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Clinical Practice Guideline

Central precocious puberty: an Endocrine Society clinical practice guideline

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Abstract

Background **Central precocious puberty (CPP), which is traditionally defined as the development of secondary sexual characteristics before age 8 years in girls and age 9 years in boys, results from the premature activation of the hypothalamic–pituitary–gonadal (HPG) axis. CPP can be associated with short adult stature, adverse psychosocial outcomes, and increased cardiometabolic and cancer risks in adulthood. Gonadotropin-releasing hormone (GnRH) agonists can effectively suppress premature activation of the HPG axis and have the potential to increase adult height as well as improve psychosocial and long-term health outcomes among patients with CPP. However, as secular trends have continued to shift toward earlier age of pubertal onset, some subpopulations of children with CPP, as it is currently defined, may not require the same extent of diagnostic evaluation and treatment.**

Objective **Develop evidence-based recommendations related to the diagnosis and treatment of CPP.**

Methods **A multidisciplinary panel of clinical experts, along with experts in guideline methodology and systematic literature review, used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to address 10**

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clinical questions related to the diagnosis and treatment of CPP. Systematic reviews of health-related benefits and harms were conducted for each clinical question. The guideline development panel (GDP) also used the GRADE evidence-to-decision (EtD) framework to address stakeholder values and preferences, costs and required resources, cost-effectiveness, acceptability, feasibility, and potential impacts on health equity.

Results **In girls with thelarche (Tanner stage B2) between ages 7.0 and 8.0 years, the GDP suggests watchful waiting via periodic physical examinations (every 4-6 months) rather than immediately performing evaluation with laboratory testing or radiologic imaging. In addition, the GDP suggests that all girls with breast development (ie, Tanner stage B2) before age 7 years should first be observed for 4 to 6 months to differentiate unsustained or slowly progressive puberty vs rapidly progressive puberty. These recommendations are largely based on evidence that girls with slowly progressive puberty attain a normal adult height without treatment. When hormonal evaluation is performed to confirm central (GnRH-dependent) activation as the cause of precocious puberty, the GDP suggests starting the evaluation with ultrasensitive basal luteinizing hormone (LH) concentration rather than routine GnRH/GnRH agonist (GnRHa) stimulation testing for all patients. While brain magnetic resonance imaging has been a traditional part of CPP evaluation, the GDP suggests that it should not be routinely performed in girls ages 6.0 to 8.0 years and boys ages 8.0 to 9.0 years without central nervous system (eg, neuro-ophthalmologic) symptoms, largely based on a low prevalence of pathologic intracranial findings in these age groups. The GDP suggests against routine genetic testing for patients with CPP, although they judged that genetic testing (eg, *MKRN3* sequencing) should be considered for patients with familial CPP through a shared decision-making process. The GDP suggests GnRHa treatment for many children with CPP, although available evidence suggests that some patient subgroups (eg, older girls with slowly progressive CPP) may be less likely to receive a net benefit with this treatment. Rather than always starting GnRHa treatment with a monthly injectable formulation, the GDP suggests that treatment should be initiated with the formulation (such as a longer-acting formulation) that is anticipated to be used long-term. The GDP suggests against routine addition of growth hormone therapy to increase adult height. They also suggest against the routine biochemical testing (eg, LH, sex steroids) to monitor pubertal suppression while receiving GnRHa, instead reserving biochemical testing to confirm clinically suspected treatment failure. Finally, the GDP suggests against routinely continuing GnRHa treatment beyond chronologic 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).**

Conclusion **These clinical recommendations were developed to address important uncertainties in the diagnosis and treatment of children with CPP. They are based on the best available scientific evidence regarding clinical outcomes judged to be most important to patients and families. The GDP's overarching goal was to suggest diagnostic and therapeutic strategies that will most likely provide net clinical benefits while simultaneously considering important contextual factors such as cost and feasibility. The guideline-development process highlighted important knowledge gaps and the substantial need for additional research.**

Keywords precocious puberty, LH levels, brain MRI, genetic testing, GnRH agonists, adult height

Abbreviations: AUC, area under the (receiver operating characteristic) curve; BMI, body mass index; BA, bone age; BMD, bone mineral density; CGC, Clinical Guidelines Committee; CA, chronologic age; CI, confidence interval; CMIA, chemiluminescent microparticle immunoassay; CNS, central nervous system; CPP, central precocious puberty; DELFIA, dissociation-enhanced lanthanide fluorescent immunoassay; *DLK1*, delta-like non-canonical Notch ligand 1 gene; E2, estradiol; ECLIA, electrochemiluminescence immunoassay; EtD, Evidence to Decision; FDA, U.S. Food and Drug Administration; FSH, follicle-stimulating hormone; GDP, Guideline Development Panel; GH, growth hormone; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; GnRH, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone agonist; HPG, hypothalamic–pituitary–gonadal; ICMA, immunochemiluminometric assay; IFMA, immunofluorometric assay; IV, intravenous; LC-MS/MS, liquid chromatography–tandem mass spectrometry; LH, luteinizing hormone; *MECP2*, Methyl-CpG-binding protein 2 gene; *MKRN3*, Makorin ring finger protein 3 gene; MRI, magnetic resonance imaging; OR, odds ratio; PAH, predicted adult height; PP, precocious puberty; PT, premature thelarche; QOL, quality of life; RCT, randomized controlled trial; RP-PP, rapidly progressive precocious puberty; RR, relative risk; SD, standard deviation; SDS, standard deviation score; SP-PP, slowly progressive precocious puberty; T2DM, type 2 diabetes mellitus.

Central precocious puberty (CPP) results from the premature activation of the hypothalamic–pituitary–gonadal (HPG) axis—namely, early pulsatile gonadotropin-releasing hormone (GnRH) secretion, downstream gonadal sex steroid production, and development of associated secondary sexual characteristics. CPP is a neuroendocrine disorder with increasing incidence globally and is approximately 10 times more common in girls than boys (1). The incidence of CPP ranges from 0.2 to 26 per 10 000 girls per year and 0.02 to 0.9 per 10 000 boys per year (2). Clinically, CPP represents the onset of central (GnRH-dependent) puberty earlier than 2 to 2.5 standard deviations (SDs) below the mean age of pubertal onset, classically defined as earlier than age 8 years in girls and 9 years in boys based on the hallmark studies by Tanner and Marshall in the 1960s (3, 4). CPP is associated with early menarche in girls and the potential for decreased adult height in both sexes. In addition, CPP has been associated with an increased prevalence of psychiatric disorders, including conduct disorder in adolescence and in adulthood (5). Moreover, early age at menarche in the general population has been associated with a future increased risk of obesity, hypertension, type 2 diabetes mellitus (T2DM), ischemic heart disease, stroke, estrogen-dependent cancers, and cardiovascular mortality (6). In recent decades, cross-sectional data from the United States and Europe have suggested that pubertal milestones are being reached earlier than in prior decades, raising the possibility that the currently employed definition of CPP could be outdated (1, 7). Additionally, in some girls, puberty may be slowly progressive, with a longer duration between thelarche and menarche and achievement of a normal adult height, suggesting that not all patients with CPP, as it is currently defined, would benefit from aggressive clinical evaluation or treatment (1, 7).

In girls, puberty onset is defined clinically as the first appearance of breast development (ie, thelarche, Tanner B2), whereas achieving a testicular volume ≥4 mL or length >2.5 cm defines puberty onset in boys (8-11). Accelerated growth velocity and an advanced bone age (BA) may also be present (9, 10). A biochemical evaluation for gonadotropins and sex steroid concentrations is frequently used to differentiate central (GnRH-dependent) from peripheral (GnRH-independent) CPP, the latter of which is much rarer (7). Historically, this differential diagnosis has been clarified using GnRH (ie, synthetic GnRH) or GnRH agonist (GnRHa) stimulation testing for gonadotropins, but more recent evidence has suggested that basal (ie, nonstimulated) luteinizing hormone (LH) concentrations via ultrasensitive LH assays may provide similar diagnostic accuracy (10). The etiologies of CPP can be further stratified into congenital and acquired causes (2, 11), with or without central nervous system (CNS) pathology. Traditionally, brain magnetic resonance imaging (MRI) has been recommended to identify a tumor or other structural anomaly as the cause of CPP (10). Notably, the prevalence of such structural intracranial lesions has been reported to be much higher in boys than in girls with CPP and decreases after age 6 years in girls (10). However, newer case series of CPP patients have suggested a relative decrease in the overall prevalence of such pathology (12). Additionally, obtaining a brain MRI may result in the identification of incidental findings, which then require additional, expensive follow-up imaging (12). The recognition of genetic factors in the underlying mechanisms of CPP has grown significantly over the last decade, as demonstrated by the identification of monogenic causes (eg, loss-of-function mutations in the genes *MKRN3*, *DLK1*, and *MECP2*), especially in familial CPP (13, 14).

GnRHas have been established as the first-line treatment for CPP since the 1980s (15, 16). The use of GnRHas is associated with regression or stabilization of pubertal development, reduction of growth velocity, slowing of BA advancement, and preservation of adult height potential (17). Several GnRHas are currently available in various depot forms, and their approval for use and recommended doses in CPP vary across different countries (18). It remains unclear whether certain GnRHa formulations offer unique health-related advantages compared to other formulations and should be preferentially recommended to patients and families (18). In some cases, other adjunctive therapies, such as recombinant growth hormone (GH) therapy, may be used to augment adult height, but their use remains debated (19). In addition to clinical evaluation, biochemical testing (GnRH/GnRHa stimulation testing) has traditionally been used to monitor pubertal suppression, although it may represent an unnecessary use of resources (20). Finally, the optimal age to discontinue GnRHa treatment has not been formally established (10).

Therefore, the guideline development panel (GDP)'s primary goal was to create a new clinical guideline for CPP with a focus on diagnostic evaluation and treatment considerations. The GDP recognized the many important clinical questions regarding the diagnosis and management of CPP; however, due to limited resources, 10 of the most controversial clinical questions were prioritized, and 3 to 7 health-related outcomes were selected for each. Because patient-important clinical outcomes may differ by patient-specific factors such as age and sex, the GDP planned numerous subgroup analyses (eg, age <6 vs 6.0-8.0 years in girls, age <8 vs 8.0-9.0 years in boys) for a subset of the clinical questions; however, limitations in the available data precluded some of the panel's preplanned subgroup analyses.

To develop clinical recommendations, the GDP used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. A systematic review was conducted for each clinical question, revealing few randomized controlled trials (RCTs) and leaving the GDP to rely predominantly on observational studies and indirect evidence. The GDP also sought evidence relevant to all elements of the GRADE evidence-to-decision (EtD) framework, including stakeholder values and preferences (drawing on input from clinical experts and a patient parent representative), costs and other resources required, cost-effectiveness, acceptability, feasibility, and potential impact on health equity. However, the GDP did not identify high-quality evidence addressing these important EtD factors.

List of recommendations

The following recommendations have been contextualized in 2 proposed clinical algorithms, 1 related to diagnosis (Fig. 1; recommendations 1-5) and 1 related to treatment (Fig. 2; recommendations 6-10).

Question 1

Should additional evaluation be performed (and treatment when indicated) vs no additional evaluation (and, therefore, no treatment) in girls who present with thelarche between ages 7.0 and 8.0 years?

Recommendation 1

In girls who present with thelarche (Tanner B2) between ages 7.0 and 8.0 years, we suggest watchful waiting via periodic physical examinations rather than immediately performing evaluation with laboratory testing and/or radiologic imaging. (2 | ⊕OOO)

Technical remarks:

- Thelarche is defined as Tanner B2 (ie, Tanner stage II) breast development and should be distinguished from lipomastia (ie, the accumulation of fatty tissue) on physical exam by palpation in girls with overweight or obesity.
- In this context, "additional evaluation" means laboratory testing (eg, serum LH and sex steroid concentrations) and a bone age assessment (ie, hand and wrist radiography), with subsequent evaluation (eg, GnRH/GnRH agonist stimulation test) performed when indicated.
- In this context, "watchful waiting" means conducting periodic physical examinations (every 4-6 months), including reassessment of growth and Tanner staging, to identify rapid growth and pubertal progression to Tanner B3 or greater.
- The panel judged that immediate additional diagnostic evaluation would be appropriate for girls younger than 8 years who present with Tanner B3 or higher, who

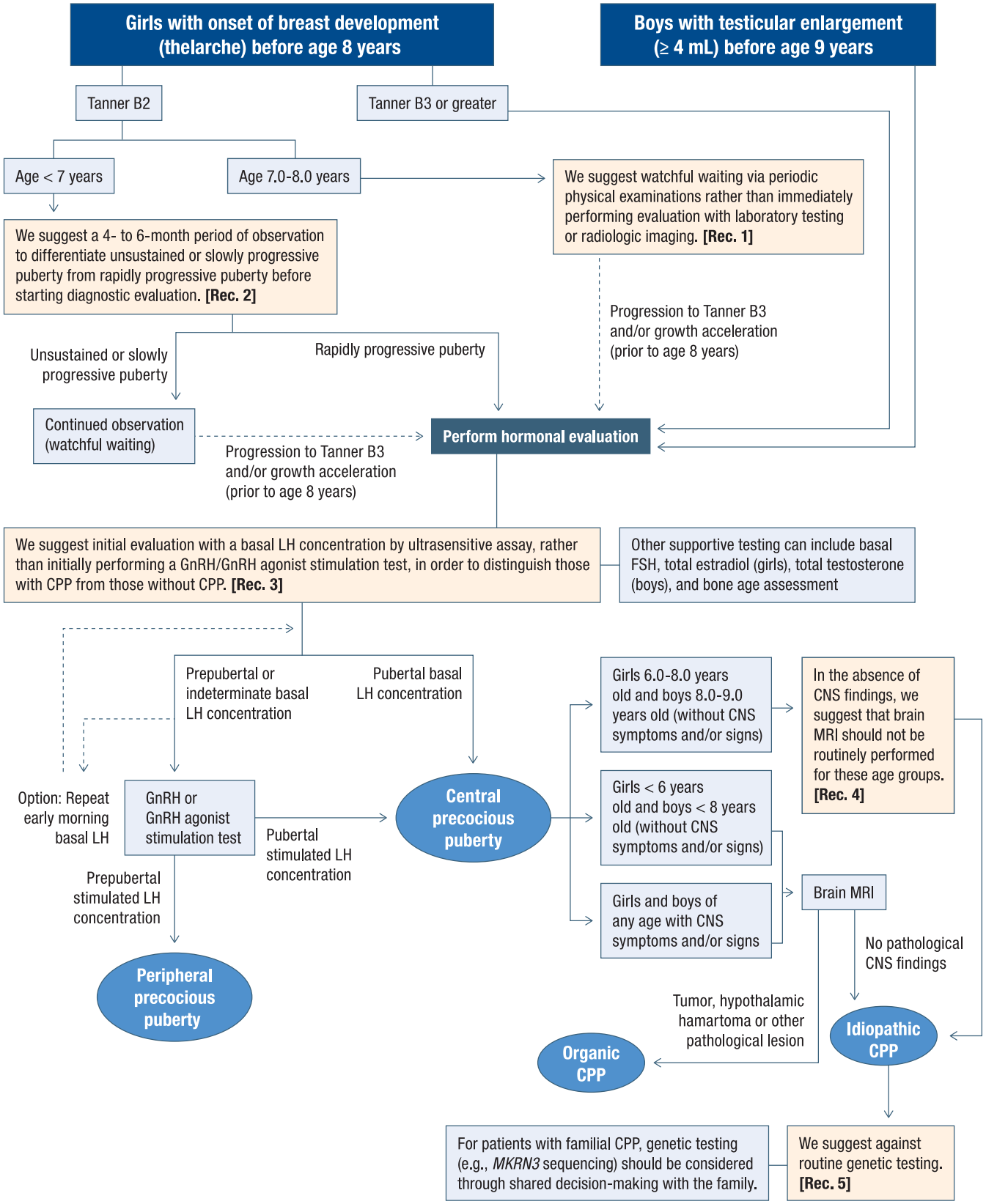

Figure 1 Assessment of children with premature development of secondary sexual characteristics. Recommendations within tan boxes were rigorously developed by the guideline-development panel using GRADE. Other facets of the algorithm were considered by the panel to be acceptable approaches but were not rigorously assessed using GRADE.

Abbreviations: CPP, central precocious puberty; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; *MKRN3*, Makorin ring finger protein 3 gene; MRI, magnetic resonance imaging; Rec., recommendation.

