Diagnosis of Central Precocious Puberty

Kanthi Bangalore Krishna, MD[a,*], Lawrence A. Silverman, MD[b]

KEYWORDS

- Precocious puberty • Gonadotropin-releasing hormone analogue
- Central precocious puberty • Peripheral precocious puberty • Bone age
- Pelvic ultrasound • Brain MRI

KEY POINTS

- A thorough history and physical examination including Tanner staging and growth assessments can guide differential diagnosis and aid in the evaluation of precocious puberty.
- Basal luteinizing hormone levels measured using a highly sensitive assay can be helpful in diagnosing central precocious puberty (CPP).
- Brain MRI is indicated with males diagnosed with CPP and females under the age of 6 with CPP. For girls with CPP between the ages of 6 and 8, shared decision making with the family should guide the need for brain imaging.
- As more information becomes available regarding the genetic etiologies of CPP, genetic testing may preclude the need for imaging studies and other hormonal testing especially in familial cases.

Gonadotropin-dependent sexual precocity, more commonly referred to as central precocious puberty (CPP), results from the premature reactivation of the hypothalamic-pituitary-gonadal (HPG) axis.[1] While data suggest that the age of onset of puberty has decreased over the past half century, clinically, the appearance of breast development before the age of 8 in girls or testicular enlargement before the age of 9 in boys is generally considered precocious.[2,3]

The mechanisms of reactivation of the HPG axis and entry into puberty are complex, with a myriad of genetic and environmental factors that regulate gonadotropin-releasing hormone (GnRH) secretion.[4] Ultimately, initiation of both normally timed and precocious puberty involves the pulsatile release of GnRH. This increased GnRH pulsatility results in the secretion of luteinizing hormone (LH) and follicle-

[a] Division of Pediatric Endocrinology and Diabetes, UPMC Childrens Hospital of Pittsburgh, 4401 Penn Avenue, Pittsburgh, PA 15224, USA; [b] Division of Pediatric Endocrinology, Goryeb Children's Hospital, Atlantic Health System, 100 Madison Avenue, Morristown, NJ 07960, USA
* Corresponding author.
E-mail address: bangalorekrishnak2@upmc.edu

Endocrinol Metab Clin N Am 53 (2024) 217–227
https://doi.org/10.1016/j.ecl.2024.02.002
0889-8529/24/

endo.theclinics.com

stimulating hormone (FSH), leading to the production of gonadal sex steroids and subsequent development of secondary sexual characteristics.[5,6]

As puberty is neither a linear process nor a single event, both boys and girls may present with variations of normal pubertal development, which can be mistaken for true puberty.[7,8] Hence, it is incumbent upon the clinician to develop a paradigm in which to approach these patients from both a clinical and investigative perspective; this will lead to an accurate diagnosis which can best classify patients as normal variants or true/central or peripheral precocious puberty and develop a treatment plan as deemed necessary.

TIMING OF PUBERTY

"When twice 7 years the men engender seed and women's breasts begin to swell."[9] The timing of the onset of puberty has evolved over the past millennium, a fact well documented by the change in age of menarche over the past 2 centuries.[10,11] The classic teaching has been that the first signs of puberty, breast development, begins in girls after 8 and in boys, testicular enlargement, after 9, has evolved over the past 50 years.[12] The observations of Tanner in the 1950s, which codified pubertal development stages, harken back to original observational work from the 1920s.[7,8] While the "normal" ages of the progressive pubertal, or Tanner stages, were based on examinations of pictures of a White British population, the clinical description/changes, if not necessarily the ages, apply to all children (**Fig. 1**).

