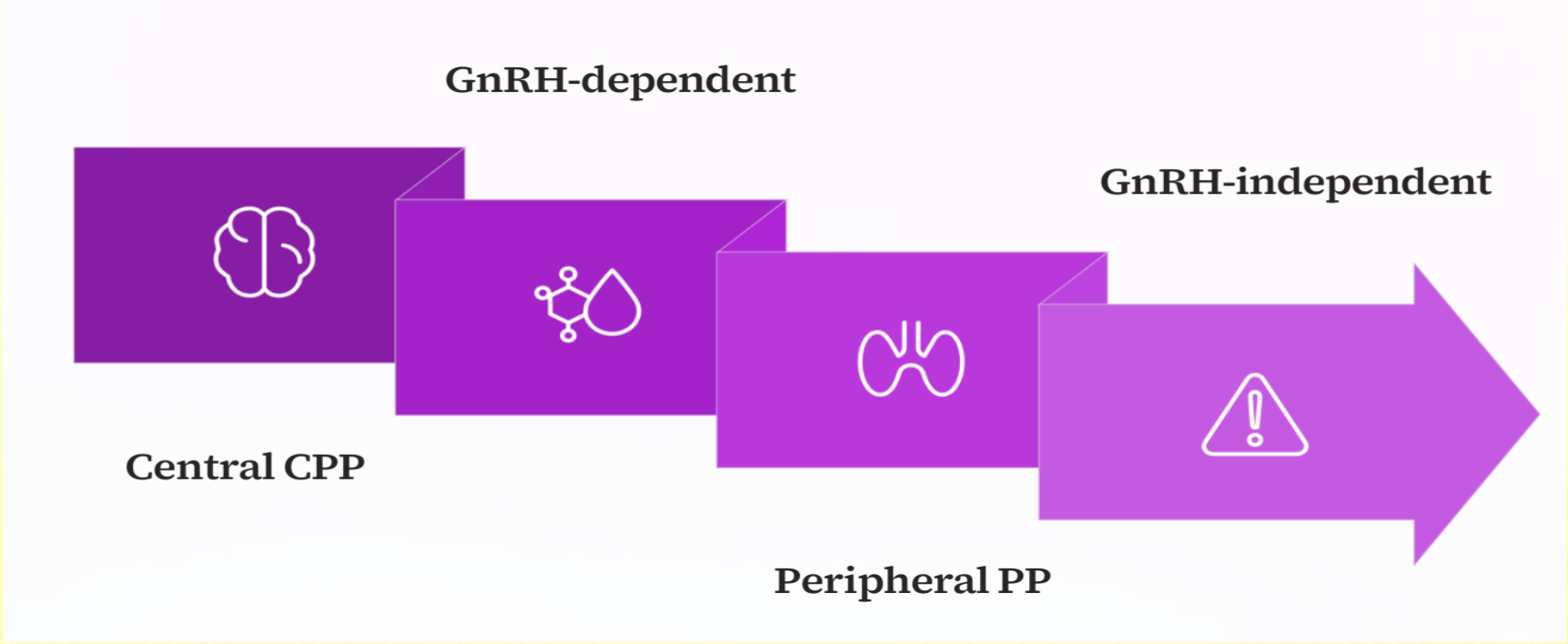
Early menarche linked to obesity, hypertension, T2DM, ischemic heart disease, stroke, and estrogen-dependent cancers.

Puberty onset: clinical definitions

- **Girls:** first appearance of **breast development (thelarche, tanner B2)**
- **Boys:** testicular volume **≥4 ml** or length **>2.5 cm**
- Accelerated growth velocity and advanced bone age may also be in both sexes.



Central vs. Peripheral precocious puberty



Etiology of CPP

Idiopathic

Most common, especially in girls. No identifiable structural or genetic cause.

Organic / CNS

Brain tumors (astrocytomas, craniopharyngiomas), hypothalamic hamartomas, other structural lesions. More prevalent in boys and younger children.

Genetic

Loss-of-function mutations in *MKRN3*, *DLK1*, *MECP2*; gain-of-function in *KISS1R*/*KISS1*. Especially relevant in familial CPP.

Evolving definitions

Slowly Progressive (SP-PP)

Transient or minimal progression. Good adult height prognosis without treatment. Observation appropriate.

Rapidly Progressive (RP-PP)

Defined as ≥1 Tanner stage advance within 6 months. Advanced BA (mean 1.48 vs. 0.48 years in SP-PP). Requires diagnostic evaluation.

Evolving definitions

- **Slowly progressive:** longer duration between thelarche and menarche and achievement of normal adult height.

- **Suggesting that not all patients currently meeting CPP criteria would benefit from aggressive evaluation or treatment.**

Diagnosis

Recommendations 1–5:

Evaluating children with premature secondary sexual characteristics

Recommendation 1: girls ages 7.0–8.0 years with thelarche

- **Watchful waiting via periodic physical exams rather than immediate laboratory or radiologic evaluation (2 |⊕○○○).**

- **Watchful waiting**:
- Periodic physical examinations **every 4–6 months.**
- Reassessment of growth velocity and tanner staging.

Recommendation 1:
girls ages 7.0–8.0 years with thelarche

- **Immediate evaluation is appropriate if :**
- The girl presents with tanner B3 or higher
- Progresses to B3 under observation
- Documented growth acceleration (>6 cm/year)
- Exhibits CNS findings (headaches, seizures, visual deficits).

Rec. 1: Summary of evidence

- **12 uncontrolled series(1,335 patients, ages 3–8 years):**
- Premature thelarche regression rates of **13–70%.**
- Progression to CPP of only **0–31%**.