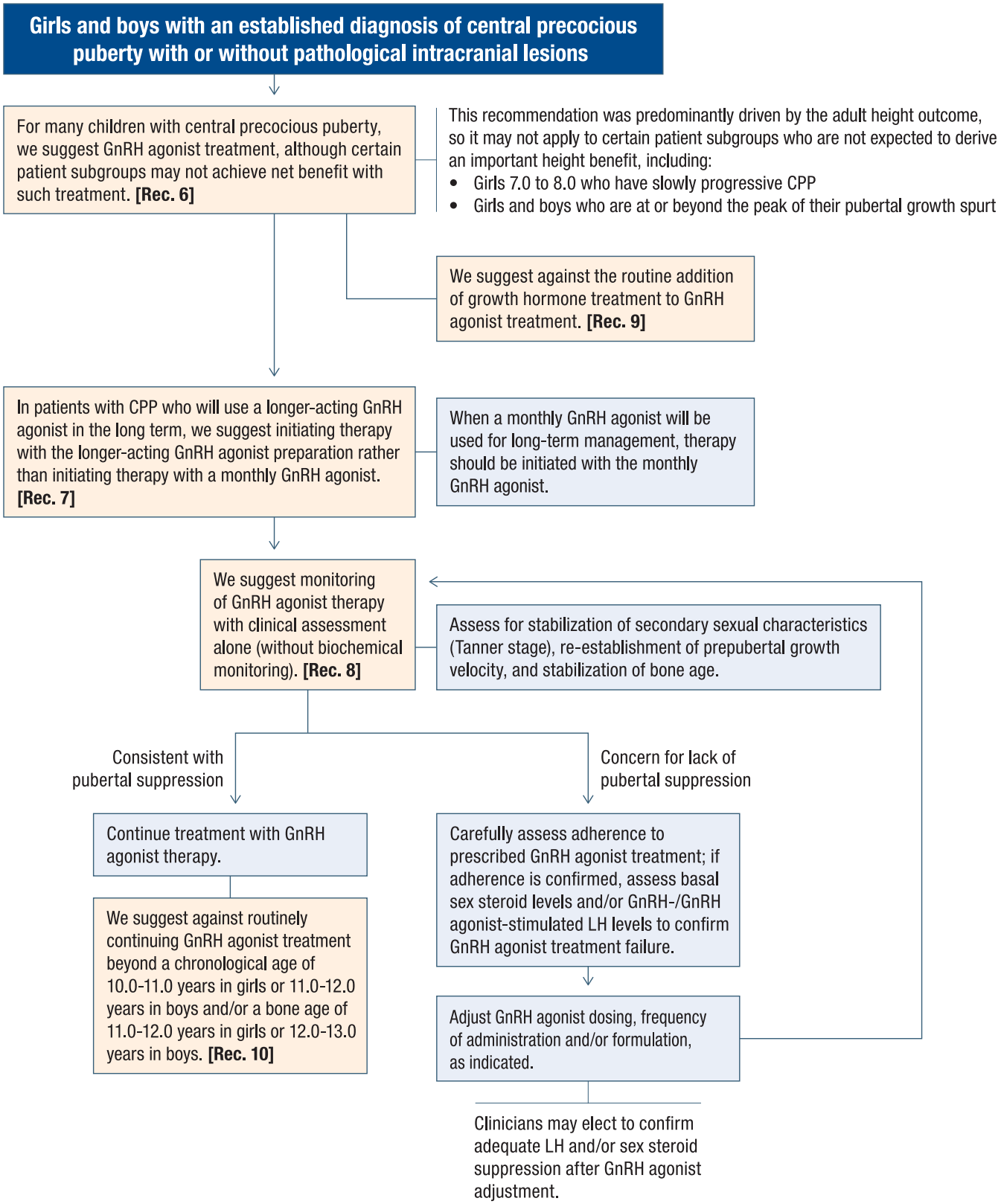

Figure 2 Treatment of children with central precocious puberty. Recommendations within tan boxes were rigorously developed by the guideline-development panel using GRADE. Other facets of the algorithm were considered by the panel to be acceptable approaches but were not rigorously assessed using GRADE. Abbreviations: CPP, central precocious puberty; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; Rec., recommendation.

progress to Tanner B3 under observation, and/or who have documented growth acceleration (ie, increasing height percentiles, pubertal growth velocity >6 cm/year).
- This recommendation does not apply to girls with early thelarche who also exhibit CNS findings (eg, headaches, seizures, and/or visual field deficits). The guideline-development panel assumed that such girls should be promptly evaluated by a pediatric endocrinologist and other appropriate specialists.
- This recommendation is not intended to discourage primary care providers from referring these patients to pediatric endocrinologists as needed.

Question 2

Should a period of observation vs no period of observation be used to differentiate unsustained or slowly progressive puberty from rapidly progressive puberty for girls with early initial breast development (Tanner B2) before starting diagnostic evaluation?

Recommendation 2

In girls younger than age 7 years with initial breast development (Tanner B2), 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. (2 | ⊕OOO)

Technical remarks:

- "A period of observation" refers to periodic physical examinations (ie, reassessment of growth velocity and Tanner staging) every 4 to 6 months.
- The panel judged that immediate additional diagnostic evaluation would be appropriate for girls younger than 7 years who present with Tanner B3 or higher, who progress to Tanner B3 before age 8 years, and/or have documented growth acceleration (ie, increasing height percentiles, pubertal growth velocity >6 cm/year). Rapid progression can be defined by progression to B3 within 6 months of the onset of thelarche.
- This recommendation does not apply to girls with early thelarche who also exhibit CNS findings (eg, headaches, seizures, and/or visual field deficits). The guideline-development panel assumed that such girls should be promptly evaluated by a pediatric endocrinologist and other appropriate specialists.

Question 3

Should a staged approach starting with basal serum LH concentration by ultrasensitive assay, with subsequent GnRH/GnRH agonist-stimulated LH concentrations only in the setting of low basal LH concentration, be utilized vs initial evaluation with GnRH/GnRH agonist-stimulated LH concentrations in all patients to diagnose CPP?

Recommendation 3

In girls and boys with evidence of precocious puberty, we suggest an initial evaluation with a basal luteinizing hormone concentration by ultrasensitive assay, rather than initially performing a gonadotropin-releasing hormone/gonadotropin-releasing hormone agonist stimulation test, in order to distinguish those with central precocious puberty from those without. (2 | ⊕OOO)

Technical remarks:

- An ultrasensitive LH assay should reliably detect very low LH concentrations (eg, <0.05-0.1 IU/L).
- While first morning (8:00-10:00 AM) basal LH testing may be optimal, especially in early puberty, the guideline-development panel judged that it is acceptable to measure basal LH at any time of the day.
- When ultrasensitive basal LH concentrations are low in the presence of clinical evidence of precocious puberty, a GnRH/GnRH agonist stimulation test would generally be the next step in diagnostic evaluation, particularly when the index of suspicion for CPP is high and/or when a rapid diagnosis is needed (eg, in the setting of rapidly progressive puberty). Otherwise, another option is to repeat an ultrasensitive basal LH concentration, preferably in the early morning (8:00-10:00 AM).

Question 4

Should brain MRI vs no brain MRI be used for assessing the presence of a congenital or acquired intracranial etiology of CPP in girls (ages 6.0-8.0 years) and boys (ages 8.0-9.0 years) with no CNS symptoms?

Recommendation 4

In girls ages 6.0 to 8.0 years and boys ages 8.0 to 9.0 years with central precocious puberty and without central nervous system findings, we suggest that brain MRI should not be routinely performed. (2 | ⊕OOO)

Technical remarks:

- This recommendation does not apply to younger patients or to patients of any age who present with CNS findings (eg, headaches, seizures, and/or visual field deficits).

Question 5

Should genetic testing (eg, to identify loss-of-function mutations in *MKRN3*, *DLK1*, and/or *MECP2*) vs no genetic testing be used for children with CPP?

Recommendation 5

For children with central precocious puberty, we suggest against routine genetic testing (eg, to identify loss-of-function mutations in *MKRN3*, *DLK1*, and/or *MECP2*). (2 | ⊕OOO)

Technical remarks:

- This recommendation relates to targeted genetic testing (including genes such as *MKRN3*, *DLK1*, and/or *MECP2*) as opposed to unbiased genomic sequencing.
- In patients with familial CPP, genetic testing should be considered based on shared decision-making with the family.

Question 6

Should treatment with GnRH agonists vs no treatment with GnRH agonists be used for the management of CPP?

Recommendation 6

For many children with central precocious puberty, we suggest gonadotropin-releasing hormone agonist treatment, although certain patient subgroups may not achieve net benefit with such treatment. (2 | ⊕OOO)

Technical remarks:

- Because this recommendation was predominantly driven by the adult height outcome, it may not apply to certain patient subgroups who are not expected to derive an important height benefit, including:
  - Girls ages 7.0 to 8.0 years who have slowly progressive CPP.
  - Girls and boys who are at or beyond the peak of their pubertal growth spurt (this will be concordant with their bone age assessment).
- 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 guideline-development panel emphasizes the importance of shared-decision making for all patients with CPP, which should include a careful weighing of anticipated benefits and potential harms of GnRH agonist use in the context of each patient's clinical presentation, patient/caretaker values, etc.

Question 7

Should initiating therapy with monthly GnRH agonists vs long-acting GnRH agonist preparations be used for CPP treatment?

Recommendation 7

In patients with central precocious puberty who will use a long-acting gonadotropin-releasing hormone agonist in the long term, we suggest initiating therapy with the long-acting gonadotropin-releasing hormone agonist preparation rather than initiating therapy with a monthly gonadotropin-releasing hormone agonist. (2 | ⊕⊕OO)

Technical remarks:

- Long-acting GnRH agonist preparations refer to those with ≥3-month duration of action (eg, 3-month and 6-month injectable formulations and the 12-month subcutaneous implant).
- Patients and families who anticipate using monthly GnRH agonist preparations in the long term should begin with a monthly GnRH agonist preparation.

Question 8

Should biochemical testing (eg, LH, sex steroids) vs clinical assessment alone be used for monitoring pubertal suppression in those being treated for CPP with GnRH agonists?

Recommendation 8

In children being treated for central precocious puberty with a gonadotropin-releasing hormone agonist, we suggest against routine biochemical testing (eg, luteinizing hormone and sex steroid concentrations) to monitor pubertal suppression. (2 | ⊕OOO)

Technical remarks:

- The guideline-development panel assumed that interval clinical assessment and monitoring (eg, growth velocity, Tanner staging, and annual bone age assessments) would be performed routinely for all children with CPP receiving GnRH agonist treatment.
- This recommendation pertains specifically to children without clinical evidence to suggest GnRH agonist treatment failure. Evidence of potential treatment failure may include progression in breast development or testicular size, acceleration in growth velocity, and/or persistent pubertal growth velocity.
- The guideline-development panel emphasized the importance of assessing GnRH agonist treatment adherence and administration technique in all patients with concern for treatment failure.
- The panel assumed that most pediatric endocrinologists would perform biochemical testing when treatment failure is suspected clinically, before implementing changes in the dose, duration, and/or formulation of GnRH agonist therapy.

Question 9

Should growth hormone plus GnRH agonist therapy vs GnRH agonist therapy alone be used to increase adult height in children treated for CPP?

Recommendation 9

In children with central precocious puberty, we suggest against the routine addition of growth hormone to gonadotropin-releasing hormone agonist therapy. (2 | ⊕OOO)

Technical remarks:

- This recommendation does not pertain to children with CPP who also have a distinct, well-established indication for growth hormone therapy.

Question 10

Should continuation of GnRH agonist treatment vs discontinuation of GnRH agonist treatment be used for children with CPP who reach a chronological age of 10 years (girls) or 11 years (boys) or a bone age of 11 years (girls) or 12 years (boys)?

Recommendation 10

In children being treated for central precocious puberty, we suggest against routinely continuing gonadotropin-releasing hormone agonist treatment beyond chronological age 10.0 to 11.0 years (girls) or 11.0 to 12.0 years (boys) and/or bone age 11.0-12.0 years (girls) or 12.0-13.0 years (boys). (2 | ⊕OOO)

Technical remarks:

- The potential reasons to consider GnRH agonist continuation beyond these recommended ages are highly individualized and may relate to growth trajectory, psychosocial considerations, and/or neurocognitive impairment (eg, developmental delay).

Methods of development of evidence-based clinical practice guidelines

This guideline was developed using the process detailed on the Endocrine Society website (https://www.endocrine.org/clinical-practice-guidelines/methodology) and summarized here. The Endocrine Society follows the GRADE methodology, which includes EtD frameworks to help ensure that all important health-related and contextual factors are considered when making recommendations (21, 22). The GRADE classifications for certainty of evidence and strength of recommendations can be found in Tables 1 and 2. The guideline development process was facilitated by the GRADEpro Guideline Development Tool (GRADEpro GDT); see https://www.gradepro.org/.

Table 1 GRADE certainty of evidence classifications

Certainty of evidence	Interpretation
High ⊕⊕⊕⊕	Confidence is high that the true value of the estimate of interest is on one side of a threshold of interest or within a specific range.
Moderate ⊕⊕⊕O	Confidence is moderate that the true value of the estimate of interest is on one side of a threshold of interest or within a certain range. The true value of the estimate may deviate slightly from the target of the certainty rating (ie, may possibly fall in a different range).
Low ⊕⊕OO	Confidence is low that the true value of the estimate of interest is on one side of a threshold of interest or within a certain range. The true value of the estimate may deviate from the target of the certainty rating (ie, likely fall in a different range).
Very Low ⊕OOO	Confidence is very low that the true value of the estimate of interest is on one side of a threshold of interest or within a certain range. The true value of the estimate may deviate significantly from target of the certainty rating (ie, probably fall in a different range).

Adapted with permission from Neumann and Schünemann, eds. The GRADE Book (Version 1.0). The GRADE Working Group; updated 2024 (23).

The GDP consisted of experts in pediatric endocrinology, pharmacy, and general pediatrics. A parent representative of a child with CPP from the United States was also included. Members were identified by the Endocrine Society Board of Directors and the Clinical Guidelines Committee (CGC) and were vetted according to the Endocrine Society's conflict-of-interest policy, which was adhered to throughout the guideline process to manage and mitigate potential conflicts of interest (25, 26). Detailed disclosures of GDP members and the management strategies implemented during the guideline-development process can be found in Appendix A. In addition, the GDP included a clinical practice guideline methodologist from the Mayo Evidence-Based Practice Center, who led the team that conducted the systematic reviews and meta-analyses, and a methodologist from the Endocrine Society, who guided clinical question development, outcome prioritization, development and application of EtD frameworks, and development of recommendations.

The primary goal of the GDP was to provide recommendations for the care of individuals with CPP. The GDP identified many important clinical questions regarding the identification and

Table 2 GRADE strength of recommendation classifications and interpretation

Strength of recommendation	Criteria	Interpretation by individuals	Interpretation by health care clinicians	Interpretation by policy makers
1: Strong recommendation for or against	Desirable consequences CLEARLY OUTWEIGH the undesirable consequences in most settings (or vice versa).	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
2: Conditional recommendation for or against	Desirable consequences PROBABLY OUTWEIGH undesirable consequences in most settings (or vice versa).	Most individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping individuals make decisions consistent with their individual risks, values, and preferences.	Clinicians should recognize that different choices will be appropriate for different individuals and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences.	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate.

Reprinted from Schünemann HJ et al. *Blood Adv,* 2018; 2(22):3198-3225. © The American Society of Hematology, published by Elsevier (24).

treatment of CPP, and 10 of these questions were prioritized for this guideline. For each clinical question, the Mayo Evidence-Based Practice Center conducted a systematic review and produced GRADE evidence profiles that summarized the body of evidence and the certainty of the evidence (27). The systematic searches for evidence were conducted in February 2025 and updated in January 2026. Additionally, for each clinical question, a group of 2 to 3 GDP members were assigned to lead the interpretation of the respective systematic review as well as identify evidence for the EtD framework criteria, which include stakeholder values and preferences, cost and resources required, cost-effectiveness, feasibility, acceptability, and the potential impact on health equity. Research evidence summaries in the EtD frameworks were guided by standardized terminology templates, designed to enhance clarity and consistency (28). During an in-person GDP meeting and a series of video conferences, the GDP judged the balance of benefits and harms, in addition to the other EtD criteria, to determine the direction and strength of each recommendation (29, 30).

The draft recommendations were posted publicly for external peer review and internally for Endocrine Society members, and the draft guideline manuscript was reviewed by the Society's CGC, representatives of co-sponsoring organizations, a representative of the Society's Board of Directors, and an Expert Reviewer. Revisions to the guideline were made based on submitted comments and approved by the CGC, the Expert Reviewer, and the Board of Directors. Finally, the guideline manuscript was reviewed before publication by the *Journal of Clinical Endocrinology and Metabolism's* publisher's reviewer.

This guideline will be reviewed annually to assess the state of the evidence and determine if any recent developments warrant updates to the guideline.

Evaluation in girls who present with thelarche between ages 7.0 and 8.0 Years

Background

The increasing incidence of thelarche occurring between ages 7.0 and 8.0 years has been confirmed in numerous epidemiologic investigations (1, 31). However, it remains unclear whether thelarche between ages 7.0 and 8.0 years should always be considered abnormal, or whether it may be a variant of normal pubertal timing in some individuals, in light of the decreasing age of thelarche and menarche in the general population (7).

When precocious puberty (PP) in girls is classically defined as thelarche before age 8 years, many girls ages 7.0 to 8.0 years will be subjected to a comprehensive diagnostic evaluation. However, the value of establishing a diagnosis of CPP in this subgroup, which would also likely encourage treatment, remains unknown. Although CPP may be associated with reduced adult height, and some studies have assessed a potential link between early thelarche and undesirable long-term outcomes such as breast cancer (8, 32, 33), the potential impact of treatment on such outcomes remains unclear, especially in this age group.

Question 1

Should additional evaluation be performed (and treatment when indicated) vs no additional evaluation (and, therefore, no treatment) in girls who present with thelarche between ages 7.0 and 8.0 years?

Recommendation 1

In girls who present with thelarche (Tanner B2) between ages 7.0 and 8.0 years, we suggest watchful waiting via periodic physical examinations rather than immediately performing evaluation with laboratory testing and/or radiologic imaging. (2 | ⊕OOO)

Technical remarks:

- Thelarche is defined as Tanner B2 (ie, Tanner stage II) breast development and should be distinguished from lipomastia (ie, the accumulation of fatty tissue) on physical exam by palpation in girls with overweight or obesity.
- In this context, "additional evaluation" means laboratory testing (eg, serum LH and sex steroid concentrations) and a bone age assessment (ie, hand and wrist radiography), with subsequent evaluation (eg, GnRH/GnRH agonist stimulation test) performed when indicated.
- In this context, "watchful waiting" means conducting periodic physical examinations (every 4-6 months), including reassessment of growth and Tanner staging, to identify rapid growth and pubertal progression to Tanner B3 or greater.
- The panel judged that immediate additional diagnostic evaluation would be appropriate for girls younger than 8 years who present with Tanner B3 or higher, who progress to Tanner B3 under observation, and/or who have documented growth acceleration (ie, increasing height percentiles, pubertal growth velocity >6 cm/year).
- This recommendation does not apply to girls with early thelarche who also exhibit CNS findings (eg, headaches, seizures, and/or visual field deficits). The guideline-development panel assumed that such girls should be promptly evaluated by a pediatric endocrinologist and other appropriate specialists.
- This recommendation is not intended to discourage primary care providers from referring these patients to pediatric endocrinologists as needed.

Summary of evidence

The systematic review results, a detailed summary of the evidence, and EtD tables can be found online at https://guidelines.gradepro.org/profile/tLf_A0WTtKI.