The common observation that children of different genetic backgrounds progress through puberty at different times has been well accepted over the years.[13,14] In an attempt to better codify these differences, Herman Giddens and colleagues[15] set out to define the age of onset of physical changes of puberty across races in a cross section of American girls. In an analysis of over 17,000 girls, in an office-based setting,

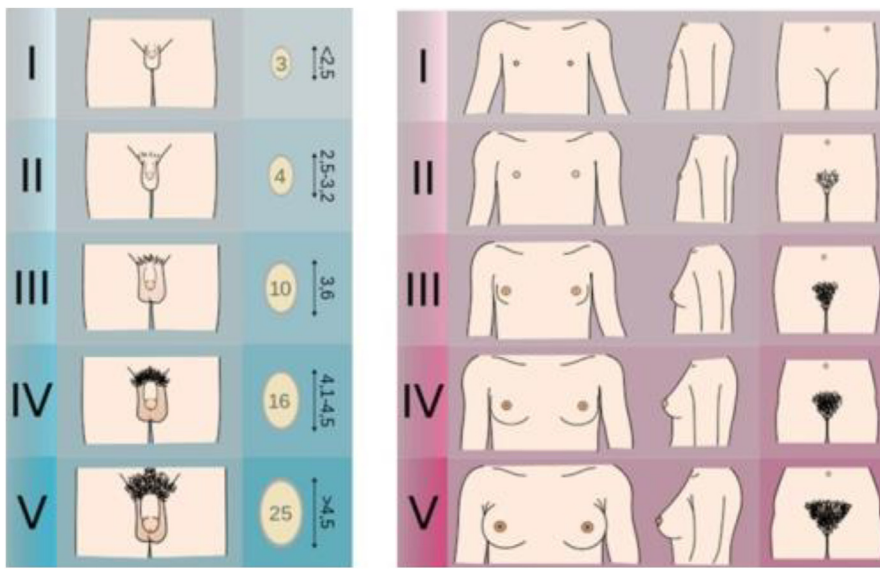

Fig. 1. Tanner staging in males and females. https://openi.nlm.nih.gov/detailedresult.php?img=PMC4478390_fnhum-09-00344-g001&req=4. (Image credit: Michał Komorniczak, 2009, CC-BY-SA 3.0. Tanner Scale Male: http://goo.gl/7cxTLM. Tanner Scale Female: http://goo.gl/haB9Cb.)

15% of African American girls and 5% of White girls were noted to have breast development before the age of 8, with a mean age of 8.87 years and 9.96, respectively. In this cohort, the mean age of menarche was 12.16 years in African American girls and 12.88 in White girls. While there are well-described concerns with the methods employed by this study, including the lack of hormonal testing, it did speak to the well-observed trend noted by primary care pediatricians and endocrinologists alike.[15] A subsequent, albeit smaller but perhaps more powerful, observational study about the timing of puberty came out of the Breast Cancer and the Environment Research Program.[3] In this study, a team of researchers were specifically trained, and cross tested, to evaluate the presence of breast development by palpation in girls over time at 3 distinct centers in 4 distinct genetic/ethnic cohorts: African American, Hispanic, white non-Hispanic, and Asian, The median ages of T2 breast development were 8.8, 9.3, 9.7, and 9.7 years, respectively. More importantly, 18% of African American and 3% of White girls had stage 2 breast development by age 7, and 22% and 5% by age 8 (**Fig. 2**). The 14.2% variance in timing was accounted for by weight/body mass index (BMI), while only 4.4% was accounted for by race. When this cohort was followed to document age of menarche, the median age of menarche for the entire group was 12.25 years: African American 12.0, Hispanic 11.83, Asian 12.75, and White 12.67 years. A correlation existed between BMI and age of menarche, with an inverse correlation between higher BMI and earlier age of first menstrual cycle.

Interestingly, those girls with the earlier timing of B2 had a slower progression of puberty, with those with B2 earlier than 8.5 years having a median tempo of 42 months to menarche, while in those with B2 after 10.5 years it was 25 months to first menses.[14]

CLINICAL EVALUATION

As with the approach to any patient, a thorough history involves focus upon timing and sequence of initial changes; timing of puberty in parents, grandparents, and siblings; general health; medications; and exposures. Other aspects including birth history, length and weight, the presence of small for gestational age[16] or prematurity, and central nervous system (CNS) insult at birth or later are informative.[17] A history of gelastic seizures may point to the presence of a hypothalamic hamartoma. A careful history to rule out exposure to hormone-containing creams or medications; exposure to lavender or tea tree oil, which can activate the E2 receptor[18]; or disease states such as congenital adrenal hyperplasia or other autonomous endocrine function may be pertinent. Data points from the growth curve can also provide further clarification of the