- Indirect evidence suggests many girls with 7–8 yr thelarche have slowly progressive/normal-variant puberty.
- No studies directly compared evaluation vs. Observation in this age group.

Rec. 1: Summary of evidence

- Pathologic intracranial findings are rare in girls ages 6–8 years.
- GnRHa height benefit is greatest when started at younger ages.
- Evaluation costs are substantial; pediatric endocrinologist shortages exist.
- Apparent thelarche may sometimes be lipomastia.

Recommendation 2: Observation period for girls with early thelarche

- **4 to 6 month observation period before starting diagnostic evaluation in girls <7 years with tanner B2 (2 |⊕○○○).**

- **<u>Immediate evaluation if:</u>**
- B3+ at presentation
- Progression to B3 before age 8
- Growth velocity >6 cm/yr
- CNS findings

Rec. 2: Summary of evidence

- Studies show 33–66% of girls with early thelarche have RP-PP.
- Girls with SP-PP achieved mean adult heights of 160.7–165.5 cm without Tx.
- Advanced BA was an important predictor of rapid progression in one study.

Rec.2: Justification for the recommendation

- The GDP found no evidence that a 4–6 month diagnostic delay negatively affects patient-important outcomes.

Recommendation 3:
Basal LH as first-line diagnostic test

- **Start with basal LH by ultrasensitive assay rather than GnRH/GnRHa stimulation testing in all patients (2 |⨁○○○).**

- An ultrasensitive LH assay : detect very low LH concentrations(< 0.05-0.1 iu/l).
- While first morning (8:00-10:00 AM) basal LH testing may is optimal, basal LH at any time of day is acceptable to increase feasibility.

Rec.3:When to proceed to stimulation testing

- If **basal LH is low/indeterminate** and **clinical suspicion remains high**
- Or **rapid diagnosis is needed** (RP-PP)

- Alternatively, **repeat early-morning basal LH**.

Rec.3: Summary of evidence

- **Basal LH thresholds:**
- Basal LH **>0.25 IU/L** in **boys** (limited data) and in **girls with Tanner B2** could confirm CPP and thus obviate the need for further testing.
- Basal LH **>0.3 IU/L** may suffice for **tanner B3.**
- Basal LH **>0.2 IU/L** in girls with **tanner B2** predicts a **peak LH > 5** IU/L by stimulation testing.

Rec.3: Summary of evidence

- Ultrasensitive **basal LH** can predict stimulated LH, but **sensitivity is variable**.
- **Basal LH sensitivity:** ~42–94%.
- **Basal LH specificity:** ~70–100% across studies.
- Cutoffs vary by assay, tanner stage, age and sex.
- Boys have substantially less evidence.

Rec.3: Summary of evidence

- **GnRH testing : gold standard** to determine a diagnosis of CPP.
- Peak **stimulated LH ≥5 IU/L : highly specific** (97%to 100%).
- However, GnRH testing has some limitations.
- **Under age 3:** Peak LH >10 IU/L may not confirm CPP due to minipuberty.
- **In obesity (BMI SDS ≥2):** Peak LH may be lower, reducing the sensitivity of GnRH/GnRHa testing for CPP.

Rec. 3: Why basal LH first?

Lower Cost

GnRH/GnRHa stimulation testing is expensive and requires trained personnel, IV access, and multiple timed blood draws.

Less Burdensome

Avoids IV catheter insertion, hours in the medical setting, and absence from school — reducing distress for children and families.

More Accessible

Basal LH testing is more feasible globally, potentially enhancing health equity — provided ultrasensitive assays are available.

Rec.3: Justification for the recommendation

- the GDP favored basal ultrasensitive LH first because high basal LH predicts a positive stimulation test, while stimulation testing is more burdensome.

- However, because basal LH has variable sensitivity, stimulation testing remains appropriate when clinical certainty is insufficient.

Recommendation 4: Brain MRI — not routine for older age groups

- **Brain MRI should not be routinely performed in girls ages 6.0–8.0 years or boys ages 8.0–9.0 years without CNS symptoms (2 |⊕○○○).**

Rec.4: When MRI is indicated

- Any age with CNS symptoms/signs.
- **Girls <6 years** with CPP.
- **Boys <8 years** with CPP.
- High clinician/family concern for CNS pathology.

Rec.4: Summary of evidence

- The recommendation is driven largely by low prevalence of pathologic intracranial findings in these age groups without CNS findings.

- **Based on 35 studies across 19 countries (5,541 children with CPP):**
- Overall MRI abnormality rate (pathologic + incidental) was 18%.
- Pathologic lesions alone: 5.5%.

Rec. 4: Prevalence of pathologic MRI findings by age

1%

Girls 6.0–8.0 yrs

Prevalence of pathologic findings (tumors or hamartomas) on brain MRI

0%

Boys 8.0–9.0 yrs

Prevalence of pathologic findings on brain MRI in this age group

11%

Girls <6 yrs

Pathologic findings — justifying MRI in younger girls

28%

Boys <8 yrs

Pathologic findings — justifying MRI in younger boys

Rec.4: Justification for the recommendation

- Low prevalence of clinically significant pathology + burden/cost of MRI + lack of demonstrated patient-important benefit favored selective rather than routine imaging.

Recommendation 5: Genetic testing — not routine

- **Suggest against routine genetic testing for CPP. For familial CPP, consider testing via shared decision making (2 |⊕○○○).**

- This recommendation relates to targeted genetic testing including genes such as *MKRN3*, *DLK1*, and/or *MECP2.*

Genetic causes of CPP: key genes

MKRN3 (15q11.2)

Most common genetic cause. Loss-of-function mutations; autosomal dominant, paternally transmitted. Found in **9% of all CPP**, **33–46% of familial CPP**. Clinically indistinct from idiopathic CPP.