Benefits and harms

Health-related outcomes prioritized by the GDP were adult height, psychological distress, missed pathologic intracranial abnormalities, timing of menarche, and long-term health risks (including cardiovascular events and estrogen-dependent cancers, such as endometrial, ovarian, and breast cancers). The commissioned systematic review identified no studies comparing the selected outcomes of patients who received evaluation vs those who were managed with observation alone (27). However, the commissioned systematic review initially identified 20 uncontrolled single-arm series (4211 patients) that reported on patients with premature thelarche (PT), including the natural history, rates of progression and regression, and risk factors for progressing to CPP (34-54). The presenting ages ranged from birth to 8 years old, with most cases presenting at younger than age 2 years in approximately half of the studies (27). As the studies related to infantile thelarche were not deemed relevant for this question, the systematic review team narrowed its synthesis to 12 uncontrolled single-arm series (1335 patients) that reported on the natural history of PT among girls ages 3 to 8 years (34, 36-38, 42, 45, 46, 49, 50, 52-54). In these studies, the rates of PT regression ranged from 13% to 70%, and the rates of progression to CPP ranged from 0% to 31%. The systematic review team was unable to identify evidence exclusive to girls ages 7.0 to 8.0 years.

While plausible desirable effects of evaluating (and subsequently treating) girls with thelarche between ages 7.0 and 8.0 years include prevention of early menarche and increased adult stature, the GDP identified no evidence to support these suppositions. However, a different commissioned systematic review (see clinical question 6) suggested that, even in the setting of confirmed CPP, the impact of GnRHas on adult height appears to be greatest when initiated at younger ages.

As for long-term outcomes, only 1 study, the population-based Rochester Epidemiology Study, suggested that among girls identified as having PT between ages 6 months and 8 years, none had subsequent breast or gynecologic cancer or autoimmune disease, and all attained normal adult height (155-173 cm), but these results include younger girls (ie, with PT in early childhood) (49). Overall, the GDP judged that evidence is currently insufficient to estimate the health benefits of evaluation, with subsequent treatment as indicated, in this specific patient population.

The commissioned systematic review did not identify evidence related to harms of evaluation. The GDP considered that potential harms could include increased psychological distress and adverse events related to radiologic evaluation. The GDP also considered the negative health effects related to incidental findings (eg, if a brain MRI is ultimately performed). Of note, a different commissioned systematic review (see clinical question 4) suggested that pathologic intracranial findings are rare in girls with thelarche between ages 6.0 and 8.0 years. The GDP also considered that, although generally safe, GnRHa treatment can cause some degree of pain and distress and can rarely cause adverse medication events such as sterile abscesses. Overall, the GDP considered the undesirable health effects of evaluation, with subsequent treatment as indicated, to be small but important.

Other evidence-to-decision criteria and considerations

As with other clinical questions, the outcomes of interest were primarily prioritized based on GDP members' extensive experience with patients and parents. However, the GDP recognized

that individual patients and parents may value the selected outcomes differently.

The GDP did not identify systematic reviews related to resources and costs required, cost-effectiveness, feasibility, or acceptability. Resources required for the investigation of thelarche, and subsequent treatment if confirmed to represent CPP, can be substantial, although this is context-dependent (eg, by specific country and health system) (55). Total costs will depend in part on the extent of evaluation. For example, medical visits are relatively inexpensive, while basal or stimulated hormone testing, bone age assessment, pelvic ultrasound, and brain MRI are more expensive. For countries like the United States, prior insurance authorization might increase work and time requirements for health care workers, in addition to stress for the parents and health care workers. Treatment with GnRHas and follow-up would further increase costs. In general, the intervention (ie, evaluation with treatment as indicated) for all girls who present with thelarche between ages 7.0 and 8.0 years would require more resources and cost more than watchful waiting. Cost-effectiveness would presumably depend on numerous factors that are currently not well defined and may vary by both patient characteristics and context, including the extent of necessary evaluation, the costs of evaluation and any subsequent treatment, the net benefits of evaluation with subsequent treatment, and potential cost savings realized by evaluation and subsequent treatment.

Based on their experience and expertise, the GDP judged that most clinicians would consider it acceptable to evaluate patients with thelarche between ages 7.0 and 8.0 years, but they may be less inclined to perform laboratory testing and imaging (eg, brain MRI, which may require sedation and could be difficult to arrange in some contexts). Indeed, as the number of girls in this clinical situation has increased over time, the acceptability of such evaluations could decrease over time. Also, based on their experience and expertise, the GDP judged that most clinicians would find treatment acceptable if it might prevent short adult stature and/or alleviate psychological distress. The GDP recognized that patient and family perspectives vary significantly, which may affect intervention acceptability. Parents who are anxious about the impact of early puberty are likely to find evaluation and treatment acceptable, assuming that important health benefits can be expected. However, the potentially high costs of evaluation and treatment could reduce acceptability for some.

Based on the GDP's experience and expertise, evaluation of these patients is feasible in many, but not all, contexts. Feasibility of radiologic imaging, for example, is expected to be lower in underresourced contexts. Feasibility of the more expensive components of evaluation may depend on the type of health care model and insurance status. In addition, the high costs of GnRHa treatment (see clinical question 6) may limit practical feasibility in some contexts. The GDP also noted that some primary care providers may lack the expertise to perform careful clinical evaluation and accurately interpret the results. However, the current shortage of pediatric endocrinologists may make it difficult to accommodate additional evaluation for all girls with thelarche at ages 7.0 to 8.0 years (56).

Lower childhood socioeconomic status is associated with a higher risk for early puberty (57). The GDP considered that the avoidance of unnecessary healthcare costs has the potential to increase health equity. If evaluation with subsequent treatment provides a net health benefit in patients with low baseline health equity, a recommendation for evaluation could plausibly reduce health inequity. On the other hand, if the intervention provides material net benefits to patients, but patients and families with lower baseline health equity do not have ready access to evaluation and subsequent treatments, the intervention could exacerbate health inequities.

Justification for the recommendation

The GDP judged that evidence is currently insufficient to estimate the benefits of evaluation (with GnRHa treatment in the setting of confirmed CPP) in 7.0- to 8.0-year-old girls presenting with thelarche (Tanner B2). The commissioned systematic review did not identify studies that directly compared the intervention (ie, evaluation and treatment of girls as indicated) with the comparator (ie, no evaluation and therefore no treatment). However, indirect evidence identified by the systematic review team suggested that, in many cases, breast development in girls with PT will not progress quickly or will regress. The GDP also noted that apparent thelarche may sometimes be lipomastia. Evidence reviewed for different clinical questions suggested that (1) missed pathologic intracranial abnormalities would be very rare in this clinical scenario and (2), even in the setting of CPP, the impact of GnRHas on adult height appears to be greatest when initiated at younger ages. The GDP also considered the potential harms related to evaluation (eg, psychological distress) and GnRHa treatment (eg, pain and psychological distress with injections). Altogether, the GDP judged that the undesirable consequences of the intervention, and evaluation with treatment when indicated, are small but important. Overall, the GDP reached consensus that available evidence probably favors the comparator (ie, no additional evaluation), recognizing that certainty of the evidence is very low. The GDP also considered the costs of evaluation and GnRHa treatments, secular trends in thelarche timing (ie, increased prevalence of thelarche in this age range could substantially change the statistical distribution of pubertal onset in the general population), that some primary care clinicians lack the expertise to assess breast development, and the current shortages of pediatric endocrinologists in some geographic areas (56, 58). For all of these reasons, the GDP issued a conditional recommendation against routine evaluation beyond watchful waiting with periodic physical examinations (every 4-6 months) in girls who present with thelarche (Tanner B2) between ages 7.0 and 8.0 years.

Additional considerations

An inability to reliably conduct watchful waiting (eg, anticipated travel difficulties, scheduling constraints, or other limitations that may make timely follow-up less feasible) may be a reason to immediately perform diagnostic evaluation.

This recommendation is not intended to apply to patients with precocious puberty and features suggesting other underlying conditions such as congenital adrenal hyperplasia (eg, hyperandrogenism) and McCune-Albright syndrome (eg, cafe au lait spots). The GDP assumed that immediate diagnostic evaluation is prudent in such girls.

In this recommendation, "additional evaluation" included both laboratory testing and a bone age assessment. However, the GDP

allows for the possibility that, in some cases, a BA assessment may provide useful information and could be obtained as an initial evaluation without concomitant hormonal testing.

When watchful waiting is advised, it is prudent to educate families about pubertal progression and expected timing (eg, menarche typically occurs 18 months to 3 years after thelarche). This counseling may help alleviate anxiety families potentially experience associated with the timing of menarche.

Research considerations

Studies are needed to define the rates of rapid pubertal progression among girls with thelarche between ages 7.0 and 8.0 years, in addition to the relationships between thelarche at these ages and patient-important outcomes such as the age at menarche and adult height.

Observation period for girls with early thelarche

Background

The presentation and progression of CPP in girls can vary, and not all cases necessarily require the same evaluation and management. For example, several studies suggest that girls with early puberty that progresses slowly may do well without treatment (59, 60). A potential benefit of an initial period of observation, rather than immediate evaluation and treatment, is that the development of thelarche does not always indicate CPP. For example, transient, low concentrations of estrogen secreted from ovarian follicles in prepubertal girls is a common cause of thelarche that is self-limited and resolves spontaneously (61, 62). Other putative causes of transient thelarche include exogenous estrogen exposure, endocrine-disrupting chemicals, and aromatization of adrenal androgens (62, 63). In addition, in girls with overweight or obesity, it is often difficult to distinguish true thelarche from lipomastia. Therefore, an initial period of observation may allow differentiation between girls who have transient thelarche or a slowly progressing form of central puberty that may not require treatment vs those with true CPP who have a rapid pubertal tempo and may therefore be more likely to benefit from GnRHa treatment.

Question 2

Should a period of observation vs no period of observation be used to differentiate unsustained or slowly progressive puberty from rapidly progressive puberty for girls with early initial breast development (Tanner B2) before starting diagnostic evaluation?

Recommendation 2

In girls younger than age 7 years with initial breast development (Tanner B2), 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. (2 | ⊕OOO)

Technical remarks:

- "A period of observation" refers to periodic physical examinations (ie, reassessment of growth velocity and Tanner staging) every 4 to 6 months.
- The panel judged that immediate additional diagnostic evaluation would be appropriate for girls younger than 7 years who present with Tanner B3 or higher, who progress to Tanner B3 before age 8 years, and/or have documented growth acceleration (ie, increasing height percentiles, pubertal growth velocity >6 cm/year). Rapid progression can be defined by progression to B3 within 6 months of the onset of thelarche.
- This recommendation does not apply to girls with early thelarche who also exhibit CNS findings (eg, headaches, seizures, and/or visual field deficits). The guideline-development panel assumed that such girls should be promptly evaluated by a pediatric endocrinologist and other appropriate specialists.

Summary of evidence

The systematic review results, a detailed summary of the evidence, and EtD tables can be found online at https://guidelines.gradepro.org/profile/SpTZtBLNP5I.

Benefits and harms

The outcomes felt to be most important for decision-making by the GDP were psychological distress, adult height, adverse events related to radiologic imaging, missed pathologic intracranial abnormalities, consequences related to incidental findings on CNS imaging, and adverse medication events related to GnRHa treatment.

The commissioned systematic review did not identify studies directly comparing an initial period of observation vs no period of observation among girls with early, isolated breast development (Tanner B2) (27). However, the review identified 11 case series published from 1992 to 2023 that mentioned slowly progressive or unsustained PP (59, 60, 64-72). Seven of the 11 studies were small (n = 18-62 girls), although 4 of the 11 studies were larger (n = 121-212 patients). Most studies were retrospective, and different studies used varied methods of patient selection and definitions of slowly progressive PP (SP-PP) vs rapidly progressive PP (RP-PP). In some studies, the latter was described as the advancement of more than 1 Tanner stage within 6 months (66). Several studies evaluated factors that might be predictive of RP-PP including BA advancement, serum LH and estradiol concentrations, and uterine and ovarian size on pelvic ultrasound (64, 69, 71, 72). Several studies also assessed adult height during long-term follow-up (59, 60, 67). Notably, the weighted average of reported mean ages among these 11 studies was approximately 7.2 years. Four of 11 studies (n = 552) only included girls older than 6 years. While 7 of the 11 studies (n = 601) included patients younger than 6 years, the weighted average of reported mean ages among these 7 studies was approximately 6.8 years.

Overall, the proportion of patients with RP-PP in these studies ranged from 33% to 66%. One of the earliest studies described a

group of 20 girls with thelarche at a mean age of 6.1 years who had biochemical evidence of CPP but did not receive treatment (59). These girls were followed for an average of 12 years, experienced menarche at an average age of 11.0 years, and achieved a mean adult height of 165.5 cm. A different study included 26 girls with a mean age at thelarche of 7.4 years and evidence of CPP, but a BA that had advanced less than 2 years (60). These girls were not treated with GnRHa therapy and were followed for an average of 6.6 years. After 2 years of follow-up, 65% had minimal changes in predicted adult height (PAH) despite not being treated. This subgroup of girls ultimately achieved menarche at a mean age of 11.9 years and a mean adult height of 160.7 cm, which was close to midparental height.

A prospective study that followed 212 girls (ages 7-8 years) from a single center in China defined RP-PP as progressing at least one breast Tanner stage during follow-up (66). According to this definition, 55% of their patient sample had SP-PP and 45% had RP-PP (66). Researchers noted that 74 of 95 girls with RP-PP had Tanner B3, whereas only 2 of 99 girls with SP-PP achieved this Tanner stage. Girls with RP-PP were taller, with a mean height standard deviation score (SDS) of 0.86 compared to 0.03. An advanced BA was the best predictor of a girl having RP-PP, with these girls having an average BA advancement of 1.48 years compared to 0.48 years in the girls with SP-PP (66).

The commissioned systematic review did not identify evidence related to imaging (eg, adverse events, likelihood of missed pathologic intracranial abnormalities, and consequences related to incidental findings) in this specific clinical scenario, but these considerations are addressed more fully in clinical question 4. Adverse medication events associated with GnRHas are addressed in detail under clinical question 6. Although such potential adverse medication events generally do not discourage use in girls with RP-PP, the GDP considered that such risks may not be justified in patients with SP-PP who appear to have good long-term height outcomes without treatment. Although the systematic review did not identify published evidence regarding the impact of a period of observation vs immediate evaluation (with treatment as indicated) on psychological distress, the clinical experts on the GDP noted that such distress can occur in the setting of diagnostic evaluation (eg, blood draws) in addition to the medicalization of a condition that may not require treatment.

While an initial observation period could involve a short delay in diagnostic evaluation for those with RP-PP, the GDP did not identify evidence suggesting that a 4- to 6-month delay in diagnosis (and therefore treatment) would negatively impact these outcomes. The GDP also considered that an initial period of observation could occasionally result in missing a diagnosis of RP-PP if the patient did not attend recommended follow-up evaluations; this could represent a missed opportunity to treat a child who would benefit from GnRHa therapy. More rarely, a lack of follow-up could lead to missing a pathologic CNS lesion as the etiology of the patient's CPP.

Other evidence-to-decision criteria and considerations

In the GDP's judgment, how patients, families, and clinicians value the main outcomes the GDP selected will vary. The GDP found no systematic reviews or primary studies regarding resources required or cost-effectiveness. However, if a portion of girls undergoing initial observation (ie, intervention) will not ultimately require further evaluation or treatment, the GDP deemed with reasonable certainty that initial observation would be associated with lower short-term costs. For example, a U.S. study found that patients with CPP have 6.42 to 12.25 times higher health care costs ($16,768–$19,940) in the first year of GnRHa treatment compared with controls (73). Since the costs for hormonal testing and radiologic imaging for CPP vary widely among institutions and geographic settings, the GDP was unable to precisely quantify short-term cost savings but judged that they could be substantial for some patients. Given that the vast majority of CPP is idiopathic in etiology, the GDP judged that an observation period of 4 to 6 months before further diagnostic evaluation in a patient later determined to have RP-PP would be unlikely to incur significant additional costs related to adverse short- or long-term health effects (eg, delayed diagnosis of intracranial pathology). Therefore, the GDP judged that, even if the patient undergoing observation is ultimately found to have rapidly progressive CPP, overall cost-effectiveness would not likely favor the comparator (ie, no period of observation).

The GDP found no systematic reviews relating to the acceptability of the intervention vs comparator in this clinical scenario. However, they identified 2 studies reporting high concentrations of parental concern and desire for aggressive treatment in children with suspected PP, although the vast majority ultimately were not given a diagnosis of CPP (74, 75). Both studies reported a striking increase in referrals for CPP in recent years. These findings suggest that a period of observation could possibly add additional stress to parents and that some parents may find it undesirable or even unacceptable. In addition, the lack of timely pediatric endocrine appointments in some regions, or anticipated difficulties with follow-up appointments (eg, anticipated travel difficulties, and scheduling constraints), may make an initial period of observation less feasible and acceptable for some caretakers.

The GDP found no systematic reviews or primary studies relating to the potential impacts on health equity. Population studies suggest that puberty onset is earlier in Black/African American girls compared to White/Caucasian girls (76). Notably, a later report suggested that social determinants of health, such as environmental exposures (eg, endocrine-disrupting chemicals), social/psychological stress, and adiposity could in part explain earlier puberty in this subgroup (77). To the degree that earlier puberty associates with lower socioeconomic status, the GDP deemed that avoiding unnecessary health care costs has the potential to increase health equity (77).

Justification for the recommendation

The commissioned systematic review suggested that a substantial proportion of girls younger than age 8 years with initial breast development (Tanner B2) will have an unsustained or slowly progressive puberty that is unlikely to have a pathologic etiology and has a good prognosis in terms of adult height. Therefore, the GDP judged that the intervention (ie, a 4- to 6-month period of observation to distinguish unsustained or SP-PP from RP-PP) likely offers a moderate benefit, mainly by avoiding unnecessary evaluation and treatment in a substantial proportion of these patients. The GDP also judged that the

anticipated undesirable effects of the intervention (ie, a period of observation)—predominantly, those related to a short delay in treatment for those with RP-PP—are likely small but important. Overall, the GDP reached consensus that available evidence probably favors the intervention, recognizing that certainty of evidence is very low. The GDP also considered anticipated short-term cost savings with the intervention, the potential for desirable effects on health equity by avoiding unnecessary costs, the likelihood of variable acceptability, and that the intervention is probably feasible to implement. Consequently, the GDP issued a conditional recommendation specific to girls with initial breast development (Tanner B2) for a period of observation (to differentiate unsustained or SP-PP from RP-PP), with subsequent diagnostic evaluation being pursued when RP-PP is identified.