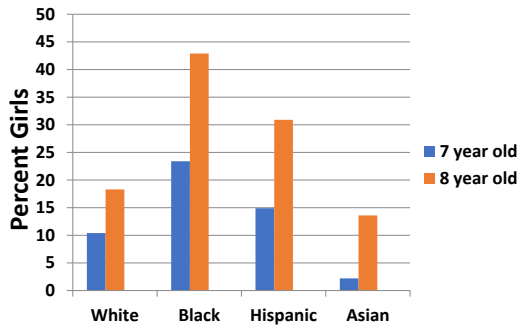

Fig. 2. Breast development by palpation in girls in different ethnic groups. (*Adapted from* Biro F, Greenspan L, Galvez M, Pinney S, Teitelbaum S, Windham G, et al. Onset of Breast Development in a Longitudinal Cohort. Pediatrics. 2013;132(6): 1019–1027.)

timing of a growth acceleration, which is generally observed in girls after Tanner 2 breast development and in boys at Tanner 3 to 4. As the first clinical signs of puberty are related to gonadal sex steroid production, a careful physical examination can help differentiate true puberty from variations in development (adrenarche and thelarche). Usually girls present with breast development, while testicular enlargement in a boy is the first finding,[7] with volume being greater than 3 mL or length being 2.5 cm or more. As originally described,[8] Tanner 2 breast development involves the present of a breast bud with elevation of the papilla and enlargement of the areola. The presence of pubic hair (Tanner stage 2 or more) does not necessarily indicate gonadal steroid secretion, that is, gonadarche, since pubarche may be secondary to adrenarche. It is not uncommon for this process to precede true central puberty.

A frequent clinical conundrum is the need to differentiate, on physical examination, between adipose chest tissue (adipomastia/lipomastia) and true breast budding in girls. Perhaps the most challenging patients are those girls who are overweight. On examination, one can attempt to discern if there is tissue directly below the nipple as the first breast buds are subareolar. In contrast, depression of the nipple on palpation, with no tissue directly under the nipple but surrounding the finger, forming the so-called "doughnut sign" may be informative. While frequently used to differentiate gynecomastia from lipomastia in overweight boys, it can be employed in peripubertal girls. Similarly, if one "pinches" the area surround the nipple, a true breast bud will be discernible between the fingers; this is unlikely in the presence of adipose tissue alone. The presence of a breast bud within significant adipose tissue in the chest is not uncommon. Some posit that this can be secondary to the effect of local aromatase activity present in the adipose tissue.[19]

For boys, staging of penis and pubic hair development plus testicular volume is necessary. Accurate measurement of either testicular volume using an orchidometer (**Fig. 3**) or testicular length is essential.

Other aspects of the physical examination that require specific focus include the skin; café au lait spots can point to either McCune-Albright syndrome or neurofibromatosis type 1. The melanocytic macules of Peutz-Jeghers syndrome could point to the presence of a sex cord tumor causing gonadotropin-independent (peripheral) sexual precocity.

LABORATORY EVALUATION

While a differential diagnosis is based on a thorough history and physical examination, laboratory evaluation is necessary to diagnose precocious puberty and the possible etiology.

Fig. 3. Orchidometer showing representative testicular volumes ranging from prepubertal (1 ml–3 ml) and pubertal testes (4 ml to 25 ml).