DLK1 (14q32.2)

Rare; paternally transmitted. Associated with higher metabolic comorbidity in adulthood (obesity, insulin resistance, T2DM). Found in **~4% of familial CPP**.

MECP2 (Xq28)

X-linked; sporadic. Associated with mild neurodevelopmental disorders. Found in **~2% of all CPP**. Median thelarche age: 5.4 years in girls.

Table 3 Monogenic causes associated with familial and sporadic central precocious puberty

Gene (OMIM) Locus	Protein Function	Inheritance Pattern	Most Common CPP Pattern	Mutation Types	Main Clinical Features	Prevalence
MKRN3 (603856) 15q11.2	• Zinc-finger protein • E3 ubiquitin ligase • Protein ubiquitination • mRNA binding	Autosomal dominant with maternal imprinting	Familial with paternal transmission	Loss-of-function mutations: • Missense • Frameshift • Nonsense • Whole-gene deletions • Promoter region deletions	Clinically indistinct from idiopathic CPP Mean age at first pubertal signs: • Girls: 6.2 (± 1.2) years • Boys: 7.1 (± 1.5) years	9% of overall cases 33–46% of familial cases
DLK1 (176290) 14q32.2	• Noncanonical ligand of Notch pathway • Negative regulator of adipogenesis • Potential regulator of neurogenesis	Autosomal dominant with maternal imprinting	Familial with paternal transmission	Loss-of-function mutations: • Frameshift • Nonsense • Splice site • Intragenic deletions	In adulthood: • Overweight/obesity • Hyperlipidemia • Glucose intolerance/T2DM	4% of familial cases
MECP2 (300005) Xq28	• DNA methylation reader • Gene transcription regulator • Neurodevelopment factor	X-linked dominant with incomplete penetrance	Sporadic	Likely loss-of-function mutations: • Missense • Insertions	Mild neurodevelopmental disorders Median age at thelarche (girls): 5.4 years	2% of overall cases

Abbreviations: CPP, central precocious puberty; OMIM, Online Mendelian Inheritance in Man; T2DM, type 2 diabetes mellitus.

Rec.5: Summary of evidence

- Evidence was observational/indirect and very low certainty.
- Targeted testing may identify etiology and help family counseling.
- Long-term patient-important outcome benefits remain uncertain.
- No direct trials comparing routine genetic testing vs no testing.
- Genetic cause identified in **13%** of all CPP (Brazilian cohort, n=270)
- Family history & neurodevelopmental disorders: clinical predictors of genetic etiology.

Rec.5: Summary of evidence

- **MKRN3 loss-of-function variants**:
- **~9%** overall CPP
- Up to **~46%** in familial CPP
- Paternal FH(+): up to **77%** of familial CPP

Familial CPP definition

- At least one **first** , **second** , or **third-degree relative** with documented CPP, early sexual development, or precocious menarche.

- **25–30%** of all CPP cases are familial.

Rec.5: Justification for the recommendation

- The benefit–harm balance for routine testing remains unclear.
- Higher diagnostic yield in familial CPP supports considering MKRN3/DLK1 testing in that subgroup.