Additional considerations

An inability to reliably conduct an observation period (eg, anticipated travel difficulties, scheduling constraints, or other limitations that may make timely follow-up difficult) may be a reason to immediately perform diagnostic evaluation.

This recommendation is not intended to apply to patients with precocious puberty and features suggesting other underlying conditions such as congenital adrenal hyperplasia (eg, hyperandrogenism) and McCune-Albright syndrome (eg, cafe au lait spots). The GDP assumed that immediate diagnostic evaluation is prudent in such girls.

The studies informing this recommendation primarily involved older children, and the weighted average of reported mean ages in the studies was approximately 7.2 years. Accordingly, the GDP considered that the applicability of the recommendation may possibly decrease as patient age decreases.

In this recommendation, "a period of observation" was not intended to include either laboratory testing or a bone age assessment. However, the GDP allows for the possibility that, in some cases, a bone age assessment may provide useful information and could be obtained as an initial evaluation without concomitant hormonal testing.

When a period of observation is advised, it is prudent to educate families about the difference between SP-PP and RP-PP, in addition to general education regarding pubertal progression and expected timing (eg, menarche typically occurs 18 months to 3 years after thelarche). This counseling may help alleviate anxiety families may experience related to the timing of menarche.

Research considerations

The GDP acknowledged that the current evidence describing the prevalence of SP-PP vs RP-PP is limited, as most of the studies are small and retrospective. More prospective multicenter studies are needed that enroll girls with thelarche and follow them clinically for 6 to 12 months without additional evaluation or treatment to more accurately determine the proportion of girls with SP-PP vs RP-PP. Additionally, it remains unclear how the tempo of precocious puberty (SP-PP vs RP-PP) relates to long-term outcomes such as fertility, body mass index (BMI), bone mineral density (BMD), and risk of polycystic ovary syndrome, and this warrants further study.

Establishing a diagnosis of central precocious puberty

Background

Traditionally, the diagnosis of CPP has involved dynamic stimulation testing with GnRH or GnRHa to document central (ie, hypothalamic-pituitary) activation, primarily through stimulated serum LH concentrations. A GnRH-stimulated LH concentration greater than 5 IU/L is generally accepted as a threshold to diagnose CPP (78). However, these stimulation tests are cumbersome, time-consuming, expensive, and may be stressful for children and families. For example, there may be pain due to insertion of an intravenous cannula, hours seated in the medical setting, and absence from school and work. It has been debated whether GnRH/GnRHa stimulation tests could be shortened or simplified, as traditional testing protocols involve obtaining blood samples at several time points. This has also led to studies assessing the diagnostic accuracy of different thresholds for basal (ie, unstimulated) serum LH and follicle-stimulating hormone (FSH) concentrations vis-a-vis GnRH-/GnRHa-stimulated LH concentrations (78). Newer research suggests that, in some cases, higher basal LH concentrations (eg, > 0.3 IU/L) may be sufficient for confirming CPP, although low or undetectable basal LH may not reliably exclude CPP (79). Importantly, the use of an ultrasensitive LH assay is critical when considering the use of basal (ie, unstimulated) LH concentrations. Nonetheless, the most appropriate diagnostic cutoffs for basal LH concentrations remain uncertain and may vary according to different factors such as age, sex, and pubertal stage.

Question 3

Should a staged approach starting with basal serum LH concentration by ultrasensitive assay, with subsequent GnRH/GnRH agonist-stimulated LH concentrations only in the setting of low basal LH concentration, be utilized vs initial evaluation with GnRH/GnRH agonist-stimulated LH concentrations in all patients to diagnose CPP?

Recommendation 3

In girls and boys with evidence of precocious puberty, we suggest an initial evaluation with a basal luteinizing hormone concentration by ultrasensitive assay, rather than initially performing a gonadotropin-releasing hormone/gonadotropin-releasing hormone agonist stimulation test, in order to distinguish those with central precocious puberty from those without. (2 | ⊕OOO)

Technical remarks:

- An ultrasensitive LH assay should reliably detect very low LH concentrations (eg, < 0.05-0.1 IU/L).
- While first morning (8:00-10:00 AM) basal LH testing may be optimal, especially in early puberty, the

guideline-development panel judged that it is acceptable to measure basal LH at any time of the day.
- When ultrasensitive basal LH concentrations are low in the presence of clinical evidence of precocious puberty, a GnRH/GnRH agonist stimulation test would generally be the next step in diagnostic evaluation, particularly when the index of suspicion for CPP is high and/or when a rapid diagnosis is needed (eg, in the setting of rapidly progressive puberty). Otherwise, another option is to repeat an ultrasensitive basal LH concentration, preferably in the early morning (8:00-10:00 AM).

Summary of evidence

The systematic review results, a detailed summary of the evidence, and EtD tables can be found online at https://guidelines.gradepro.org/profile/OloaV3bAHq8.

Benefits and harms

The outcomes of interest selected by the GDP were psychological distress, missed pathologic intracranial abnormalities, adult height, timing of menarche, and long-term cardiovascular and cancer risks (27). The commissioned systematic review did not identify any direct evidence comparing the initial use of basal LH concentrations (followed by subsequent GnRH/GnRHa stimulation testing only in the setting of a low basal LH concentration) vs the routine initial diagnostic use of stimulated LH concentrations via GnRH/GnRHa stimulation testing. The GDP therefore collected indirect evidence, primarily related to the testing characteristics (eg, diagnostic sensitivity and specificity) of basal LH testing vs GnRH/GnRHa stimulation testing, in addition to how basal LH concentrations may predict stimulated LH concentrations during GnRH/GnRHa testing. The indirect evidence comes mainly from retrospective (mostly cross-sectional) studies, a few prospective studies, and 1 meta-analysis (80-94). Each study included from 30 to several hundred patients who were predominantly girls with Tanner B2 or B3 and described as White/Caucasian.

Historically, GnRH testing is considered the gold standard to determine a diagnosis of CPP. A peak LH at least 5 IU/L after stimulation is reported to have a specificity ranging from 97% to 100% (80, 81). However, GnRH testing has some limitations. For example, in patients younger than age 3 years, a peak LH value greater than 10 IU/L may be inadequate to confirm CPP because of the co-occurrence of the minipuberty of infancy, which makes the expected LH peak higher compared to that at ages 3 to 6 years (82). Additionally, in children with obesity (BMI SDS $\geq$2), peak LH after GnRH/GnRHa stimulation tends to be lower and thus less sensitive for CPP (86).

Among GnRHas used for stimulation testing, peak LH after triptorelin administration is reported to have similar accuracy to GnRH stimulation testing (area under the receiver operating characteristic curve [AUC] 0.97 vs 0.99) (78) and to have a specificity of 79% (83). A different study reported that a peak LH concentration of 4.52 IU/L or higher at 120 minutes after triptorelin stimulation had a 100% sensitivity and 96% specificity for diagnosing CPP (84). One study using a triptorelin stimulation test reported that a basal LH of 0.795 IU/L or higher by chemiluminescence microparticle assay (CMIA) had a specificity of 100%, but because of the variability attributed to the time of day and Tanner stage, the authors concluded that basal LH concentrations could not be used alone for diagnosing CPP (80). Similarly, peak LH after subcutaneous leuprolide (leuprorelin) stimulation yielded a 100% specificity in diagnosing CPP; a basal LH higher than 0.1 IU/L alone had a specificity of 94%, and a basal LH higher than 0.8 IU/L had a specificity of 100% (85).

Overall, when using ultrasensitive methods such as immunoradiometric assay (IRMA), CMIA, immunofluorometric assay (IFMA), and electrochemiluminescence immunoassay (ECLIA), a random basal LH higher than 0.2 IU/L in girls with Tanner B2 predicts a peak LH higher than 5 IU/L by stimulation testing (79, 87-91). By the GDP's review, if breast development is more advanced, a basal LH higher than 0.3 IU/L appears sufficient to exclude isolated PT (88, 92), and this response is reported to be independent of age, sex, ethnicity, BMI, BA, menarchal status in girls, or etiology. Summarizing the above studies, basal LH sensitivity ranged from 42% to 94%, and specificity ranged from 70% to 100%. One study reported that a basal LH cutoff of 0.2 IU/L has a different sensitivity for Tanner B2 (42%) compared with Tanner B3 (59%) (88). Another study reported greater sensitivity in boys than in girls (96 vs 85%) with a basal LH cutoff concentration of 0.3 IU/L (92).

A more detailed review by the GDP determined that, with immunochemiluminometric assay (ICMA), random basal LH values above 0.1 IU/L were reported to have a sensitivity of 94% and specificity of 88% in detecting patients with pubertal onset (93), and a basal LH higher than 0.2 IU/L had a sensitivity of 89% and a specificity of 99% (35). ICMA is reported to be more sensitive than IFMA and preferable in one study, with a suggested cutoff of 0.2 IU/L (83). With dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA), the highest value detected was 0.15 IU/L in prepubertal girls and 0.24 IU/L in one boy (93). With the IMMULITE chemiluminescence assay, a basal LH cutoff of 0.14 IU/L was reported to have a sensitivity for CPP of 91% and a specificity of 78% (94).

A basal LH higher than 0.25 IU/L in boys (based on a single study) and in girls with Tanner B2 could confirm CPP and thus obviate the need for further testing. A higher cutoff value (>0.3 IU/L) might be necessary in girls with Tanner B3 (79, 87-94). Importantly, published evidence in boys is sparse and seems insufficient; available data may permit reliable conclusions for girls only. Overall, however, indirect evidence suggests that higher basal LH, measured using an ultrasensitive method, predicts a positive GnRH/GnRHa test result.

Additional considerations regarding potential benefits and harms

The undesirable short-term health effects related to GnRH/GnRHa stimulation testing may include pain with intravenous catheter insertion, flushing symptoms, and other minor side effects related to infusion of the stimulation agent. Allergic reactions to GnRH/GnRHa are rare (95). If a basal serum LH is less accurate than stimulated LH concentrations, undesirable long-term health effects could relate to inaccurate or delayed diagnosis. In general, failing to make the diagnosis would result in a missed or delayed opportunity for GnRHa treatment as indicated, which could potentially lead to impaired adult height,

precocious menarche, and other long-term risks—depending on the length of diagnostic delay. This might also contribute to delayed diagnosis of a rare intracranial tumor. As peak LH in response to GnRH/GnRHa simulation testing has a higher specificity and less variability compared to basal LH values, the GDP's judgment is that clinicians should still consider GnRH/GnRHa stimulation testing if basal LH concentrations and clinical assessment alone do not allow a high-certainty of a diagnosis of CPP.

Other evidence-to-decision criteria and considerations

The GDP identified no studies that refer to patient and family values related to this clinical scenario. As with other clinical questions, they chose outcomes based on their clinical experience and expertise and recognized that how stakeholders value the selected outcomes may vary considerably.

The GDP found no studies that addressed resources required for initial basal LH testing vs routine GnRH/GnRHa stimulation testing. However, GnRH/GnRHa stimulation testing is relatively expensive and requires trained personnel for the administration of stimulatory agents and repeated, timed blood draws. A strategy of first using basal LH concentrations would not generate as many expenses as stimulation testing and would require less phlebotomy and fewer blood draws and associated laboratory tests. Importantly, accurate basal LH testing requires using ultrasensitive LH assays, which may be more expensive than non-ultrasensitive LH assays. Nevertheless, the GDP considered that this strategy may be more cost-effective overall. However, if a basal LH testing strategy is substantially less accurate than routine GnRH/GnRHa stimulation testing, then the costs related to incorrect initial diagnoses (eg, false negatives, false positives) may make this less cost-effective. The GDP identified only one study related to cost-effectiveness (88), which included patients with Tanner B2 and B3, suggesting that initial basal LH testing, followed by stimulation testing when basal LH is lower than 0.2 IU/L, had lower diagnostic costs with more effectiveness compared to performing stimulation testing when basal LH is less than 0.3 IU/L.

The GDP found no studies relating to the potential impacts (of the intervention vs the comparator) on health equity in this clinical scenario. The GDP determined that basal LH testing may be more accessible than GnRH/GnRHa stimulation testing. This consideration, along with lower overall cost, implies that basal serum LH testing could enhance overall health equity. However, a wide range of methods and assays are being used to measure gonadotropins (96), and not all individuals will have access to ultrasensitive assays. This is important because the impact on health equity could depend on differences in diagnostic accuracy.

The GDP found no studies related to acceptability or feasibility. However, they deemed GnRH/GnRHa stimulation testing generally acceptable to stakeholders, including patients, medical staff, and parents/caregivers. Even so, if serum basal LH concentrations were sufficient, this approach would likely be more acceptable to all stakeholders, as it would prevent the need for GnRH/GnRHa stimulation testing in a subset of patients. The feasibility of this type of stimulation testing depends on the availability of GnRH or GnRHas, in addition to trained personnel. In this regard, basal LH testing almost certainly has a feasibility advantage compared to stimulation testing, at least when ultrasensitive LH assays are available.

Justification for the recommendation

No direct evidence was identified that would indicate how these diagnostic strategies could differentially impact health outcomes important to patients and families. However, based on indirect evidence, the GDP judged that GnRH/GnRHa testing will not be required to confirm CPP in many patients, as an elevated serum basal LH is compelling evidence of central activation of puberty. The GDP therefore issued a conditional recommendation to start evaluation with an ultrasensitive basal LH (rather than immediate GnRH/GnRHa stimulation testing for all) to distinguish those with vs without CPP.

Additional considerations

While first morning (8:00-10:00 AM) basal LH testing may be optimal, especially in early puberty, the GDP judged that it is generally acceptable to measure basal LH at any time of the day in order to increase feasibility. In particular, the panel recognized that a strict recommendation for first-morning sampling would often require an additional visit and thus would be inconvenient for some patients/caretakers.

Since peak LH in response to GnRH/GnRHa testing has a higher specificity and less variability, the GDP judged that a GnRH/GnRHa stimulation test would generally represent the next diagnostic step when ultrasensitive basal LH does not identify the presence vs absence of CPP. This could be especially important when the index of suspicion for CPP is high and/or when a rapid diagnosis is needed to facilitate timely treatment (eg, in the setting of rapidly progressive puberty). Otherwise, the panel judged that another reasonable option is to repeat a serum basal LH, preferably between 8:00 and 10:00 AM, as the next diagnostic step; this alternative may be most pertinent to situations in which the initial basal LH sample was obtained after 10:00 AM.

Research considerations

The GDP encourages new research directly addressing the diagnostic utility of basal LH testing using ultrasensitive assays compared to GnRH/GnRHa stimulation testing. Such research should be expanded to include patients from different ancestries, to boys, and to younger patients with thelarche to understand age-appropriate cutoffs in young girls who may have PT without CPP. More studies on the clinical validity of a first morning urinary LH concentration as a noninvasive tool to determine puberty onset are also encouraged.

Assessing the potential for a structural intracranial etiology of central precocious puberty

Background

Historically, estimates of the proportion of patients with CPP due to organic CNS causes were as high as 20% for girls and approximately 50% for boys, justifying the recommendation of performing CNS imaging (eg, brain MRI of the hypothalamus and

pituitary) in all patients with CPP (2). However, over the past few decades, the number of children (especially girls) diagnosed with CPP has increased (97, 98). While the causes are incompletely understood, the obesity epidemic may in part explain this observation (97, 98). Speculatively, this may help explain recent studies suggesting that only a small percentage of patients with CPP are associated with a brain tumor (99, 100). The increase in CPP prevalence is less pronounced in boys, but recent studies indicate that the prevalence of brain lesions in boys with CPP is also lower than previously described (12). Thus, the diagnostic utility of routine brain MRI may now be lower, and the question of which children with CPP benefit from brain imaging is of high priority.

Question 4

Should brain MRI vs no brain MRI be used for assessing the presence of a congenital or acquired intracranial etiology of CPP in girls (ages 6.0-8.0 years) and boys (ages 8.0-9.0 years) with no CNS symptoms?

Recommendation 4

In girls ages 6.0 to 8.0 years and boys ages 8.0 to 9.0 years with central precocious puberty and without central nervous system findings, we suggest that brain MRI should not be routinely performed. (2 | ⊕OOO)

Technical remarks:

- This recommendation does not apply to younger patients or to patients of any age who present with CNS findings (eg, headaches, seizures, and/or visual field deficits).

Summary of evidence

The systematic review results, a detailed summary of the evidence, and EtD tables can be found online at https://guidelines.gradepro.org/staging/profiles/r9PebLyppYs.

Benefits and harms

The health-related outcomes selected by the GDP included missed pathologic intracranial abnormalities, adverse consequences related to incidental findings, and adverse events related to undergoing a brain MRI (eg, complications of receiving IV contrast, sedation risks, and magnet-related risks). The commissioned systematic review identified no studies comparing the use vs non-use of brain MRI among patients with CPP (27). However, the systematic review team identified 35 uncontrolled single-arm studies across 19 countries comprising 5541 children diagnosed with CPP who underwent brain MRI (12, 100-133). The mean age at CPP diagnosis was 7 years, and the average proportion of girls was 83%. The methodologic quality was generally considered to be good, at least for uncontrolled single-arm studies. Most studies used traditional criteria to diagnose CPP, and MRI was performed in these studies regardless of neurologic symptoms.

The overall rate of MRI abnormalities—both pathologic and incidental findings—was 18%, while the rate of pathologic lesions, including all ages and limited by the GDP to brain tumors or hypothalamic hamartomas, was 5.5% (27). Overall, significantly higher rates of pathologic lesions were observed in boys and in children younger than age 6 years. The more common tumors identified in this study included astrocytomas, craniopharyngiomas, and optic gliomas. It was not possible to determine what proportion of patients with pathologic MRI findings also had CNS-related symptoms or signs.