Circulating gonadotropin and sex steroid concentrations assess the status of the HPG axis.[20,21] Historically, the established gold standard was the LH and FSH response to a standard bolus of native GnRH. However native GnRH is no longer available in the United States, and most stimulation tests are now performed with the GnRH analogue (GnRHa) leuprolide acetate, a synthetic nonapeptide with much greater potency. Due to the pharmacodynamic differences between these 2 medications, the timing and peak values of FSH and LH levels are different. Following native GnRH administration, LH levels peak after 20 to 40 minutes, followed by a decline in values compared with leuprolide acetate, which can similarly stimulate LH to peak as early as 30 minutes to 4 hours followed by sustained LH elevation.[22–24]

The development of highly sensitive and pediatric-specific gonadotropin assays has added to our diagnostic armamentarium. With the development of more sensitive assays, many practitioners have come to rely on the utility of random LH levels, with a cutoff of 0.3 to 0.5 IU/L.[25] While this cutoff value has high sensitivity greater than 90%, it has a relatively low specificity, as a percentage of girls with true central puberty will have a random LH lower than the aforementioned cutoff values.[21,26] The lower limit of detection for most ultrasensitive immunochemiluminescent assays (ICMA) is $\leq$ 0.1 mIU/mL.[26–28] Elevated basal LH levels show high sensitivity and specificity for boys when a high-quality ICMA is used.[29] Different cut-points need to be used to interpret LH concentrations in girls under 2 years of age because LH concentrations may normally be higher (minipuberty of infancy); CPP may frequently be misdiagnosed during this phase of development.[30]

As the short-acting GnRHas have greater affinity for the GnRH receptor than native GnRH, they lead to both an immediate release of LH and FSH from pituitary stores as well as transcription, translation, and production of LH and FSH, with subsequent spikes in sex hormones.[31] Hence, evaluating a 1-hour to 2-hour post-stimulation LH and FSH, as well as an 18-hour to 24-hour sex steroid level, has led to development of a modified stimulation test.[32] Not infrequently, there can be a less than pubertal peak LH, with a markedly pubertal sex hormone level the next day; this stimulation test does provide significant utility in confirming the presence of central puberty.[31] Both short-acting, aqueous leuprolide acetate and triptorelin have been used for this purpose[33]

As highly sensitive and specific assays have been developed, random sex hormone levels can define the presence of biochemical puberty. These levels will not differentiate gonadotropin-dependent (central) versus gonadotropin-independent (peripheral) puberty, thus the presence of a pubertal LH is necessary to confirm the diagnosis. Given the minor structural differences between steroid molecules, immunoassays measuring sex steroids are prone to cross-reactivity. Most commercial immunoassays for estradiol are designed to measure estradiol within the “normal adult female” reference range and therefore have low sensitivity and specificity to quantify the low concentrations (<30 pg/mL) typically found in prepubertal children. More recently, methods utilizing liquid chromatographic separation followed by tandem mass spectrometry (LC-MS/MS) have been developed. Serum testosterone is also best measured using LC-MS/MS technology to limit cross-reactivity.

In children with precocious pubarche, the measurement of adrenal steroids may be necessary to help distinguish between peripheral precocity and benign premature adrenarche. Children with premature adrenarche can have mild elevation in adrenal hormones.[34] An early-morning 17-hydroxyprogesterone value greater than 200 ng/dL (6 nmol/L) has a high sensitivity and specificity for nonclassic congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency. An adrenocorticotropic hormone stimulation test may still be needed to confirm the diagnosis.[35,36]

A thyroid-stimulating hormone concentration should be measured if chronic primary hypothyroidism is suspected as the underlying cause for the sexual precocity.[37,38]

IMAGING STUDIES

Bone Age

The assessment of skeletal maturation is based on an X ray of the left hand and wrist, most commonly using the Greulich and Pyle method in which the patient's bone age radiograph is compared with an atlas of radiographs from children of known ages.[39] Another method which is used less frequently is the Tanner-Whitehouse 2 method, in which 20 different hand and wrist bones are individually scored. Additional factors such as other hormones, obesity, genetics, nutritional status, various disease states, and certain medications can influence the rate of epiphyseal maturation[40 .41] Using the tables of Bayley and Pinneau, a median predicted adult height (PAH) may be calculated and compared to the patient's target height based on the mid parental height.