Diagnostic Algorithm Overview

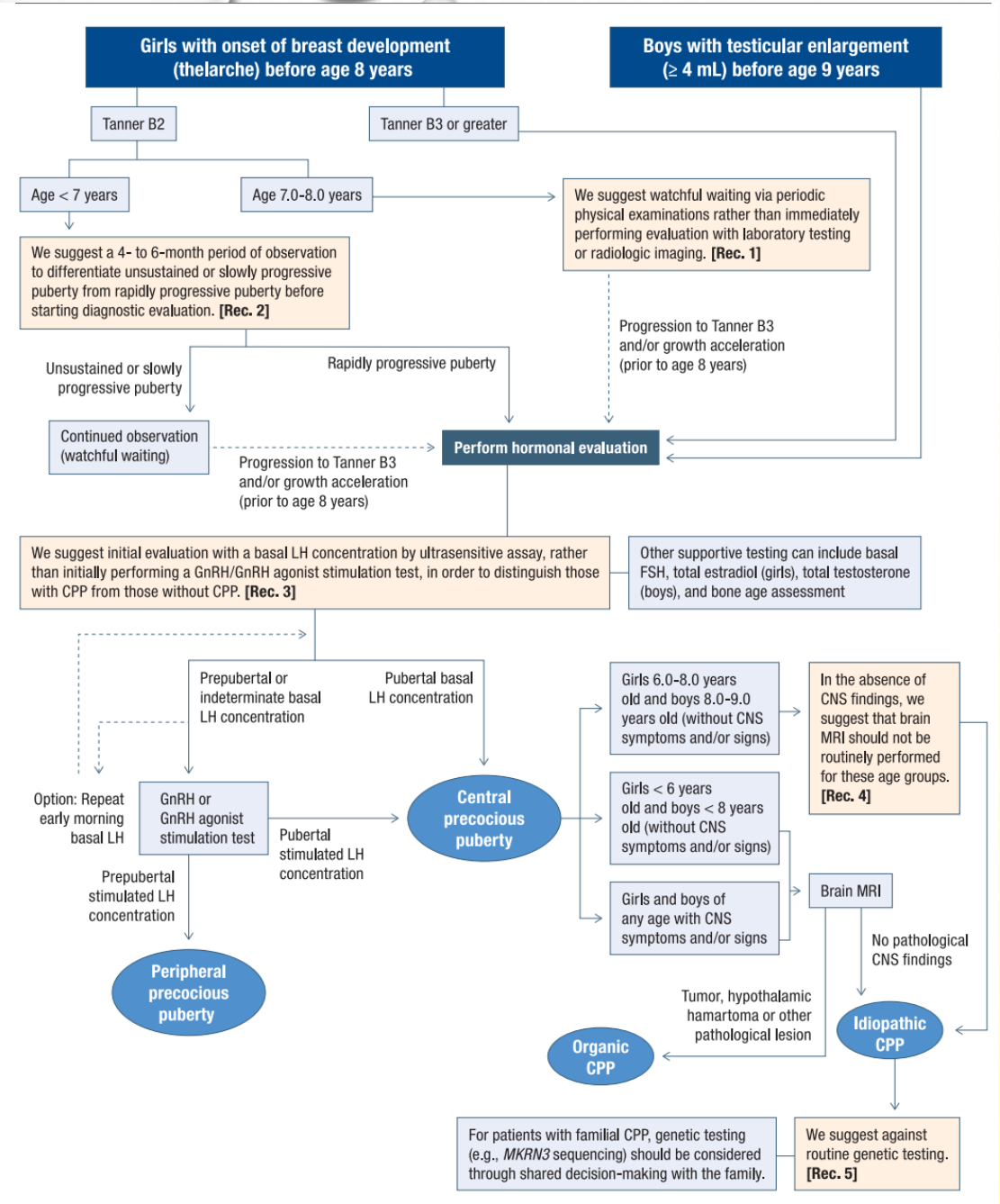
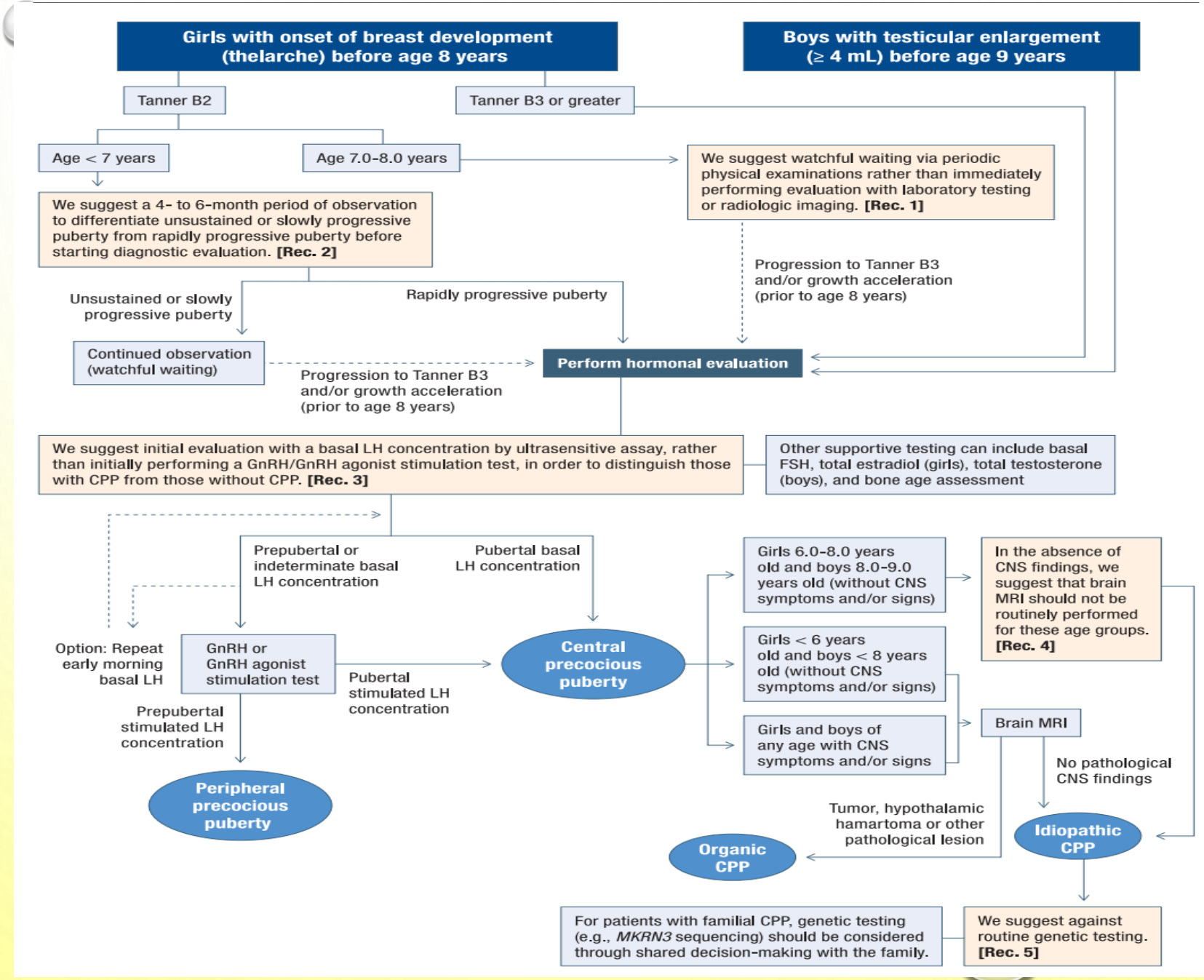


Figure 1: Assessment algorithm for children with premature secondary sexual characteristics, incorporating all five diagnostic recommendations (Rec. 1–5). Tan boxes represent GRADE-developed recommendations.