Importantly, the GDP primarily focused on the 14 studies that permitted estimates of prevalence according to age group (12, 100-103, 105, 106, 108, 111, 117, 121, 126, 130, 132). Among these, the estimated prevalence of pathologic findings (ie, hamartomas and tumors) was 11% (49/443) for girls younger than age 6 years, 1% (22/2154) for girls ages 6.0 to 8.0 years, 28% (39/139) for boys younger than age 8 years, and 0% (0/337) for boys ages 8.0 to 9.0 years. When broken down by type of pathologic finding, the estimated prevalence of hamartomas was 9% (41/443) for girls younger than age 6 years, 0.4% (8/2154) for girls ages 6.0 to 8.0 years, 13% (18/139) for boys younger than age 8 years, and 0% (0/337) for boys ages 8.0 to 9.0 years. For brain tumors, the estimated prevalence was 2% (8/443) in girls younger than age 6 years, 0.6% (14/2154) in girls ages 6.0 to 8.0 years, 15% (21/139) in boys younger than age 8 years, and 0% (0/337) in boys ages 8.0 to 9.0 years.

The GDP noted that a desirable effect of universal brain imaging for all patients with CPP is that no patients with serious CNS lesions requiring intervention and treatment would be missed. The GDP judged that this desirable impact is small but important among girls with CPP ages 6.0 to 8.0 years and boys with CPP ages 8.0 to 9.0 years, given the low prevalence of pathologic intracranial abnormalities in these age groups.

Undesirable effects of brain MRIs may include risks associated with sedation and IV contrast as well as anxiety for the child and family. The GDP also considered the negative impact of incidental (ie, non-pathologic) findings, which can also generate anxiety and require consultation with other types of specialists, and potentially follow-up brain imaging. The GDP considered these undesirable effects to be small but important.

Other evidence-to-decision criteria and considerations

The GDP did not identify any systematic reviews that address resources required for brain MRI. It was difficult to estimate MRI-related costs as they vary widely among countries and among facilities. Regardless, compared to routine brain MRI for all patients with CPP, a strategy of performing MRI only in the presence of CNS symptoms for the older age groups would certainly be associated with lower short-term, MRI-related costs. Additional short-term cost savings could relate to avoiding additional visits and imaging associated with the evaluation of incidental findings. The potential impacts on long-term costs are

unknown. The GDP identified no cost-effectiveness studies relating to routine brain MRI among patients with CPP.

The GDP likewise did not identify studies addressing the acceptability and feasibility of routine brain MRI in patients with CPP. While brain MRIs are generally considered to be feasible in well-resourced contexts, the feasibility of routine brain MRI is expected to vary depending on the health care context, in addition to patient and family circumstances. Importantly, the GDP judged that the acceptability of the intervention vs comparator will also vary, largely related to different risk tolerances (eg, risk of failing to identify a pathologic intracranial finding) among pediatric endocrinologists and families. This intuition is supported by a recent survey of North American pediatric endocrinologists (134), which indicated that brain MRIs were ordered by most pediatric endocrinologists routinely for girls younger than age 6 years with CPP, but whether imaging was ordered for girls presenting after age 7 years was more variable.

To the degree that the diagnostic yield of MRI is low among girls with CPP ages 6.0 to 8.0 years and boys with CPP ages 8.0 to 9.0 years, requiring routine brain MRI, which would prove unnecessary in most cases, could place an undue burden on many patients and parents, especially those with fewer financial resources and/or health insurance. Conversely, avoiding unnecessary imaging and associated costs could enhance health equity.

Justification for the recommendation

The commissioned systematic review indicated that the overall rates of pathologic findings on MRI, defined by the GDP as the presence of brain tumors or hypothalamic hamartomas, approximates 1% for girls ages 6.0 to 8.0 years and 0% for boys ages 8.0 to 9.0 years, while the overall rate of MRI abnormalities (ie, both pathologic and incidental findings) approximates 10% for girls ages 6.0 to 8.0 years and 3% for boys ages 8.0 to 9.0 years (27). Although the GDP judged that brain MRI is typically low yield in these age groups, they considered the desirable effect of the intervention (ie, routine brain MRI), namely that few (if any) serious CNS lesions would be missed, to be small but important. The GDP also judged that the undesirable effects, such as adverse events of imaging, including increased anxiety, and consequences of incidental findings, are small but important. Overall, however, the GDP judged that the balance of effects probably favors the comparator (ie, not routinely doing brain MRI). The GDP also considered that the costs of brain MRI are moderate to large, raising questions about cost-effectiveness and whether routine MRI could potentially harm health equity. Considering these factors, the GDP issued a conditional recommendation against routine brain MRI in girls with CPP ages 6.0 to 8.0 years and boys with CPP ages 8.0 to 9.0 years without CNS symptoms. They recognized, however, that individual family risk tolerance is important to consider when engaging in shared decision-making.

Additional considerations

The GDP emphasized that this recommendation does not apply to patients with CPP who present with CNS findings (eg, headaches, seizures, and/or visual field deficits); the panel assumed that brain MRI should be performed in such patients regardless of age. The GDP also acknowledged that brain MRI may be considered if a clinician and/or family has a high level of concern about missing a pathologic CNS finding.

Genetic testing for central precocious puberty

Background

Compelling evidence of the influence of genetic factors on pubertal timing has been further supported by studies identifying monogenic causes in some children with CPP, including rare gain-of-function mutations in genes encoding the kisspeptin receptor (*KISS1R*) and its ligand (*KISS1*) and more prevalent loss-of-function mutations in 2 imprinted genes. *Makorin ring finger protein 3* (*MKRN3)* and *Delta-like non-canonical Notch ligand 1* (*DLK1)* (2, 135-138). More recently, rare deleterious variants in the gene *Methyl-CpG-binding protein 2* (*MECP2*) have been identified in children with CPP both with and without neurodevelopmental disorders (139, 140) (Table 3).

Notably, 25% to 30% of all CPP cases are familial, highlighting the importance of a detailed pubertal family history. Familial CPP is defined by the presence of at least one first-, second-, or third-degree relative with documented CPP, a clinical history of early sexual development, or precocious menarche (141, 142).

Loss-of-function mutations in the *MKRN3* or *DLK1* genes result in non-syndromic autosomal-dominant CPP that is exclusively paternally transmitted, as these genes are maternally imprinted. *MKRN3*, an imprinted gene located on the chromosome 15q11.2 in the Prader-Willi syndrome critical region, encodes a factor involved in gene transcription and ubiquitination. This factor is a key inhibitor of the HPG axis, acting as a brake on GnRH secretion during childhood (2). Remarkably, patients with CPP due to *MKRN3* loss-of-function mutations have clinical and hormonal features of CPP that are indistinguishable from those with CPP without mutations. Among these patients, the onset of pubertal signs occurs at a mean age of 6.2 ± 1.2 years in girls and 7.1 ± 1.5 years in boys (143). Although CPP due to *MKRN3* mutations is clinically indistinct from idiopathic CPP, the type of genetic defect may affect phenotype severity (143). Many loss-of-function mutations in *MKRN3* have been identified across multiple families with CPP from different ancestries and geographic areas (14). These defects are the most common genetic cause of CPP, reaching a frequency around 9% among patients with apparently idiopathic CPP, which increases to 33% to 46% among familial cases, and has been reported in about 20% of boys (14, 135, 144). If there is a positive family history on the paternal side, *MKRN3* genetic defects have been reported to represent up to 77% of cases of familial CPP (145).

Loss-of-function mutations in the *DLK1* gene, located on chromosome 14q32.2 in the Temple syndrome critical region, have been rarely identified in cases of familial CPP (8, 14, 136, 146). Notably, these individuals have a higher frequency of adverse metabolic outcomes in adulthood such as obesity, early-onset insulin resistance, and T2DM when compared to individuals with idiopathic CPP, suggesting that *DLK1* is a factor linking reproduction and metabolism (146, 147). Of note, in some studies, all patients with CPP due to loss-of-function mutations in *MKRN3* and *DLK1* genes were genetically screened after having a negative brain MRI (and thus were previously considered to be idiopathic cases) (14, 143, 146).

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.

MECP2 (chromosome Xq28) is an X-linked gene that encodes a chromatin-associated protein with a role in gene transcription and neurodevelopment. Loss-of-function mutations in *MECP2* are typically associated with a neurodevelopmental disorder, particularly with Rett syndrome (148). Recently, rare heterozygous deleterious variants in *MECP2* were identified in children with apparently sporadic CPP, both in patients with and without mild neurodevelopmental disorders (139, 140).

Notably, among families and medical providers, interest in recognizing the cause of CPP in each patient is increasing. As genetic testing is not widely available clinically, it is important to determine whether it should be routinely recommended for patients with idiopathic CPP.

Question 5

Should genetic testing (eg, to identify loss-of-function mutations in *MKRN3*, *DLK1*, and/or *MECP2*) vs no genetic testing be used for children with CPP?

Recommendation 5

For children with central precocious puberty, we suggest against routine genetic testing (eg, to identify loss-of-function mutations in *MKRN3*, *DLK1*, and/or *MECP2*). (2 | ⊕OOO)

Technical remarks:

- This recommendation relates to targeted genetic testing (including genes such as *MKRN3*, *DLK1*, and/or *MECP2*) as opposed to unbiased genomic sequencing.
- In patients with familial CPP, genetic testing should be considered based on shared decision-making with the family.

Summary of evidence

The systematic review results, a detailed summary of the evidence, and EtD tables can be found online at https://guidelines.gradepro.org/profile/9T56NpjCT-U.

Benefits and harms

The health-related outcomes selected by the GDP included the likelihood of missing genetic causes of CPP, timeliness of identified comorbidities such as mild neurodevelopmental disorders, psychological stress (eg, related to variants of unknown significance), timeliness of establishing a CPP diagnosis in other family members, and timeliness of treatment in other affected family members. The commissioned systematic review did not identify eligible studies comparing outcomes from genetic testing vs no genetic testing (27). Two retrospective cohort studies were selected by the GDP that reported the frequency of genetic findings in girls and boys with CPP (142, 143). A tertiary-center Brazilian study assessed a large cohort of patients with CPP, including 241 girls and 29 boys (142). Among those with negative brain MRIs, genetic causes were identified in 13% of all children, further stratified to 12% in girls and 22% in boys (142). Family history (odds ratio [OR] 3.3 [95% confidence interval (CI): 1.3, 8.3]; $P = .01$) and neurodevelopmental disorders (OR 4.1 [95% CI: 1.3, 13.5]; $P = .02$) were estimated as potential clinical predictors of CPP secondary to a genetic etiology (142). In addition, the GDP reviewed a multicenter study that assessed a large multiethnic cohort of patients with CPP (716 patients, 64% girls) with negative brain MRIs (143). All patients underwent targeted *MKRN3* sequencing, which identified loss-of-functions *MKRN3* mutations in 10% (71/716) of patients. Adult height was similar in patients with *MKRN3*-related CPP treated with GnRHas compared to patients with idiopathic CPP treated with GnRHas (143). Additionally, menarche normalized to average timing in GnRHa-treated patients with *MKRN3*-related CPP (treated 11.3 $\pm$ 1.2 years vs untreated 8.2 $\pm$ 1.0 years) (143). Limitations of the selected studies included their retrospective nature and the lack of control groups (ie, patients with CPP who were not submitted to genetic testing). To date, no study has evaluated psychological distress associated with performing genetic testing in children with CPP. Overall, the certainty of evidence was considered very low for all outcomes.

The GDP considered that the potential benefits of the intervention (ie, targeted genetic testing) could include earlier diagnosis and treatment for affected family members, more precise long-term management surveillance of any associated comorbidities, and genetic counseling for the family. The harms of genetic testing could include psychological stress and anxiety related to an abnormal genetic finding, potential fear of stigmatization, and stress associated with a variant of unknown long-term significance.

The GDP recognized the lack of studies directly comparing the effectiveness and potential harms of routinely performing genetic testing vs not performing genetic testing in children with CPP, especially as it relates to patient-important outcomes such as adult height, psychological distress, and long-term cardiometabolic health.

Other evidence-to-decision criteria and considerations

The GDP found no direct evidence regarding resources required or cost-effectiveness for genetic testing in patients with CPP. Overall, genetic testing is still a relatively onerous diagnostic tool that requires specialized genetic laboratories and medical centers. Based on their experience, GDP members were moderately confident that targeted genetic testing in children with CPP would have moderate costs. They found no studies to evaluate the cost-effectiveness of genetic testing in patients with CPP.

The GDP found no systematic reviews regarding health equity, acceptability, and feasibility. Regarding the potential impact on health equity, they considered that the availability and cost of genetic testing remains variable across distinct countries and health systems. However, the GDP acknowledged that the growing use of genetic diagnosis in the pediatric population, including in pediatric endocrinology, has helped guide clinical decision-making for patients and affected family members with other

conditions. Overall, given incomplete access to genetic testing, in addition to uncertainties regarding net health benefits, the GDP considered that genetic testing in children with CPP could potentially reduce health equity.

The GDP judged that both acceptability and feasibility of the intervention are likely to vary depending on several factors. Indirect evidence (ie, studies of genetic testing for other disorders) has shown that the acceptability of genetic testing is usually high, as it may offer precise etiologic diagnosis and treatment guidance and potential surveillance of other health risks (149). In addition, indirect evidence suggests that acceptance rates of genetic testing can vary across different groups and cultures, highlighting the need for more accessible, understandable information to support informed decision-making (149). For instance, a personal history of early pubertal development in a parent may be linked to more favorable attitudes toward genetic testing. It is important to consider parent/caregiver perceptions and understanding when a genetic cause is found, which can impact the family positively (eg, feelings of relief or control) or negatively (eg, feelings of guilt or distress) (150). From a technical standpoint, genetic testing has become more feasible in recent years with the increasing number of specialized laboratories and techniques. The practical feasibility of genetic testing as a clinical strategy depends on several factors, such as accessibility, interpretability, and cost. For some clinicians, genetic information may be challenging to interpret. Collaborating with clinical geneticists is important for most laboratories to be able to provide a clear report to medical providers. Overall, the GDP judged that the feasibility of genetic testing for patients with CPP varies across distinct regions and centers due to variable availability and costs.

Subgroup considerations

The GDP considered the possibility that genetic testing may be more useful in the setting of familial CPP. For example, the prevalence of causal genetic variants among patients with familial CPP is higher than that among all patients with CPP (eg, *MKRN3* mutations occur in 9% of overall cases but up to 46% of familial cases), suggesting a higher diagnostic yield of genetic testing in patients with familial CPP. In addition, the identification of a causal genetic variant in an index case offers the possibility of earlier CPP diagnosis among at-risk family members. The GDP also considered early studies suggesting that CPP related to *DLK1* variants is associated with higher metabolic comorbidity risks in adulthood. Lastly, pathologic intracranial MRI findings have not been reported among patients with causal genetic variants, suggesting that MRI may not be necessary for them. However, a negative brain MRI was used as an inclusion criterion for genetic testing in the 2 studies reviewed. Nevertheless, the degree to which genetic testing would ultimately translate into improvements in patient-important health outcomes (eg, psychological distress, comorbidity burden, and treatment) remains unclear.

Justification for the recommendation

The GDP suggests against using routine genetic testing (eg, for loss-of-function mutations in *MKRN3*, *DLK1*, and/or *MECP2*) for all children with CPP, based on the lack of studies directly comparing anticipated benefits and potential harms of testing vs not testing, as well as the heterogeneous availability of genetic testing across distinct centers and countries. The certainty of evidence for both benefits and harms was considered very low, predominantly due to reliance on indirect evidence and observational studies. The GDP ultimately judged that the balance of benefits and harms of genetic testing for all patients with CPP remains unclear. However, this conditional recommendation allows for the possibility that some subgroups of patients/families might benefit from genetic testing. In particular, the GDP judged that genetic testing (particularly *MKRN3* and *DLK1* sequencing) should be considered for the subgroup of children with familial CPP but that shared decision-making with patients and their families remains critically important.

Additional considerations

CPP can be a manifestation of a larger syndromic disorder caused by genetic or epigenetic defects. Examples of such syndromes include Temple syndrome (maternal uniparental disomy of chromosome 14 or 14q32.2 epimutation), Prader-Willi syndrome (15q11-q13 paternal deletion or maternal uniparental disomy of chromosome 15), Silver-Russell syndrome (11p15.5 epimutation or maternal uniparental disomy of chromosome 7), Rett syndrome (loss-of-function mutations in *MECP2*), and Williams-Beuren syndrome (7q11.23 deletion) (2). If any of these syndromes is suspected, the type of specific genetic testing should rely on the diagnostic criteria for the syndrome being considered.

Research considerations

Future research studies in children with CPP may identify new genetic causes, including maternally transmitted mutations, genetic abnormalities in noncoding regions, and epigenetic defects. Further studies, including long-term follow-up into adulthood could also yield information that might allow individuals with CPP to benefit from a precision medicine approach.

Management of central precocious puberty with gonadotropin-releasing hormone agonist treatment

Background

The current standard of care for CPP is GnRHa therapy, which suppresses the HPG axis. GnRHas have been approved for this indication since the early 1990s (16). CPP has been associated with reduced adult height, but evidence for associations with adverse psychosocial outcomes remains limited and less conclusive. Moreover, earlier pubertal timing has been associated with increased risks of different adult diseases, although most of these data come from large population-based cohorts rather than from

long-term follow-up of patients with CPP (151). In this context, it is essential to define the beneficial effects and potential harms of GnRHas on patient-important outcomes among patients with CPP.

Question 6

Should treatment with GnRH agonists vs no treatment with GnRH agonists be used for the management of CPP?

Recommendation 6

For many children with central precocious puberty, we suggest gonadotropin-releasing hormone agonist treatment, although certain patient subgroups may not achieve net benefit with such treatment. (2 | ⊕OOO)

Technical remarks:

- Because this recommendation was predominantly driven by the adult height outcome, it may not apply to certain patient subgroups who are not expected to derive an important height benefit, including:
  - Girls ages 7.0 to 8.0 years who have slowly progressive CPP.
  - Girls and boys who are at or beyond the peak of their pubertal growth spurt (this will be concordant with their bone age assessment).
- 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 guideline development panel emphasizes the importance of shared-decision making for all patients with CPP, which should include a careful weighing of anticipated benefits and potential harms of GnRH agonist use in the context of each patient's clinical presentation and patient/caretaker values.

Summary of evidence

The systematic review results, a detailed summary of the evidence, and EtD tables can be found online at https://guidelines.gradepro.org/profile/jLu7cEetMFo.