Although the PAH using the bone age may help guide treatment decisions,[42] there is a tendency to overestimate adult height.[43] As the use of automated measurement systems with artificial intelligence has increased, previous limitations were apparently in part due to intraobserver and interobserver variability.[44,45]

Pelvic Ultrasound

During puberty, increased gonadotropin secretion promotes ovarian growth and increased estradiol secretion. Concomitantly, pelvic ultrasound shows increased uterine size and ovarian volume. In general, uterine lengths greater than 3.5 to 4 cm and ovarian volumes greater than 2 mL are consistent with puberty.[46] However, overlap of these measurements between prepubertal and early pubertal size may confound interpretation.[47,48] The use of Doppler ultrasound to assess utero-ovarian blood flow may provide helpful information.[49–52]

Brain MRI

Brain MRI defines brain and pituitary anatomy. Due to the higher probability of finding a CNS anomaly, most studies recommend a contrast-enhanced, pituitary-focused, brain MRI for all males with CPP[53] and for females with onset of secondary sexual characteristics before 6 years of age because of higher rates of CNS abnormalities in these groups of patients.[25] Females with CPP onset between 6 and 8 years of age may not need the MRI if there is no clinical evidence of CNS pathology and if there is a family history of earlier pubertal onset, or if the child has an increased BMI.[54] The low prevalence of CNS lesions in females with the onset of puberty after age 6 years does challenge the need for all females in this age group to have imaging,[55,56] and hence MRI should be limited to high-risk individuals.[57] In a 2018 meta-analysis,[58] the prevalence of intracranial lesions was 3% among females presenting with CPP after 6 years of age, compared with 25% among those presenting before 6 years. Current guidelines recommend that in otherwise asymptomatic girls with CPP, a discussion must occur with the parents regarding the pros and cons of brain imaging to assist in informed decision-making.[25,59,60] While brain MRIs are recommended for all boys presenting with CPP, 1 study found that these rates may be overestimated and none of the identified lesions necessitated treatment, suggesting the need to globally reevaluate the prevalence of pathologic brain lesions among boys with CPP.[61]

Genetic Testing

CPP can be sporadic or familial.[62] The past 15 years have seen a marked increase in the discovery and characterization of both normally functioning genes and pathologic

variants associated with CPP. Genome-wide association studies and other technologies have further increased the discovery of genetic loci associated with pubertal timing.[63] Among children with familial CPP, those with defects in MKRN3 and DLK1(both paternally expressed imprinted genes) do not have structural lesions in brain MRI.[64] It is likely that with the expanded use of genetic tools in the clinic, understanding of what truly controls the onset of puberty will further expand and point not only to what controls the timing but also the tempo of pubertal progression. Perhaps in the not-too-distant future, true genotype/phenotype correlations will help drive therapeutic considerations.[63]

SUMMARY

While the mechanisms underlying the control of the onset of puberty are yet to be fully comprehended, there has been an evolution in both the diagnostic and therapeutic approach to such patients. The astute clinician will recognize the need for evaluation based on signs and symptoms encountered and only then should employ the most appropriate focused approach to define if true puberty is present. While the approach can be algorithm driven, there is not a "one-size-fits-all" paradigm, and one should choose the most informative and specific tests for the clinical situation at hand.

CLINICS CARE POINTS

- Re-emergence of GnRH pulsatility results in the anterior pituitary secretion of LH and FSH, leading to the production of gonadal sex steroids and subsequent development of secondary sexual characteristics.
- Although GnRH stimulation testing has been considered the gold standard for the diagnosis of CPP, a basal ultrasensitive LH level of greater than 0.2 IU/L may be used for the diagnosis of CPP.
- Pelvic ultrasound has been found to be a useful adjunct to support the diagnosis of CPP over other forms of puberty in girls, especially when laboratory studies are equivocal.
- Guidelines regarding the need for brain imaging have been debated. Brain imaging is recommended in the evaluation of all boys with CPP and in girls under the age of 6 years. For girls older than age 6, shared decision-making after assessing the risk for neurologic manifestations, reviewing the family history, assessing the tempo of puberty as well as the risk for the procedure itself, is recommended.