Girls with onset of breast development (thelarche) before age 8 years
Boys with testicular enlargement (≥ 4 mL) before age 9 years
Tanner B2
Tanner B3 or greater
Age < 7 years
Age 7.0–8.0 years
We suggest watchful waiting via periodic physical examinations rather than immediately performing evaluation with laboratory testing or radiologic imaging. [Rec. 1]
We suggest a 4- to 6-month period of observation to differentiate unsustained or slowly progressive puberty from rapidly progressive puberty before starting diagnostic evaluation. [Rec. 2]
Progression to Tanner B3 and/or growth acceleration (prior to age 8 years)
Unsustained or slowly progressive puberty
Rapidly progressive puberty
Continued observation (watchful waiting)
Progression to Tanner B3 and/or growth acceleration (prior to age 8 years)
Perform hormonal evaluation
We suggest initial evaluation with a basal LH concentration by ultrasensitive assay, rather than initially performing a GnRH/GnRH agonist stimulation test, in order to distinguish those with CPP from those without CPP. [Rec. 3]
Other supportive testing can include basal FSH, total estradiol (girls), total testosterone (boys), and bone age assessment
Prepubertal or indeterminate basal LH concentration
Pubertal basal LH concentration
Option: Repeat early morning basal LH
GnRH or GnRH agonist stimulation test
Pubertal stimulated LH concentration
Prepubertal stimulated LH concentration
Central precocious puberty
Peripheral precocious puberty
Girls 6.0–8.0 years old and boys 8.0–9.0 years old (without CNS symptoms and/or signs)
Girls < 6 years old and boys < 8 years old (without CNS symptoms and/or signs)
Girls and boys of any age with CNS symptoms and/or signs
In the absence of CNS findings, we suggest that brain MRI should not be routinely performed for these age groups. [Rec. 4]
Brain MRI
No pathological CNS findings
Tumor, hypothalamic hamartoma or other pathological lesion
Idiopathic CPP
Organic CPP
For patients with familial CPP, genetic testing (e.g., MKRN3 sequencing) should be considered through shared decision-making with the family.
We suggest against routine genetic testing. [Rec. 5]

Treatment

Recommendations 6–10:

Managing CPP with GnRH agonist therapy

Background

- **GnRH agonists** : **First-line treatment for CPP since the early 1990s.**

Pubertal Regression

Regression or stabilization of secondary sexual characteristics

Growth Modulation

Reduction in growth velocity and slowing of bone age advancement

Height Preservation

Preservation of adult height potential

Recommendation 6: GnRHa treatment for CPP

- **Suggest GnRHa treatment for many children with CPP, though certain subgroups may not achieve net benefit (2 |⨁○○○).**

- The recommendation is for both girls and boys; however, the available evidence was from studies of girls only, as evidence in boys was lacking.

- The GDP emphasizes the importance of shared-decision making for all patients with CPP.

Rec. 6: Subgroups less likely to benefit

Girls Ages 7.0–8.0 with SP-PP

Slowly progressive CPP in this age group is unlikely to yield important height benefit from GnRHa treatment.

At or Beyond Peak Pubertal Growth Spurt

GnRHas are not expected to substantially alter adult height when started during or after peak growth velocity (concordant with bone age assessment).

Late Diagnosis / Advanced Bone Age

Children presenting with BA ≥12 years (girls) or ≥13 years (boys) are not expected to derive substantive height benefits.

Tall Girls with Normal PAH

For girls with CPP who are tall and have a normal predicted adult height, reassurance and education may be more appropriate than treatment.

Rec.6: Summary of evidence

- No RCTs directly comparing GnRHa vs no treatment in idiopathic CPP.
- 21 comparative observational studies identified; 15 remained after exclusions
- 1835 girls; mean treatment start 8.2 ± 1.1 yr.
- 14 studies (1,017 treated, 480 controls): adult height: +2.7 cm (95% CI 1.1–4.4).

Rec.6: Summary of evidence

- **Treatment duration ≥3 yr:** +3.9 cm; **Treatment duration <3 yr:** +2.1 cm.
- GnRHa treatment also delayed menarche by a weighted mean of 1.3 years (treated: 12.0–12.4 years vs. controls: 9.6–11.4 years).
- **Psychosocial and neurocognitive outcomes**: Evidence was insufficient.
- **BMI:** No meaningful impact of GnRHa on BMI at adult height attainment

  Meta-analysis (5 studies, 459 patients) .

Rec. 6: Other outcomes

- **BMD:** Insufficient evidence. Short-term BMD differences likely reflect delayed bone accretion — not necessarily reduced peak bone mass in adulthood.

- **Fertility:** One study found GnRHa treatment associated with **higher spontaneous pregnancy rates** and lower need for assisted fertilization. Another found no clear differences in fertility-related outcomes in treated vs. Untreated men with CPP history.

GnRHa costs in the united states (2025)

$31K

Leuprolide Monthly

Average annual wholesale price (7.5 mg IM monthly formulation)

$62K

Leuprolide 6-Month

Average annual wholesale price (45 mg SC every 6 months)

$66K

Triptorelin

Average annual wholesale price (22.5 mg IM)

$60K

Histrelin Implant

Average annual wholesale price (50 mg SC yearly implant)

In France and Spain, annual GnRHa costs approximate $1,100–$1,300 USD. Cost-effectiveness is highly variable and context-dependent.

Rec.6: Justification for the recommendation

- The balance favors GnRHa for many children, but expected benefit is strongly subgroup-dependent.

- Therefore the recommendation is conditional and requires shared decision-making.

Recommendation 7: Start with long-acting GnRHa

- **In patients who will use a long-acting GnRHa long-term, initiate therapy with the long-acting preparation rather than a monthly formulation (2|⊕⊕○○).**

- Long-acting preparations: **≥3-month duration of action** (3-m and 6-m injectables; 12-month subcutaneous histrelin implant).
- Patients who plan to use monthly formulations long-term should begin with the monthly preparation.