Benefits and harms

The GDP prioritized the following outcomes: medication adverse events, fertility, BMI, adult height, psychological distress, BMD, and neurocognitive function. The commissioned systematic review did not identify any RCTs directly comparing GnRHa treatment vs no GnRHa treatment in girls with idiopathic CPP (27). The systematic review identified 21 comparative observational studies comparing GnRHa therapy vs no treatment in idiopathic CPP (67, 152-168). Six studies were excluded due to inadequate control groups (152-157); for example, studies in which treatment decisions were based on predicted outcomes (eg, low predicted adult height) were considered unacceptably biased and thus excluded. This left 15 studies from 12 different countries, published from 1997 to 2025, with a total of 1835 girls (mean age at start of treatment 8.2 ± 1.1 years) (67, 155, 158-168). Several endpoints were considered in these studies, although adult height was the most common. In the 14 studies that measured adult height involving 1017 treated patients and 480 controls, the meta-analysis indicated a mean difference in adult height of +2.7 cm (95% CI: 1.1, 4.4) with GnRHa treatment (27). In a study subgroup analysis, studies involving mean treatment durations ≥3 years suggested height differences of +3.9 cm (95% CI: 0.9, 6.8), while studies involving mean treatment durations <3 years suggested height differences of +2.1 cm (95% CI: 0.5, 3.7). Although not formally assessed in the metanalysis, the panel considered that patients with treatment durations ≥3 years were likely to be those who started treatment at an earlier age, suggesting that treatment may provide greater adult height benefit in younger patients with CPP (eg, age <6 years vs 6.0-8.0 years). In another subgroup analysis, studies of patients with lower mean predicted adult height (PAH) (<155 cm) at treatment initiation suggested similar adult height differences (+2.5 cm [95% CI: −0.9, 5.9]) compared to studies of patients with higher mean PAH (>155 cm) at treatment initiation (+1.8 cm [95% CI: −1.4, 5.1]).

The effect of treatment on BMI measured at the time of adult height measurement was evaluated in 5 studies (304 treated patients and 155 controls) (159, 162, 163, 165). Meta-analysis suggested no meaningful impact of GnRHa treatment on BMI at the time of adult height attainment (mean difference 0.4 kg/m^2 [95% CI: −0.7, 1.6]).

The commissioned systematic review found insufficient evidence to estimate an effect on BMD (27). The GDP considered that any short-term differences in BMD may simply reflect a delay in bone accretion, an anticipated finding with sex steroid suppression, and would not necessarily translate into reduced peak bone mass (or fracture risk) in adulthood. Other outcomes of interest identified by the GDP included psychological distress, neurocognitive function, and fertility, but the systematic review did not identify sufficient evidence relevant to these outcomes. However, based on their experience, the GDP noted that the apparent impact of GnRHas on psychosocial outcomes can be variable. In addition, 1 identified study suggested that among women with a history of CPP, GnRHa treatment was associated with higher spontaneous pregnancy rates and lower need for assisted fertilization, despite a lower proportion attempting conception (162), and another identified study suggested no clear differences in fertility-related outcomes, psychological diagnoses, and bone health between GnRHa-treated vs untreated men with a history of CPP (162).

The GDP also noted that many families are concerned about premature menarche. Although the timing of menarche was not originally selected by the GDP as an outcome of interest for this clinical question, the systematic review team provided information about this outcome at the GDP's request. In particular, a synthesis of data from 4 of the previously identified studies suggested that GnRHa treatment was associated with menarche at an average of 12.0 to 12.4 years compared to an average of 9.6 to 11.4 years in controls, for a weighted mean difference of 1.3 years (95% CI: 1.07, 1.96) (67, 162, 163, 169).

Table 4 Gonadotropin-releasing hormone agonist average annual cost in the United States (2025)

Active medication	Strength (mg)	Route of administration	Frequency of administration	Cost per dose (average wholesale 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

Source: Developed by the Guideline Panel Using Data From Medispan (2025).

Additionally, GnRHa-related adverse events can include rare sterile abscesses (even rarer with the newer GnRHa formulations) and headaches, among other symptoms, and the GDP recognized that such adverse events are rare. Notably, a warning for idiopathic intracranial hypertension (pseudotumor cerebri) has been recently added to GnRHa drug labels, and children with CPP treated with GnRHas should be monitored for symptoms and signs such as headaches, blurred vision, and/or papilledema (170).

Other evidence-to-decision criteria and considerations

As with other clinical questions posed by the GDP, the outcomes of interest were primarily prioritized on the basis of their extensive experience with patients and families. However, the GDP recognized that individual patients and parents may value the selected outcomes differently.

Regarding costs and resources required, the GDP recognized that the price of GnRHas can vary significantly among countries and among health care contexts. For example, in France and Spain, the annual price of the various forms of GnRHas approximates $1,100 to $1,300 USD. As of 2025, the average annual wholesale price for GnRHas in the United States ranged from approximately $30,000 to $60,000, depending on the formulation (Table 4). Moreover, out-of-pocket costs to families can vary considerably depending on health care system and insurance coverage. In addition to the monetary costs of the GnRHa medication itself, required resources include personnel costs for administration, follow-up clinic visits to monitor pubertal progression, and potentially costs related to laboratory surveillance to confirm effective gonadotropin suppression. In the case of the subcutaneous histrelin acetate implant, facilities and infrastructure for implantation and removal are necessary, including clinicians with specialized procedural expertise and the ability to administer anesthesia. The GDP identified no systematic reviews addressing cost-effectiveness of GnRHa therapy for CPP. However, since costs are inconsistent, in addition to the GDP's judgment that the net benefit of GnRHas will vary for different patient subgroups, the GDP concluded that cost-effectiveness is likely highly variable.

The GDP was uncertain regarding the potential impact of GnRHas on health equity among patients with CPP. The age of pubertal onset may be lower among children with lower baseline health equity; however, whether such differences in pubertal timing cause harms that could be mitigated with GnRHa treatment remains unclear. The GDP considered that the moderate-to-high costs of GnRHa treatment could mean that those with low baseline health equity might have less access to such treatments. These factors could negatively impact health equity. On the other hand, the GDP considered the possibility that GnRHa treatment could preferentially benefit CPP patients with low baseline health equity. The GDP concluded that the potential impact on health equity may depend on different patient populations and health care settings.

Based largely on their clinical expertise, the GDP judged that the acceptability of CPP treatment likely varies among patients and families. In particular, while some children and families are highly concerned by early pubertal development and its potential consequences, others are less so, which might make a potentially expensive treatment with significant implementation burdens less acceptable to them. The GDP recognized that GnRHa treatment is variably feasible in high-income countries, in part based on variable insurance coverage, but may be even less feasible in lower-income countries. In particular, since GnRHa treatment is expensive, feasibility for individual patients

and their caretakers may largely depend on the degree to which treatment is covered by insurance.

Justification for the recommendation

Overall, a majority of GDP members judged that the desirable effects of GnRHas—including an increase in adult height and a delay of menarche in girls—are moderately substantial, that the undesirable effects are small but important, and that the balance of effects probably favors the use of GnRHas for many patients with CPP. However, the certainty of evidence was very low for all outcomes. The GDP also recognized that GnRHa treatment is expensive, and acceptability of treatment would depend heavily on how individual patients and families prioritize the outcomes for which we have evidence (eg, adult height, menarche) in addition to out-of-pocket treatment costs. In addition, and very importantly, the GDP agreed that certain patient subgroups with CPP may be less likely to realize net benefits with GnRHas. For all of these reasons, they issued a conditional recommendation for GnRHa treatment for many patients with CPP, with an important caveat being that some patient subgroups may be less likely to achieve net benefit with such treatment.

Subgroup considerations

The GDP noted that important subgroups of patients, especially among girls, may not benefit from GnRHa treatment. In particular, this recommendation was predominantly driven by the adult height outcome, and some patient subgroups may not be expected to derive an important height benefit with GnRHas. For example, for some girls with CPP who are tall and have a normal PAH, reassurance and education on how to handle menarche when it occurs may be more appropriate than GnRHa treatment. In addition, GnRHas are not expected to substantially alter adult height when started during or after the peak pubertal growth spurt. Similarly, children with a very late diagnosis of central precocious puberty, including those who present with advanced bone ages (eg, 12 years in girls and 13 years in boys), are not expected to derive substantive benefits (especially regarding adult height) with GnRHa therapy.

The studies in the systematic review did not, in most cases, perform subgroup analyses according to age of puberty onset. However, several studies, including one meta-analysis, suggest that starting treatment after age 7 years may not be effective for improving adult height, especially as compared with starting treatment before age 6 years, when the benefit has been reported to be greatest (171-174). While treatment of those with puberty onset between ages 8.0 and 9.0 years technically does not fall within the scope of this guideline, it was the GDP's clinical experience that some patients being treated with GnRHas have had pubertal onset after age 8 years, and several studies have found little if any height benefit in this group (175). In addition, analyses supporting recommendations 1 and 2 imply that girls with the onset of CPP at borderline ages (7.0-8.0 years), as well as girls ages 6.0-8.0 years with slowly progressive puberty, are unlikely to achieve an important height benefit with GnRHa treatment.

The GDP emphasized the importance of carefully discussing expected benefits and potential risks with all patients and families, and using an individualized, shared decision-making approach. In addition to PAH, factors such as the age of pubertal onset, potential psychological impacts of continued pubertal progression, and attainment of menarche should be carefully weighed (176).

Although GnRHas are generally well-tolerated by children with CPP, their use is contraindicated in certain medical conditions or circumstances, including a known allergy or hypersensitivity to GnRHas or any other components of the medication. The frequency of allergic reactions is generally low but varies, and one should refer to the package insert of the manufacturer for these estimations.

Research considerations

In the absence of comparative research, more data should be acquired on outcomes of GnRHa treatments for CPP other than adult height and BMI. These include, but are not limited to, short-term outcomes on BMD, cognition, and psychosocial well-being, as well as longer-term outcomes such as psychosocial outcomes and bone and cardiometabolic diseases in adulthood. Evidence in boys was lacking, highlighting the critical need for additional research in this group. RCTs comparing GnRHa treatment vs observation alone would also be valuable, especially for patients with CPP who may be less likely to derive an adult height benefit with GnRHa treatment (eg, older girls with CPP).

Treatment initiation with gonadotropin-releasing hormone agonists: monthly vs longer acting

Background

GnRHas are currently offered in various formulations, including monthly injections and longer-acting formulations, such as 3- and 6-month injectables and a subcutaneous implant (Table 4). No oral GnRHa formulations are currently clinically available. The longest clinical experience is with the monthly GnRHa injectable formulations, which have been widely used and offer flexibility in dosing. However, longer-acting GnRHa formulations provide the advantage of reduced injection frequency, thereby improving convenience and potentially long-term adherence to therapy. These latter options may have higher upfront costs compared to monthly injectables, and they have less long-term comparative data regarding efficacy and safety. Furthermore, the subcutaneous implant requires additional infrastructure and expertise for placement and removal.

Access to these different GnRHa formulations, expertise in their administration, and costs may vary considerably among different countries and clinical settings. The decision to initiate therapy with monthly vs long-acting GnRHas depends on several factors, such as patient and caregiver preferences, provider comfort, likelihood of adherence, and cost. Given that the monthly GnRHa formulations were the first to be introduced for the treatment of CPP, and were followed by the 3-monthly and much later the 6-monthly GnRHa formulations, they were more extensively studied in terms of safety and efficacy. Therefore, many

clinicians continue to choose them for initiating CPP treatment, although they may convert to long-acting GnRHa formulations after the first 3 to 4 months of treatment once pubertal suppression has been confirmed. This stepwise strategy, however, may be unnecessary.

Question 7

Should initiating therapy with monthly GnRH agonists vs long-acting GnRH agonist preparations be used for CPP treatment?

Recommendation 7

In patients with central precocious puberty who will use a long-acting gonadotropin-releasing hormone agonist in the long term, we suggest initiating therapy with the long-acting gonadotropin-releasing hormone agonist preparation rather than initiating therapy with a monthly gonadotropin-releasing hormone agonist. (2 | ⊕⊕OO)

Technical remarks:

- Long-acting GnRH agonist preparations refer to those with ≥3-month duration of action (eg, 3-month and 6-month injectable formulations and the 12-month subcutaneous implant).
- Patients and families who anticipate using monthly GnRH agonist preparations in the long term should begin with a monthly GnRH agonist preparation.

Summary of evidence

The systematic review results, a detailed summary of the evidence, and EtD tables can be found online at https://guidelines.gradepro.org/profile/_TJtoyM7kGc.

Benefits and harms

The GDP prioritized the following outcomes: Tanner stage progression, degree of gonadotropin or sex steroid suppression, growth velocity, and medication-related adverse events. The commissioned systematic review identified 3 RCTs (177-179) and 7 observational comparative studies (180-186), encompassing a total of 759 participants across 7 countries with a mean age of 8.3 ± 1.3 years (27). Most outcomes were assessed between 6 months and 2.5 years after GnRHa initiation. Eight studies (603 patients) assessed peak GnRHa-stimulated serum LH concentrations (177-179, 181-184, 186). The pooled mean difference in peak GnRHa-stimulated serum LH concentrations was −0.16 IU/L (95% CI: −0.50, 0.19) favoring long-acting formulations; this was deemed to be a trivial difference by the GDP. Eight studies (581 patients) included an analysis of the proportion of patients achieving serum LH suppression (177-179, 181, 182, 184-186). Despite some variation in LH assay methods and definitions of serum LH suppression thresholds (ranging from <2 IU/L to <4 IU/L), the estimated proportion of patients achieving adequate LH suppression was equivalent between monthly vs long-acting GnRHas (relative risk [RR]: 1.00 [95% CI: 0.94, 1.07]). Five studies (301 patients) reported GnRHa-stimulated FSH concentrations with a mean difference of −0.11 IU/L favoring the long-acting formulations (95% CI: −0.91, 0.69), which the GDP judged to be a trivial difference (177, 181, 183, 185, 186).

Seven studies (415 patients) reported growth velocity during treatment; all followed patients for a period of at least 1 year, with the exception of Yang et al., with a follow-up of 6 months (177-181, 183, 185). Growth velocity outcomes were comparable, with pooled data suggesting no meaningful difference between monthly and long-acting GnRHa regimens (mean difference −0.18 cm/year [95% CI: −0.84, 0.48]) (27).

Finally, a sensitivity analysis limited only to the 3 RCTs had similar findings, showing consistent results across all outcomes including growth velocity (mean difference 0.13 cm/year [95% CI: −1.28, 1.55]), peak LH concentrations after stimulation (mean difference −0.23 IU/L [95% CI: −0.93, 0.46]), and the proportion achieving adequate LH suppression (RR: 1.05 [95% CI: 0.92, 1.20]) (177-179).

The commissioned systematic review did not identify studies comparing the 2 treatments that also reported medication-related adverse events (eg, allergic reaction and sterile abscesses) (27). All studies included patients on injectable therapies; no studies were identified that compared monthly injectables to a GnRHa implant, which is frequently used as a treatment option in the United States but is currently unavailable in other countries. Furthermore, the studies identified were limited to comparing 1-month vs 3-month formulations, with no data available for 6-month formulations. Importantly, the evidence review was intended to address initiation of therapy and did not address ongoing treatment decisions or switching between formulations during the treatment course.

Other evidence-to-decision criteria and considerations

The GDP agreed that both shorter- and longer-acting GnRHa formulations are generally expensive (Table 4); however, the costs, including out-of-pocket costs to families, can vary significantly due to multiple factors, including the clinical setting in which they are administered (eg, outpatient vs inpatient), differences in drug formulations and dosing schedules, the specific dose prescribed, the country where the patient receives care, insurance coverage and reimbursement policies, and variations in billing practices and markup costs across health care systems.

Primary studies were identified related to resources used with the histrelin acetate implant. In a U.S. study of 746 patients with CPP (or alternate diagnosis) who underwent 1794 unique procedures of implant placement, replacement, or removal, 60% were performed in the clinic, 35% in the sedation unit, and 5% in the operating room (187). This has been noted to shift with time in one study to more clinic-based procedures (188). In a similar patient population, up to 82% were performed with sedation, and younger age was a risk factor for requiring sedation (189); similarly, conscious sedation was administered to 73% of patients

at different U.S. centers (190). In a U.S. study of 114 cases, 96% were achieved with local anesthesia, 50% of whom also received inhaled nitrous oxide, and 4% received general anesthesia (191). In a survey of more than 200 pediatric endocrine providers, a mix of inpatient (41%), outpatient (35%), or both types of settings (23%) was used for these procedures (134).

The GDP did not identify any systematic reviews comparing the cost-effectiveness of different formulations for GnRHa initiation. Although monthly formulations can have a lower upfront cost per dose, when considering the total cost of therapy over a full year, longer-acting formulations could offer similar or potentially greater economic value. For example, a retrospective U.S. cohort study of 1177 commercially insured and 658 Medicaid-insured patients with CPP found commercially insured patients treated with histrelin acetate used more services in general than those treated with leuprolide acetate but had fewer office visits, while health care service use was similar between Medicaid-insured treatment groups (73). Another U.S. study of more than 4000 patients found that the median annual total treatment costs of histrelin acetate ($23,071 [interquartile range, $16,833-31,050]) were lower than those with leuprolide acetate monthly or quarterly ($27,021 [interquartile range, $18,314-34,995]; $P < .0001$) (192). In this study, the total histrelin acetate implant treatment cost included the medication, implantation and explantation procedures (including surgical time), anesthesia, imaging, and office visits, while the total leuprolide acetate treatment cost included medication, injection procedures, and office visits (192).

The GDP identified no studies that addressed the potential for differential health-equity impacts between the 2 treatment strategies. Patients and families with lower socioeconomic status may face greater barriers to long-acting formulations due to higher upfront costs, and many are often not fully covered by insurance in the United States, but such barriers would presumably impact both short-term accessibility (ie, treatment initiation) and long-term accessibility. Since these medications are intended to be administered by a health care provider, monthly injections may pose an adherence barrier if transportation or parental missed time from work is a barrier, and this may be more likely impact families with lower baseline health equity.