DISCLOSURE

K. Bangalore Krishna has no relevant disclosures to this article. L.A. Silverman has been a consultant for Tolmar, a Data and Safety Monitoring Board member for Myovant, and with the Speaker's Bureau for Abbvie.

REFERENCES

1. Apter D, Butzow TL, Laughlin GA, et al. Gonadotropin-releasing hormone pulse generator activity during pubertal transition in girls: pulsatile and diurnal patterns of circulating gonadotropins. J Clin Endocrinol Metab 1993;76(4):940–9.
2. Biro FM, Pajak A, Wolff MS, et al. Age of Menarche in a Longitudinal US Cohort. J Pediatr Adolesc Gynecol 2018;31(4):339–45.
3. Biro F, Greenspan L, Galvez M, et al. Onset of Breast Development in a Longitudinal Cohort. Pediatrics 2013;132(6).

4. Garcia JP, Guerriero KA, Keen KL, et al. Kisspeptin and Neurokinin B Signaling Network Underlies the Pubertal Increase in GnRH Release in Female Rhesus Monkeys. Endocrinology 2017;158(10):3269–80.
5. Fuqua JS, Eugster EA. History of Puberty: Normal and Precocious. Horm Res Paediatr 2022;95(6):568–78.
6. Grumbach MM. The neuroendocrinology of human puberty revisited. Horm Res 2002;57(Suppl 2):2–14.
7. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970;45(239):13–23.
8. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44(235):291–303.
9. Aristotle Cresswell R, Schneider JG. Aristotle's History of animals. In ten booksix. London: H. G. Bohn; 1862. p. 326.
10. Liu W, Yan X, Li C, et al. A secular trend in age at menarche in Yunnan Province, China: a multiethnic population study of 1,275,000 women. BMC Publ Health 2021;21(1):1890.
11. Cabrera SM, Bright GM, Frane JW, et al. Age of thelarche and menarche in contemporary US females: a cross-sectional analysis. J Pediatr Endocrinol Metab 2014;27(1–2):47–51.
12. Eckert-Lind C, Busch AS, Petersen JH, et al. Worldwide Secular Trends in Age at Pubertal Onset Assessed by Breast Development Among Girls: A Systematic Review and Meta-analysis. JAMA Pediatr 2020;174(4):e195881.
13. Biro FM, McMahon RP, Striegel-Moore R, et al. Impact of timing of pubertal maturation on growth in black and white female adolescents: The National Heart, Lung, and Blood Institute Growth and Health Study. J Pediatr 2001;138(5):636–43.
14. Biro FM, Galvez MP, Greenspan LC, et al. Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. Pediatrics 2010;126(3):e583–90.
15. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics 1997;99(4):505–12.
16. Ibanez L, Ferrer A, Marcos MV, et al. Early puberty: rapid progression and reduced final height in girls with low birth weight. Pediatrics 2000;106(5):E72.
17. Partsch CJ, Sippell WG. Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens. Hum Reprod Update 2001;7(3):292–302.
18. Henley DV, Lipson N, Korach KS, et al. Prepubertal gynecomastia linked to lavender and tea tree oils. N Engl J Med 2007;356(5):479–85.
19. Carlson L, Flores Poccia V, Sun BZ, et al. Early breast development in overweight girls: does estrogen made by adipose tissue play a role? Int J Obes 2019;43(10):1978–87.
20. Carel JC, Léger J. Clinical practice. Precocious puberty. N Engl J Med 2008;358(22):2366–77.
21. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123(4):e752–62.
22. Chin VL, Cai Z, Lam L, et al. Evaluation of puberty by verifying spontaneous and stimulated gonadotropin values in girls. J Pediatr Endocrinol Metab 2015;28(3–4):387–92.