Rec.7: Summery of evidence

- **Meta-analysis of 3 RCTs & observational studies(759 patients,7 countries):**
- Trivial differences between monthly and long-acting formulations in:
- Growth velocity (–0.18 cm/year)
- Peak stimulated LH (–0.16 IU/L)
- Proportion achieving adequate LH suppression (RR: 1.00)

Rec. 7: Practical considerations for formulation choice

Injection Frequency

Monthly injections require more frequent clinic visits, which may be a barrier for families with transportation or work constraints.

Histrelin Implant

Requires procedural expertise and often sedation. 60% of procedures performed in clinic, 35% in sedation unit. 88% of parents preferred implant over depot injection in one study.

Insurance & Access

64% of surveyed providers reported insurance coverage significantly influenced formulation choice. Access varies widely by country and health system.

Histrelin implant: extended duration

- FDA-approved for **12 months.**
- **Extended duration of action of up to 2–7 years.**
- In a US study of 4,000+ patients:
- Median annual total treatment costs for histrelin ($23,071) were **lower** than for leuprolide acetate monthly or quarterly ($27,021; P<0.0001).

Active medication	Strength (mg)	Route of administration	Frequency of administration	Cost per dose (average whole-sale price)	Average monthly cost	Average annual cost
Leuprolide acetate (pediatric formulation)	7.5	Intramuscular injection	Monthly	$2,600	$2,600	$31,201
	11.25			$4,720	$4,720	$56,645
	15			$5,199	$5,199	$62,389
	11.25		Every 3 months	$14,161	$4,720	$56,645
	30			$15,597	$5,199	$62,389
	45		Every 6 months	$31,194	$5,199	$62,389
	45	Subcutaneous injection		$32,932	$5,489	$65,863
Triptorelin pamoate	22.5	Intramuscular injection		$26,757	$4,460	$53,514
Histrelin acetate	50	Subcutaneous implant	Yearly	$60,218	$5,018	$60,218

Rec.7: Justification for the recommendation

- Health effects were similar.
- Fewer injections and likely better acceptability favored long-acting therapy when it is intended for long-term use.

Recommendation 8:
Clinical monitoring — no routine biochemical testing

- **Suggest against routine biochemical testing (LH, sex steroids) to monitor pubertal suppression during GnRHa treatment (2 |⊕○○○).**
- **Monitoring GnRHa therapy with clinical assessment alone:**
- Growth velocity
- Tanner staging
- Annual bone

Recommendation 8:
Clinical monitoring — no routine biochemical testing

- **Biochemical testing** (basal or stimulated LH, sex steroids) should be reserved to confirm **clinically suspected treatment failure:**

→ **Breast/Testicular Progression**

Advancement in breast development (girls) or testicular size (boys) during treatment

→ **Growth Acceleration**

Acceleration in growth velocity or persistent pubertal growth velocity — though this may be a relatively late indicator

Rec. 8: Treatment failure

Assess Adherence First

Always assess GnRHa treatment adherence and administration technique before concluding treatment failure

Then Biochemical Confirmation

If adherence confirmed, assess basal sex steroids and/or GnRH/GnRHa-stimulated LH to confirm failure before adjusting dose/formulation

Rec. 8: Summery of evidence

- In one study, 14.5% of patients on **leuprolide 3.75 mg/month** had biochemically inadequate suppression at 3 months — yet **none had clinical evidence of treatment failure**.

- By 1 year, all achieved biochemical suppression.

Rec.8: Justification for the recommendation

- Routine preemptive use of biochemical cutoffs, in the absence of clinical evidence of failure, could lead to **overtreatment**.

- A 4–6 month period of inadequate biochemical suppression is unlikely to significantly impact patient-important outcomes.

Recommendation 9:
No routine addition of growth hormone

- **Suggest against routine addition of growth hormone (GH) to GnRHa therapy to increase adult height (2 |⨁○○○).**

- This recommendation does *not* apply to children with CPP who also have a distinct, well-established indication for GH therapy.

Recommendation 9:
No routine addition of growth hormone

- A key aim of GnRHa treatment is to increase adult height ,However, linear growth commonly slows to well below a normal rate in children on GnRHa therapy and even arrests in some cases.

- So dilemma exists when that same therapy might prevent a child from interval height gains in the short term.

Recommendation 9:
No routine addition of growth hormone

- Therefore, the potential use of GH as adjunctive therapy in CPP has long been of interest.

- Given that GH therapy is an expensive and somewhat burdensome treatment, it is essential to determine whether it should be routinely recommended in the setting of CPP.

Rec.9: Summary of evidence

- **Meta-analysis of 8 retrospective cohort studies (1,024 girls, 276 receiving GH):**
- Combination GnRHa + GH therapy was associated with an estimated **–0.16 cm** (95% CI: –2.12, 1.81) difference in adult height vs. GnRHa alone — a **trivial difference**.

Rec.9: Summary of evidence

- All identified studies included girls only. **No data in boys**.
- Studies were retrospective with variable sample sizes and follow-up.
- Large-scale RCTs are needed.
- No relevant studies for cancer,adverse events, psychological effects or QOL.

Rec. 9: Subgroups that may warrant GH consideration

Possible Exceptions

- Patients with **extremely low PAH** (noting PAH is unreliable in CPP)
- Children with growth velocity **<4 cm/year** during GnRHa treatment where cessation is not appropriate
- Children with CPP who also have **approved GH indications** (GH deficiency, Prader-Willi, idiopathic short stature, SGA, SHOX defects)

Rec.9: Justification for the recommendation

- No meaningful height benefit + additional burden/cost + potential harms → balance disfavors routine GH addition.

Recommendation 10: When to stop GnRHa treatment?

- **Suggest against routinely continuing GnRHa beyond chronological age 10.0 to 11.0 years (girls) or 11.0 to 12.0 years (boys) and/or bone age 11.0 to 12.0 years (girls) or 12.0 to 13.0 years (boys)(2 |⊕OOO).**

- GnRH agonist continuation are highly individualized.