The GDP found no systematic reviews specifically addressing the acceptability of short- vs longer-duration GnRHa formulations. However, it was noted that the short-acting GnRHa formulation may be perceived as more acceptable due to its longer history of clinical use. Family preference and ease of treatment for families were reported by 87% of surveyed pediatric endocrine providers as key determinants influencing the choice of GnRHa preparation (134). Acceptability may also be affected by route of administration, concerns related to coping with adverse effects, the need for a procedure with or without sedation (specifically relevant to the subcutaneous histrelin acetate implant), the frequency of injections (which impacts the number of clinical visits), and the cumulative amount of discomfort or pain. In a retrospective chart review of 44 children with CPP, 18% received injectable GnRHa before the histrelin acetate implant. Among these families, 88% of parents preferred the implant to the depot injection, and 95% stated they would agree to have their child undergo surgical implantation again (190). In this same study, 7% considered the need for a surgical procedure to be a disadvantage.

The GDP found no systematic reviews addressing the feasibility of the various approaches in this clinical scenario. In a survey of 223 pediatric endocrine practitioners, 64% reported that insurance coverage played a significant role in determining the type of GnRHa formulation (134). The feasibility of a monthly formulation compared to long-acting formulations may be constrained by insurance formularies; availability across countries; and a medical center's capacity to procure, transport, and store medications. Additionally, training on medication administration (eg, injections, implantation) may limit feasibility as well as access to care (eg, travel to the medical center). Specific to the subcutaneous implant, geographic disparities may exist even within countries as access to pediatric endocrinologists or surgeons who place, replace, and remove these implants may impact medication access. The histrelin acetate implant is U.S. Food and Drug Administration (FDA) approved for 12 months; however, subsequent studies, in both CPP and other populations, have demonstrated that it has an extended duration of action of up to 2 to 7 years (193-202).

Justification for the recommendation

The GDP suggested that in many but not all patients with CPP, treatment with GnRHa should be used (clinical question 6), but the current clinical question specifically relates to which formulation (ie, monthly vs long-acting GnRHa formulations) should be used at treatment initiation. The commissioned systematic review indicated trivial differences in stimulated gonadotropins (eg, peak after GnRH/GnRHa stimulation testing), likelihood of adequate LH suppression, and growth velocity suppression between monthly and long-acting GnRHas. No data were available for sex steroid suppression or Tanner stage progression, but the GDP considered gonadotropin suppression to be an excellent surrogate for these outcomes. They judged that the undesirable effects of monthly compared to long-acting GnRHas—particularly more frequent injection-related pain and associated psychological distress—were small but important. Therefore, the GDP reached consensus that the balance of health effects probably favors the comparator (ie, initiating therapy with a long-acting GnRHa). While the GDP concluded that the resources required vary based on different types of GnRHa and geographic and health care settings, they deemed cost-effectiveness to probably favor long-acting formulations. The GDP judged that in most contexts, both options are generally feasible; however, they judged that many might find monthly injections less acceptable than longer-acting injections. The GDP therefore issued a conditional recommendation that, in patients with CPP whose treatment plan is to use a long-acting GnRHa long term, therapy should be initiated with the long-acting GnRHa preparation rather than with a monthly GnRHa. However, if a patient will use monthly GnRHas over the long term, the GDP judged that it would make most sense for them to begin treatment with monthly GnRHas.

Research considerations

Adequately powered clinical trials that compare monthly vs long-acting GnRHa formulations (eg, ≥ 3 months) for the

initiation of treatment should be conducted in patients with CPP. Optimal treatment of CPP with the best formulation of GnRHa is a priority, given that inadequately treated CPP may lead to compromised final height and other potential long-term risks. Cost-effectiveness studies comparing different GnRHa formulations are also needed. Such studies should model efficacy, costs, and adherence to therapy, among other factors. Additional research into patient and family values would also be valuable.

Monitoring pubertal suppression in children treated with gonadotropin-releasing hormone agonists

Background

GnRHa treatment is generally very effective in achieving pubertal suppression. Rarely, however, standard doses and dosing intervals may not adequately suppress the HPG axis. Pubertal suppression on GnRHa therapy can be confirmed using a GnRH/GnRHa stimulation test or assessing an LH concentration following a subsequent dose of GnRH/GnRHa treatment. A GnRH/GnRHa stimulated LH response lower than 1 to 3 IU/L has been considered an indicator of adequate pubertal suppression (182). If this approach is used, once pubertal suppression is determined, subsequent biochemical monitoring may be performed using unstimulated serum LH concentrations; however, these do not revert to low prepubertal concentrations (<0.3 IU/L) in many children on GnRHa treatment.

Conversely, pediatric endocrinologists may choose to monitor clinical signs of puberty (eg, Tanner staging and growth velocity) without biochemical monitoring. Signs of inadequate pubertal suppression for the anticipated duration of therapy may be subtle, such as breast tenderness in girls. While important to assess, growth acceleration in GnRHa-treated children may be a later manifestation of inadequate pubertal suppression. When inadequate pubertal suppression is detected, pediatric endocrinologists may respond by shortening the time interval of injectable GnRHa (eg, from 4 to 3 weeks for monthly formulations) or consider increasing the dose of the same formulation, if possible.

One consideration is that clinical monitoring alone could fail to identify inadequate suppression of puberty while on GnRHa treatment. However, GnRH/GnRHa testing during treatment is time consuming and costly. Therefore, the optimal monitoring of pubertal suppression with GnRHa therapy in children with CPP was prioritized by the GDP.

Question 8

Should biochemical testing (eg, LH, sex steroids) vs clinical assessment alone be used for monitoring pubertal suppression in those being treated for CPP with GnRH agonists?

Recommendation 8

In children being treated for central precocious puberty with a gonadotropin-releasing hormone agonist, we suggest against routine biochemical testing (eg, luteinizing hormone and sex steroid concentrations) to monitor pubertal suppression. (2 | ⊕OOO)

Technical remarks:

- The panel assumed that interval clinical assessment and monitoring (eg, growth velocity, Tanner staging, and annual bone age assessments) would be performed routinely for all children with CPP receiving GnRH agonist treatment.
- This recommendation pertains specifically to children without clinical evidence to suggest GnRH agonist treatment failure. Evidence of potential treatment failure may include progression in breast development or testicular size, acceleration in growth velocity, and/or persistent pubertal growth velocity.
- The guideline-development panel emphasized the importance of assessing GnRH agonist treatment adherence and administration technique in all patients with concern for treatment failure.
- The panel assumed that most pediatric endocrinologists would perform biochemical testing when treatment failure is suspected clinically, before implementing changes in the dose, duration, and/or formulation of GnRH agonist therapy.

Summary of evidence

The systematic review results, a detailed summary of the evidence, and EtD tables can be found online at https://guidelines.gradepro.org/profile/_jM9OM0FTgM.

Benefits and harms

The commissioned systematic review did not identify direct evidence to address this clinical question (27). In particular, the systematic review team did not identify any studies addressing whether the outcomes selected by the GDP, including adult height, psychological distress, and age at menarche differ based on a strategy that includes biochemical monitoring vs clinical assessment alone. Therefore, they relied on indirect evidence.

The potential value of determining serum LH (eg, basal or GnRH/GnRHa-stimulated concentrations) or sex steroid concentrations in patients receiving injectable GnRHa treatment relates to identifying patients who do not remain under pubertal suppression for the expected duration of action, thus requiring adjustment in medication frequency or dosing. Many studies have used a basal LH concentration of lower than 1.0 IU/L or a

GnRH/GnRHa-stimulated LH concentration lower than 3 IU/L to confirm pubertal suppression (131, 203, 204).

In 1 study, leuprolide treatment at a dose of 3.75 mg intramuscularly every 28 days resulted in pubertal suppression, defined in this study as a peak LH response lower than 3 IU/L, in 85.5% of patients at the start of the third treatment month (131). However, 9 patients (14.5%) exhibited inadequate pubertal suppression, and their leuprolide dose was increased to 7.5 mg per month. Among these 9 patients, GnRH stimulation testing at 6 months demonstrated adequate pubertal suppression in only 5 of them (8%); however, because none of the patients exhibited clinical evidence of treatment failure, GnRHa doses were not altered. Subsequently, pubertal suppression was not achieved in 3 patients at 9 months. However, in the absence of clinical evidence of pubertal progression in these patients, GnRHa doses were again not altered. In this study, the number of patients with inadequate pubertal suppression was inversely proportional to treatment duration, and by 1 year of treatment, pubertal suppression was documented biochemically in all patients.

In a prospective, uncontrolled, observational study of 33 children (26 girls; mean age 7.2 $\pm$ 2.5 years) with CPP treated at a tertiary pediatric endocrinology center, random ultrasensitive LH measurement was obtained at 6 months, and a GnRH/GnRHa stimulation test was performed at 12 months (203). In 59%, a random basal LH concentration at 6 months exceeded 0.3 IU/L, while GnRH/GnRHa stimulation tests revealed complete pubertal suppression (peak LH <4 IU/L) in 100%. No patient in this study had clinical evidence of pubertal progression. Similarly, in a study of 14 patients with CPP, short stature, or small-for-gestational-age who were treated with leuprolide acetate 3.75 mg subcutaneously every 4 weeks (204), peak GnRHa-stimulated LH concentration indicated insufficient pubertal suppression in 6 of the 14 boys (43%) at 3 months, although all boys had exhibited cessation of pubertal progression clinically.

Additionally, it is generally well accepted that sex steroid concentrations should be below the pubertal reference range during GnRHa treatment; however, the GDP was not aware of any well-substantiated cutoff values that would indicate effective vs ineffective suppression of (clinical) pubertal progression. Notably, estradiol (E2) concentrations by gold standard liquid chromatography-tandem mass spectrometry (LC-MS/MS) are age-dependent, and prepubertal E2 concentrations may be up to 40 pmol/L (205), but many clinical E2 assays are not LC-MS/MS and therefore may be of limited value. Total testosterone concentrations by LC-MS/MS in boys are a useful clinical tool in assessing for pubertal suppression.

Although this indirect evidence suggests that standard GnRHa doses sometimes fail to achieve pubertal suppression, as determined biochemically, the GDP did not identify evidence that would indicate how often standard GnRHa doses clinically fail to suppress puberty. In this regard, while growth velocity may be the most reliable clinical indicator of pubertal progression, it may be a relatively late indicator of inadequate pubertal suppression. Similarly, pubertal staging may not be an accurate indicator, at least not over the short term, and BA advancement may be influenced by other factors, such as obesity (206, 207). Overall, based on the GDP's collective clinical experience, they suspected that it could take 4 to 6 months—the minimum time required to reliably detect an increase in growth velocity and advancement in pubertal stages—to reliably identify clinical progression of puberty. Although a 4- to 6-month period with inadequate pubertal suppression might be concerning, especially to families, the GDP was not aware of studies suggesting that a 4- to 6-month period of inadequate HPG axis suppression would significantly impact patient-important outcomes. In addition, the GDP considered the possibility that, if apparent biochemical treatment failure does not reliably translate to clinical treatment failure and/or worse patient-important outcomes, then acting on biochemical findings alone could potentially lead to overtreatment.

Other evidence-to-decision criteria and considerations

As a general rule, fewer unnecessary test procedures would be viewed as desirable. For example, if no available evidence suggests increased adult height in those monitored with biochemical testing vs those monitored with clinical investigations alone, clinical assessment might be preferred by patients and families. In addition, the resources required for biochemical testing under consideration can be substantial. As noted in clinical question 3, pharmacologic stimuli and required hormonal assays can be expensive, and GnRH/GnRHa stimulation testing requires expert personnel for administration and for repeated blood draws.

Based on their collective experience and expertise with biochemical monitoring, the GDP judged that most stakeholders would find the intervention (ie, biochemical monitoring) generally acceptable. The GDP recognized that acceptability would partly depend on whether biochemical monitoring could reasonably lead to greater improvements in treatment effectiveness (compared to clinical monitoring alone). The GDP also recognized that some patients and families may want the reassurance that biochemical monitoring might provide (ie, they might find clinical monitoring alone unacceptable), even in the absence of evidence to suggest tangible improvements in patient-important outcomes.

Regarding feasibility, the availability of GnRHa testing differs among, and sometimes within, countries and different medical settings. Gonadotropin and sex steroid assays are expected to be available in all contexts in which GnRHa treatment is feasible, but some may not have access to ultrasensitive gonadotropin or gold-standard mass spectrometry-based steroid assays. If biochemical testing is not associated with improved outcomes, reducing the number of unnecessary GnRH/GnRHa stimulation tests and basal LH determinations could be advantageous from a health equity standpoint.

Justification for the recommendation

The GDP relied on indirect evidence for this clinical question, as no clinical studies have addressed the impact of different monitoring strategies on the patient-important outcomes they selected. The GDP's review of the available indirect evidence focused on how biochemical parameters (eg, basal or stimulated LH concentrations) relate to progression of puberty. However, although commonly accepted standards regarding cutoff values

that suggest pubertal suppression exist, the ability of such therapeutic targets to accurately predict GnRHa treatment failure remains unclear. In addition, the GDP considered the possibility that the routine preemptive use of such accepted serum LH cutoffs, in the absence of clinical evidence for treatment failure, could lead to overtreatment. A majority of GDP members judged that the balance of desirable and undesirable effects likely favors the comparator (ie, not doing biochemical monitoring). The GDP also considered the added costs and potentially reduced feasibility of routine biochemical monitoring. The GDP ultimately reached consensus on a conditional recommendation against routine biochemical monitoring. Importantly, the GDP emphasized the importance of interval clinical assessments (eg, growth velocity, Tanner staging, and annual bone age assessments) in all children with CPP receiving GnRHa treatment, and they agreed that biochemical testing should be used to confirm clinically suspected treatment failure rather than altering GnRHa treatment on the basis of clinically suspected treatment failure only.

Research considerations

Adequately powered clinical trials that compare biochemical testing (eg, determination of basal or GnRH/GnRHa-stimulated LH and sex steroid concentrations) in addition to clinical assessment vs clinical assessment alone to monitor pubertal suppression, and its impact on final adult height, should be conducted in patients with CPP. Studies addressing the cost-effectiveness of different monitoring strategies would also be valuable.

Addition of growth hormone to increase adult height in children treated with gonadotropin-releasing hormone agonists for central precocious puberty

Background

One goal of therapy in CPP is to restore the rate of linear growth to that of a prepubertal child. However, linear growth commonly slows to well below a normal rate in children on GnRHa therapy and even arrests in some cases. This may be particularly observed when puberty has progressed to the point that skeletal maturation is significantly advanced (208). Although the underlying mechanisms are poorly understood, pubertal concentrations of sex steroids are required for continued linear growth once a certain BA is attained. Since a key aim of GnRHa treatment is to increase adult height, a dilemma exists when that same therapy might prevent a child from interval height gains in the short term. Therefore, the potential use of GH as adjunctive therapy in CPP has long been of interest (19, 209). 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.

Question 9

Should growth hormone plus GnRH agonist therapy vs GnRH agonist therapy alone be used to increase adult height in children treated for CPP?

Recommendation 9

In children with central precocious puberty, we suggest against the routine addition of growth hormone to gonadotropin-releasing hormone agonist therapy. (2 | ⊕OOO)

Technical remarks:

- This recommendation does not pertain to children with CPP who also have a distinct, well-established indication for growth hormone therapy.

Summary of evidence

The systematic review results, a detailed summary of the evidence, and EtD tables can be found online at https://guidelines.gradepro.org/profile/96QxeRALnZk.

Benefits and harms

The health-related outcome judged to be most critical for decision-making in this context was adult height. Additional patient-important outcomes selected by the GDP included medication-related adverse events, psychological effects, quality of life, and cancer risk.

A commissioned systematic review (27) identified 8 retrospective cohort studies that assessed height outcomes with combination GH and GnRHa therapy compared to GnRHa therapy alone (168, 210-216). Studies had high heterogeneity, were conducted in three countries, and comprised 1024 girls, 276 of whom received GH. Mean age was 8.9 ± 0.9 years, and clinical follow-up ranged from 4 to 9 years. Individual study sample sizes ranged from 10 to 95 in treatment groups and 10 to 244 in control groups. Although individual studies reported mixed results, meta-analysis suggested that combination (GnRHa + GH) therapy was associated with an estimated −0.16 cm (95% CI: −2.12, 1.81) difference in adult height compared to GnRHa treatment alone. The GDP judged this difference to be trivial. In a subgroup analysis based on PAH, studies of patients with mean baseline PAH more than 155 cm suggested a mean adult height difference of −1.2 cm (95% CI: −5.96, 3.55) with GH, while studies of patients with mean baseline PAH lower than 155 cm suggested a mean height difference of +0.72 cm (95% CI: −2.78, 4.21) with GH, with no demonstrable difference between subgroups ($P = .33$). The systematic review did not identify relevant studies reporting on cancer, medication-related adverse events, psychological effects, or quality of life. Study limitations include that they were retrospective, had variable sample sizes and length of follow-up, and only included girls (27). Regardless,

based on available evidence related to adult height outcomes, the GDP judged the beneficial effects of the intervention (addition of GH to GnRHa therapy) to be trivial.

No medication adverse events were reported in the identified studies. The undesirable effects of GH considered by the GDP were based on indirect evidence related to GH use in other contexts such as GH deficiency (217). Rare but potentially serious adverse effects of GH therapy include scoliosis, slipped capital femoral epiphysis, glucose intolerance, and pseudotumor cerebri. Overall, the GDP considered the undesirable effects of GH to be small but important.

Other evidence-to-decision criteria and considerations

The GDP recognized that adult height is considered an important outcome for many families and that short stature may be perceived as detrimental and stigmatizing, particularly for boys. Although related to children evaluated for short stature, the book "Normal at Any Cost: Tall Girls, Short Boys, and the Medical Industry's Quest to Manipulate Height" (217) provides multiple examples of parents' intense desire to increase their child's height.