23. Ibanez L, Potau N, Zampolli M, et al. Use of leuprolide acetate response patterns in the early diagnosis of pubertal disorders: comparison with the gonadotropin-releasing hormone test. J Clin Endocrinol Metab 1994;78(1):30–5.
24. Houk CP, Kunselman AR, Lee PA. The diagnostic value of a brief GnRH analogue stimulation test in girls with central precocious puberty: a single 30-minute post-stimulation LH sample is adequate. J Pediatr Endocrinol Metab 2008;21(12): 1113–8.
25. Bangalore Krishna K, Fuqua JS, Rogol AD, et al. Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium. Horm Res Paediatr 2019;91(6):357–72.
26. Neely EK, Hintz RL, Wilson DM, et al. Normal ranges for immunochemiluminometric gonadotropin assays. J Pediatr 1995;127(1):40–6.
27. Neely EK, Silverman LA, Geffner ME, et al. Random unstimulated pediatric luteinizing hormone levels are not reliable in the assessment of pubertal suppression during histrelin implant therapy. Int J Pediatr Endocrinol 2013;2013(1):20.
28. Martinez-Aguayo A, Hernández MI, Capurro T, et al. Leuprolide acetate gonadotrophin response patterns during female puberty. Clin Endocrinol 2010;72(4): 489–95.
29. Howard SR. Interpretation of reproductive hormones before, during and after the pubertal transition-Identifying health and disordered puberty. Clin Endocrinol 2021;95(5):702–15.
30. Bizzarri C, Spadoni GL, Bottaro G, et al. The response to gonadotropin releasing hormone (GnRH) stimulation test does not predict the progression to true precocious puberty in girls with onset of premature thelarche in the first three years of life. J Clin Endocrinol Metab 2014;99(2):433–9.
31. Sathasivam A, Garibaldi L, Shapiro S, et al. Leuprolide stimulation testing for the evaluation of early female sexual maturation. Clin Endocrinol 2010;73(3):375–81.
32. Garibaldi LR, Aceto T Jr, Weber C, et al. The relationship between luteinizing hormone and estradiol secretion in female precocious puberty: evaluation by sensitive gonadotropin assays and the leuprolide stimulation test. J Clin Endocrinol Metab 1993;76(4):851–6.
33. Strich D, Kvatinsky N, Hirsch HJ, et al. Triptorelin depot stimulation test for central precocious puberty. J Pediatr Endocrinol Metab 2013;26(7–8):631–4.
34. Rosenfield RL. Normal and Premature Adrenarche. Endocr Rev 2021;42(6): 783–814.
35. Chesover AD, Millar H, Sepiashvili L, et al. Screening for Nonclassic Congenital Adrenal Hyperplasia in the Era of Liquid Chromatography-Tandem Mass Spectrometry. J Endocr Soc 2020;4(2):bvz030.
36. Witchel SF, Pinto B, Burghard AC, et al. Update on adrenarche. Curr Opin Pediatr 2020;32(4):574–81.
37. Reddy P, Tiwari K, Kulkarni A, et al. Van Wyk Grumbach Syndrome: A Rare Consequence of Hypothyroidism. Indian J Pediatr 2018;85(11):1028–30.
38. Baranowski E, Hogler W. An unusual presentation of acquired hypothyroidism: the Van Wyk-Grumbach syndrome. Eur J Endocrinol 2012;166(3):537–42.
39. Greulich WWPS. Radiographic atlas of skeletal development of the hand and wrist. 2nd edition. CA, USA: Stanford University Press; 1999.
40. Klein KO, Newfield RS, Hassink SG. Bone maturation along the spectrum from normal weight to obesity: a complex interplay of sex, growth factors and weight gain. J Pediatr Endocrinol Metab 2016;29(3):311–8.
41. Oh MS, Kim S, Lee J, et al. Factors associated with Advanced Bone Age in Overweight and Obese Children. Pediatr Gastroentero 2020;23(1):89–97.