Recommendation 10: When to stop GnRHa treatment?

- Considerations relevant to the timing of treatment discontinuation include:
- Therapy duration / Growth velocity
- CA, BA , height
- Midparental target height
- Appropriate ages for menarche in girls
- Appropriate ages for virilization in boys
- Psychosocial maturity /neurocognitive impairment

Rec.10: Summery of evidence

- No direct studies comparing different ages of treatment cessation.
- Height outcomes appear more strongly related to pretreatment characteristics than exact stopping age.
- **Early CPP onset (<6 years)** yielded mean height gain of 10.8 cm vs. 7.2 cm for **later onset (6–8 years),** despite similar end-of-treatment characteristics.
- Earlier treatment tended to produce larger height gains.

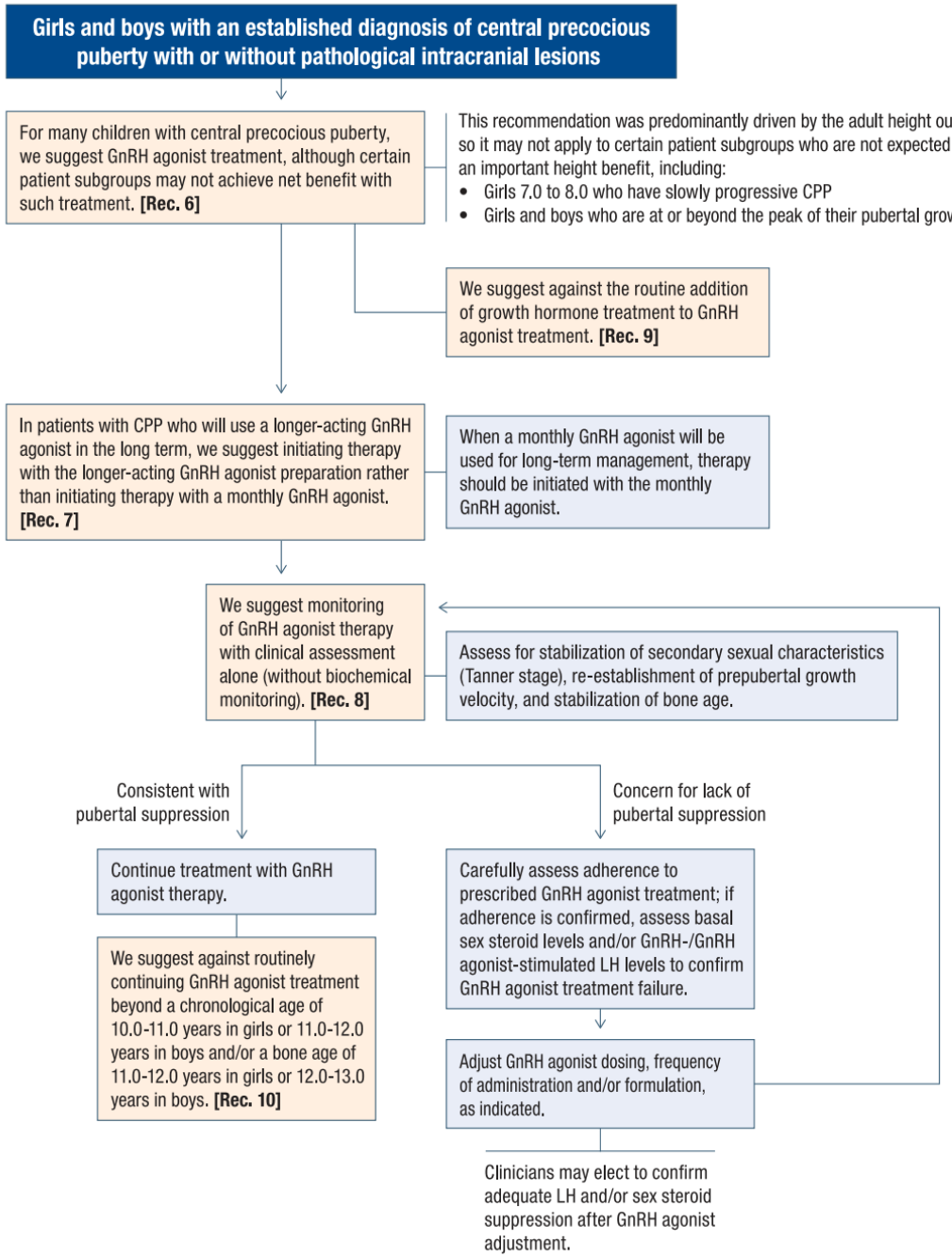
Rec.10: Summery of evidence

- Time to menarche after GnRHa discontinuation did not vary significantly with age at cessation (>11 vs. <11 years).
- **Menarche** occurs on average **12–18 months after** treatment cessation.