The GDP did not identify any systematic reviews regarding resources required or cost-effectiveness for GH therapy in children with CPP. A primary study in a very small cohort of Cypriot girls with CPP (n = 5) and low PAH reported the costs of combined treatment with GnRHa and GH (218). After a mean treatment duration of 3.5 years, the study identified a mean height gain of approximately 5 cm (+0.8 SDS), and the cost analysis estimated that each centimeter gained cost approximately €2700 (euros). In addition, a retrospective study evaluated treatment data from a small cohort of Chinese girls with CPP, comparing the cost of GnRHa alone with combined GnRHa and GH (219). Estimated total costs for the latter group were nearly 3.8 times higher ($25,143 vs $6,657 U.S. dollars) with no statistically significant increase in PAH, implying poor cost-effectiveness for the addition of GH to GnRHa therapy. In both of these studies, authors suggested that combined therapy should be considered only in those patients with CPP with extremely low PAH due to its high economic cost. The GDP considered that the costs of GH therapy could have an undesirable economic impact for families and public health systems. The practical availability of combined therapy for children with CPP would vary widely across countries, since it would depend on how GH therapy is financed (eg, public health system, insurance, or out of pocket). Currently, CPP is not an approved indication for GH therapy in any country. Therefore, most families would presumably be responsible for its costs. Notably, low PAH in children with CPP does not meet the criteria for the diagnosis of idiopathic short stature (currently, an indication for GH therapy in the United States). Therefore, the GDP judged that the intervention would have large costs, and they had high confidence in this judgment based on indirect evidence related to GH therapy for non-CPP indications (220). Consequently, the GDP indicated that cost-effectiveness probably favors the comparator (ie, GnRHas alone).

Given that GH therapy would likely have high costs and that it is not an approved indication for CPP worldwide, the GDP concluded that the intervention could exacerbate health inequities, since not all families or public health systems would be able to afford routine GH therapy for children with CPP. Moreover, large costs for an ineffective treatment would inequitably burden families with fewer resources. Indirect evidence came from literature on disparities in the use of GH for non-CPP indications, such as reduced clinical investigation and undertreatment in children from underrepresented communities (221) or excessive diagnostic investigation and overtreatment in boys compared to girls (222). These findings indicated that the intervention would probably reduce health equity.

The collective experience of GDP members is that key stakeholders usually consider GH therapy acceptable to increase height gain in children with low PAH. In addition, the GDP agreed that GH should be considered in children with distinct growth disorders (ie, approved indications for GH). Conversely, the GDP judged that the feasibility of this intervention varies across clinical and geographic settings. In fact, several practical aspects may impact the acceptability and feasibility of GH combined with GnRHa in patients with CPP. These include the need for daily or weekly subcutaneous injections, administration by the caregivers or patients themselves, additional biochemical testing (eg, serum insulin-like growth factor-1 concentrations), and the particularly high cost of the combined regimen. These findings might suggest that GH therapy could impart substantial burden and adherence challenges that should be incorporated in the decision-making process, especially in disorders that are not approved indications for its use, such as CPP.

Justification for the recommendation

The available evidence in girls with CPP suggested that addition of GH to GnRHa treatment is associated with no meaningful difference in adult height (−0.16 cm [95% CI: −2.1, 1.8). Studies were not identified in boys. Evidence was insufficient for other selected outcomes (medication-related adverse effects, psychological effects, quality of life [QOL], and cancer risk). However, extrapolating from evidence related to GH use in other contexts, the GDP judged that the undesirable health effects of GH are likely small but important. Overall, they judged that the balance of health effects likely disfavors the addition of GH to GnRHa treatment. In addition, GH treatment is generally very expensive and, thus, would likely not be cost-effective for most individuals with CPP. For these primary reasons, the GDP issued a conditional recommendation against adding GH therapy to GnRHa treatment.

Subgroup considerations

The GDP acknowledged that the addition of GH to GnRHa may possibly lead to a meaningful increase in adult height in specific patient populations, although specific evidence to support this statement is sparse. Subgroups that may derive greater adult height benefits may include patients with extremely low PAH, with the caveat that PAH has been reported to be unreliable in the setting of CPP, and/or those who experience a decrement in growth velocity below prepubertal ranges (eg, < 4 cm/year) during GnRHa treatment but in whom cessation of therapy is not appropriate (223, 224). Additionally, the GDP acknowledged that GH therapy would be completely appropriate in children with CPP who also have approved indications for GH therapy such as growth hormone deficiency, Prader-Willi syndrome,

idiopathic short stature, short stature and born small-for-gestational age, and *SHOX* gene defects (225).

Research considerations

Definitive information regarding the potential benefit of adding GH to GnRHa therapy in children with CPP will depend on large-scale, long term RCTs that follow patients to adult height. In particular, data in boys are sparse, and relevant research in boys with CPP is clearly needed. Given the relative rarity of CPP, especially among boys, studies would likely need to be multicenter and international. Additional barriers to such studies include the high cost of GH, that CPP is not an approved indication for its use, and the inherently long-time frame necessary in order to determine reliable conclusions.

Discontinuing treatment for central precocious puberty

Background

When GnRHa treatment has been initiated, patients and family often desire to discuss the age at which treatment will be discontinued. Considerations relevant to the timing of treatment discontinuation include the appropriate ages for menarche in girls or virilization in boys, psychosocial maturity, and whether continuing treatment could increase adult height. The 2009 Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology consensus conference on GnRHa therapy analyzed the various factors that could be used to decide on the best timing for treatment discontinuation (10). This group of experts concluded that evidence is insufficient to rely on any one clinical variable (eg, CA, therapy duration, BA, height, midparental target height, growth velocity) to guide the timing of GnRHa discontinuation (10). Therefore, the consensus statement suggested it is reasonable to consider these parameters in the context of parent and patient preferences, with the goal of menarche occurring near population norms for timing (10). Given the uncertainty regarding the optimal timing of GnRHa discontinuation, the GDP prioritized this clinical question.

Question 10

Should continuation of GnRH agonist treatment vs discontinuation of GnRH agonist treatment be used for children with CPP who reach a chronological age of 10 years (girls) or 11 years (boys) or a bone age of 11 years (girls) or 12 years (boys)?

Recommendation 10

In children being treated for central precocious puberty, we suggest against routinely continuing gonadotropin-releasing hormone agonist treatment 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)

Technical remarks:

- The potential reasons to consider GnRH agonist continuation beyond these recommended ages are highly individualized and may include growth trajectory, psychosocial considerations, and/or neurocognitive impairment (eg, developmental delay).

Summary of evidence

The systematic review results, a detailed summary of the evidence, and EtD tables can be found online at https://guidelines.gradepro.org/profile/f6Wi-8_qGzM.

Benefits and harms

The clinical outcomes selected by the GDP were adult height, menarche occurring at a normal age in girls, psychological distress, BMD (as a surrogate for fracture risk), and medication-related adverse effects. The commissioned systematic review did not identify direct evidence to address this clinical question (27). In particular, the systematic review team found no published studies comparing outcomes based on different ages at treatment cessation. The GDP therefore relied on indirect evidence to address this question.

Several studies suggest that height outcomes are more closely related to patient characteristics at the start of treatment rather than at the time of treatment discontinuation. Early age at the onset of CPP and, thus, early age at treatment initiation tend to predict more favorable adult height outcomes (169). In 1 study, adult height was higher in the group with early CPP (starting age <6 years), with a mean gain in height of 10.8 ± 2.5 cm compared to the group with late CPP (starting ages 6-8 years; 7.2 ± 4.3 cm) despite similar characteristics at the end of treatment (169). This indirect evidence suggests pretreatment characteristics may be more important determinants of adult height than age at discontinuation of therapy.

Additional indirect evidence comes from the use of GnRHas in short stature in children without PP. It was previously suggested that delaying pubertal development with GnRHa therapy could pharmacologically increase adult height by prolonging the duration of growth. One meta-analysis suggested that the mean impact of GnRHas on height was +2.5 cm when started after age 8 years in patients with CPP (226). Another meta-analysis including only girls with early-normal puberty (in general, ages 8-9 years) showed minimal or no effect on height (226). In a pivotal study, Yanovski et al. suggested a mean 4.2-cm increase in adult height with an average of 3.5 years of GnRHa when treatment was initiated at age 12 years in girls with short stature without CPP and age 13 years in boys with short stature without CPP (227). However, this approach was associated with a decrease in BMD during treatment. Taken together, these data may imply that delaying puberty to increase adult height is inefficient when conventional treatment duration is utilized; however, an effect may be observed if pubertal delay is continued to older ages (eg, ages 15-16 years in girls), an option that is not likely

to be acceptable to most and that has not been formally studied in CPP.

The determinants of age at menarche have been evaluated in observational studies, but no RCTs were identified that evaluated the impact of age at treatment cessation on age at menarche (169, 226). Menarche will not occur during effective GnRHa treatment but occurs on average 12 to 18 months after treatment cessation. Several retrospective studies have examined the impact of patient characteristics, both pretreatment as well as at the end of treatment, on age at menarche. Menarche attained pretreatment has been reported as a predictor of earlier menses after GnRHa discontinuation in some studies (228) but not others (229). In the latter study, in which time to menarche was analyzed using survival plots, time to menarche after GnRHa discontinuation did not vary with age at treatment cessation (>11 vs < 11 years) and was longer when BA at treatment discontinuation was more advanced (~18 months with BA <12 years vs ~21 months with BA ≥12 years), although the study had several limitations (229). In summary, although age at treatment cessation strongly influences age at menarche, it does not appear to have a major impact on time between treatment cessation and menarche.

The GDP did not identify any studies that evaluated the influence of age at treatment discontinuation on psychological distress. However, a number of studies have identified an association between age at pubertal onset and several psychosocial parameters, with earlier puberty associated with more unfavorable outcomes such as rule breaking and depressive symptoms (5, 230). However, these studies do not prove causality. Of interest, genetic factors associated with age at menarche may also be associated with risk of depression in adulthood. For example, a Mendelian randomization study suggested that each 1-year increase in self-reported age at menarche is associated with a 4% reduction in odds of depression as an adult (adjusted OR 0.96 [95% CI: 0.94, 0.99]) (231). In men, early pubertal timing has been associated with depressive symptoms, increased risk for anxiety and substance use, although more rigorous Mendelian randomization studies have not shown this association (232).

Other evidence-to-decision criteria and considerations

The outcomes of interest were primarily selected on the basis of GDP members' extensive experience with patients with CPP and their families, as they found no studies that address how such patients and families value specific outcomes in this particular clinical scenario. However, a robust literature exists regarding the general population and the value placed on adult height, especially in relation to QOL, self-esteem, and income (233). However, the effect of height on QOL may be most prominent among those with unusually short or tall heights. The GDP judged that height increments that could plausibly be observed with the intervention would likely not influence long-term QOL. Based on the GDP's collective experience, patients and parents tend to value age at menarche and psychosocial outcomes. In addition, BMD predicts fracture risk, an outcome that can be highly valued, especially in older adults. However, the GDP found no specific literature regarding how pediatric patients with CPP and their parents value BMD (and future fracture risk) as an outcome when making treatment decisions.

The GDP found no systematic reviews or primary studies that address resources required for the intervention vs comparator in this particular clinical scenario. The costs and resources required for GnRHa treatment are addressed in clinical questions 6 and 7. A key factor in the total cost of GnRHa treatment is its duration. Therefore, the degree to which costs increase will be proportional to the amount of additional treatment time when comparing the intervention vs the comparator. The GDP found no systematic reviews or primary studies that address the cost-effectiveness of the intervention. However, given the absence of compelling evidence that would suggest important health benefits of treatment continuation, the GDP judged that cost-effectiveness most likely favors the comparator.

The GDP found no systematic reviews or primary studies that address the potential impact of the intervention vs comparator on health equity. In general, however, those with lower baseline health equity (eg, lower socioeconomic status) are likely to have more difficulty accessing GnRHas over longer periods. Moreover, substantially increased costs for an ineffective intervention would inequitably burden families with fewer resources. Based on these considerations, the GDP judged that a recommendation for longer periods of treatment could have a negative impact on health equity.

The GDP found no systematic reviews (or primary studies) that address acceptability of longer treatment duration. In published studies, the mean age at interruption of treatment is around 11 years in girls with a relatively narrow SD (234). Based on the GDP's collective experience and expertise, earlier rather than later treatment discontinuation is likely to be considered more acceptable to patients and families and other stakeholders. In addition, acceptability of the intervention (ie, longer treatment duration) likely depends on out-of-pocket medication and surveillance costs, degree of certainty that prolonging treatment will improve outcomes, and the patient's desire to restart puberty at an age similar to peers. Some patients may be eager to stop treatment as soon as they reasonably can, and the value they place on putative incremental benefits on adult height (eg, an additional cm of adult height), for example, may vary as a function of their newly predicted adult height. Some parents may be eager to continue treatment as a form of "choice-supporting bias." In addition, fear of psychosocial problems during adolescence could potentially orient parents toward continued treatment.

The GDP found no systematic reviews or primary studies that address feasibility of the intervention in this particular clinical scenario. They judged that it is likely feasible for many to continue GnRHa treatment beyond typical ages. However, feasibility could be negatively impacted by the expected additional costs and burdens associated with treatment continuation. In some contexts, GnRHas may be less accessible (eg, not covered by insurance) after certain ages.

Justification for the recommendation

The GDP relied on indirect evidence for this clinical question, as no clinical studies were identified that addressed the impact of different GnRHa-discontinuation strategies on the patient-important outcomes they selected. The GDP judged that evidence was insufficient to estimate the desirable effects of

routinely continuing GnRHas beyond the specified ages, but that the undesirable effects (eg, pain/anxiety associated with injections, longer exposure to the potential for medication-related adverse events) are likely small but important. Accordingly, the GDP reached consensus that the balance of effects likely favors the comparator (ie, discontinuing GnRHas at the specified ages). The GDP also considered the additional costs that would accrue with longer treatment duration and that acceptability of continuation could be highly variable. Notably, the GDP allowed that continuation beyond the specified ages could potentially be beneficial in some contexts. For these primary reasons, they issued a conditional recommendation against routinely continuing GnRHa treatment beyond CA 10.0 to 11.0 years (girls) or 11.0 to 12.0 years (boys) and/or BA 11.0 to 12.0 years (girls) or 12.0 to 13.0 years (boys).

Additional considerations

The GDP emphasized that the timing of GnRHa discontinuation should be individualized and based on shared decision-making with the patient and caretakers. The GDP also emphasized that, when applying this conditional recommendation, both CA and BA should be considered together, not one or the other in isolation. Moreover, the GDP highlighted that important considerations in the decision-making process may include, growth trajectory and predicted adult height, psychosocial wellness, and the presence of neurocognitive impairment (eg, developmental delay).

Research considerations

RCTs comparing interval height gains and adult height outcomes based on different ages are needed, especially in boys. Additionally, RCTs based on discontinuation of GnRHa therapy determined by CA vs BA would be valued.

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Data availability

The data underlying this article are available as supplemental material to the companion systematic review (https://doi.org/10.1210/clinem/dgag168).

Summary

- Total number of GDP members = 15
- Percentage of total GDP members with relevant (or potentially relevant) COI = 20%

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- None

Open Payments Database: N/A
ASSESSMENT AND MANAGEMENT

- No industry relationships relevant to this CPG.
- No COI management required.

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- None

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- No industry relationships relevant to this CPG.
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- Rhythm Pharmaceutical, Advisory Committee in Bardet-Biedl syndrome

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- No disclosures

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ASSESSMENT AND MANAGEMENT

- No industry relationships relevant to this CPG.
- No management required.

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- Pfizer, Speaking Engagement
- Novo Nordisk, Speaking Engagement
- LUMOS pharmaceutical company, Research and Speaking Engagement
- Debiopharm, investigator

Open Payments Database: N/A
ASSESSMENT AND MANAGEMENT

- Dr. Cassorla's speaking engagements were on the topics of growth hormone, which was considered relevant to the topic of this guideline. Debiopharm is a Swiss Pharmaceutical company which markets the 3-, 6-, and 12-month formulation for the GnRHa Triptorelin. He recused himself from voting and writing on topics related to these relationships.

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Open Payments Database: N/A
ASSESSMENT AND MANAGEMENT

- No industry relationships relevant to this CPG.
- No COI management required.

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- Forsee, Research
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Open Payments Database:
ASSESSMENT AND MANAGEMENT

- Dr. Eugster's research funding is from Forsee, which is developing a pharmaceutical product for central precocious puberty. This is relevant to the topic of this guideline, and she recused herself from voting and writing on topics related to this relationship. Dr. Eugster's relationship with Neurocrine biosciences is related to Congenital Adrenal Hyperplasia, which is not addressed in this guideline and therefore did not need to be managed.

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- Dr. Gradone's relationships with industry, including speaking engagements and research, focused on the topic of Growth Hormone Deficiency. This is relevant to the topic of this guideline, and she recused herself from voting and writing on topics related to this relationship.

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ASSESSMENT AND MANAGEMENT

- No industry relationships relevant to this CPG.
- No management required.

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- No industry relationships relevant to this CPG.
- No COI management required.

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- None

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- No industry relationships relevant to this CPG.
- No COI management required.

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- None

Open Payments Database: N/A
ASSESSMENT AND MANAGEMENT

- No industry relationships relevant to this CPG.
- No COI management required.

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Open Payments Database: No entries
NOTES:

- No industry relationships relevant to this CPG.
- No management required.

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Open Payments Database: N/A
ASSESSMENT AND MANAGEMENT

- Dr. Street's relationships with industry, including speaking engagements and consultations, focused on growth hormone treatment. This is relevant to the topic of this guideline, and she recused herself from voting and writing on topics related to these relationships.

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- None

Open Payments Database: N/A
ASSESSMENT AND MANAGEMENT
No industry relationships relevant to this CPG. No management required.

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- Endocrine Society: Editor or member of an editorial board, Vice Chair Ethics and Professionalism Committee, Chair of COI Advisory Group, Clinical Science Chair Annual Meeting Steering Committee

Open Payments Database: No entries
NOTES:

- No industry relationships relevant to this CPG.

No management required.

Appendix A

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Co-Chair	Stephanie Roberts	No	
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	Evangelia Charmandari	No	
	Erica Eugster	Yes	Pediatric Endocrine Society Representative
	Anna Grandone	Yes	
	Louise Greenspan	No	
	Elizabeth Hawse	No	American Academy of Pediatrics Representative
	Anders Juul	No	
	Paul Kaplowitz	No	American Academy of Pediatrics Representative
	Maria E. Street	Yes	European Society for Paediatric Endocrinology Representative
	Vayana Walker	No	Patient Representative
Methodologists	Christopher McCartney	No	
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