Rec.10:Justification for the recommendation

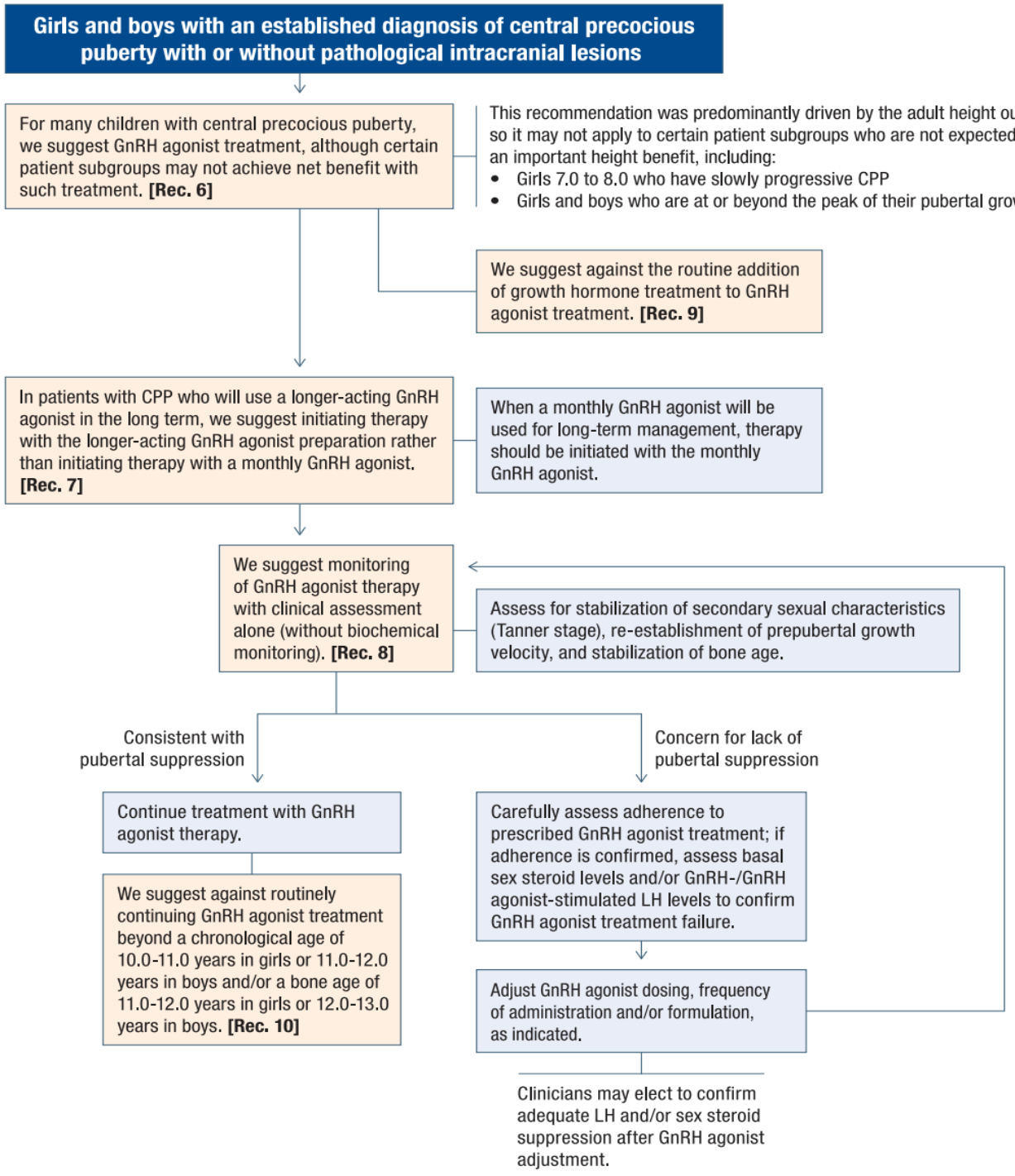
- No direct evidence establishes an optimal stopping age.
- Pretreatment characteristics are more important than exact cessation age.
- Therefore, routine continuation beyond the recommended CA/BA is discouraged, but individualized exceptions remain appropriate.

Girls	Boys
Chronological age **10.0–11.0 years** and/or bone age **11.0–12.0 years**	Chronological age **11.0–12.0 years** and/or bone age **12.0–13.0 years**



Treatment Algorithm Overview

Figure 2: Treatment algorithm for children with CPP. Tan boxes represent GRADE-developed recommendations (Rec. 6–10).


Girls and boys with an established diagnosis of central precocious puberty with or without pathological intracranial lesions
For many children with central precocious puberty, we suggest GnRH agonist treatment, although certain patient subgroups may not achieve net benefit with such treatment. [Rec. 6]
This recommendation was predominantly driven by the adult height outcome, so it may not apply to certain patient subgroups who are not expected to derive an important height benefit, including:
• Girls 7.0 to 8.0 who have slowly progressive CPP
• Girls and boys who are at or beyond the peak of their pubertal growth spurt
We suggest against the routine addition of growth hormone treatment to GnRH agonist treatment. [Rec. 9]
In patients with CPP who will use a longer-acting GnRH agonist in the long term, we suggest initiating therapy with the longer-acting GnRH agonist preparation rather than initiating therapy with a monthly GnRH agonist. [Rec. 7]
When a monthly GnRH agonist will be used for long-term management, therapy should be initiated with the monthly GnRH agonist.
We suggest monitoring of GnRH agonist therapy with clinical assessment alone (without biochemical monitoring). [Rec. 8]
Assess for stabilization of secondary sexual characteristics (Tanner stage), re-establishment of prepubertal growth velocity, and stabilization of bone age.
Consistent with pubertal suppression
Concern for lack of pubertal suppression
Continue treatment with GnRH agonist therapy.
We suggest against routinely continuing GnRH agonist treatment beyond a chronological age of 10.0-11.0 years in girls or 11.0-12.0 years in boys and/or a bone age of 11.0-12.0 years in girls or 12.0-13.0 years in boys. [Rec. 10]
Carefully assess adherence to prescribed GnRH agonist treatment; if adherence is confirmed, assess basal sex steroid levels and/or GnRH-/GnRH agonist-stimulated LH levels to confirm GnRH agonist treatment failure.
Adjust GnRH agonist dosing, frequency of administration and/or formulation, as indicated.
Clinicians may elect to confirm adequate LH and/or sex steroid suppression after GnRH agonist adjustment.


thank
you.