42. Bar A, Linder B, Sobel EH, et al. Bayley-Pinneau Method of Height Prediction in Girls with Central Precocious Puberty - Correlation with Adult Height. J Pediatr Urol 1995;126(6):955–8.
43. Eitel KB, Eugster EA. Differences in Bone Age Readings between Pediatric Endocrinologists and Radiologists. Endocr Pract 2020;26(3):328–31.
44. Wang X, Zhou B, Gong P, et al. Artificial Intelligence-Assisted Bone Age Assessment to Improve the Accuracy and Consistency of Physicians With Different Levels of Experience. Frontiers in Pediatrics 2022;10.
45. Thodberg HH, Thodberg B, Ahlkvist J, et al. Autonomous artificial intelligence in pediatric radiology: the use and perception of BoneXpert for bone age assessment. Pediatr Radiol 2022;52(7):1338–46.
46. de Vries L, Horev G, Schwartz M, et al. Ultrasonographic and clinical parameters for early differentiation between precocious puberty and premature thelarche. Eur J Endocrinol 2006;154(6):891–8.
47. Sathasivam A, Rosenberg HK, Shapiro S, et al. Pelvic ultrasonography in the evaluation of central precocious puberty: comparison with leuprolide stimulation test. J Pediatr 2011;159(3):490–5.
48. Lee SH, Joo EY, Lee JE, et al. The Diagnostic Value of Pelvic Ultrasound in Girls with Central Precocious Puberty. Chonnam Med J 2016;52(1):70–4.
49. Battaglia C, Mancini F, Regnani G, et al. Pelvic ultrasound and color Doppler findings in different isosexual precocities. Ultrasound Obstet Gynecol 2003;22(3):277–83.
50. Long MG, Boultbee JE, Hanson ME, et al. Doppler time velocity waveform studies of the uterine artery and uterus. Br J Obstet Gynaecol 1989;96(5):588–93.
51. Paesano PL, Colantoni C, Mora S, et al. Validation of an Accurate and Noninvasive Tool to Exclude Female Precocious Puberty: Pelvic Ultrasound With Uterine Artery Pulsatility Index. Am J Roentgenol 2019;213(2):451–7.
52. Cheuiche AV, Moro C, Lucena IRS, et al. Accuracy of doppler assessment of the uterine arteries for the diagnosis of pubertal onset in girls: a scoping review. Sci Rep 2023;13(1):5791.
53. Topor LS, Bowerman K, Machan JT, et al. Central precocious puberty in Boston boys: A 10-year single center experience. PLoS One 2018;13(6):e0199019.
54. Pedicelli S, Alessio P, Scire G, et al. Routine screening by brain magnetic resonance imaging is not indicated in every girl with onset of puberty between the ages of 6 and 8 years. J Clin Endocrinol Metab 2014;99(12):4455–61.
55. Kaplowitz PB. Do 6-8 year old girls with central precocious puberty need routine brain imaging? Int J Pediatr Endocrinol 2016;2016:9.
56. Mogensen SS, Aksglaede L, Mouritsen A, et al. Pathological and Incidental Findings on Brain MRI in a Single-Center Study of 229 Consecutive Girls with Early or Precocious Puberty. PLoS One 2012;7(1).
57. Hansen AB, Renault CH, Wojdemann D, et al. Neuroimaging in 205 consecutive Children Diagnosed with Central Precocious Puberty in Denmark. Pediatr Res 2023;93(1):125–30.
58. Cantas-Orsdemir S, Garb JL, Allen HF. Prevalence of cranial MRI findings in girls with central precocious puberty: a systematic review and meta-analysis. J Pediatr Endocrinol Metab 2018;31(7):701–10.
59. Kim SH, Ahn MB, Cho WK, et al. Findings of Brain Magnetic Resonance Imaging in Girls with Central Precocious Puberty Compared with Girls with Chronic or Recurrent Headache. J Clin Med 2021;10(10).
60. Eugster EA. Update on Precocious Puberty in Girls. J Pediatr Adol Gynec 2019;32(5):455–9.

61. Yoon JS, So CH, Lee HS, et al. The prevalence of brain abnormalities in boys with central precocious puberty may be overestimated. PLoS One 2018;13(4).
62. de Vries L, Kauschansky A, Shohat M, et al. Familial central precocious puberty suggests autosomal dominant inheritance. J Clin Endocrinol Metab 2004;89(4):1794–800.
63. Moise-Silverman J, Silverman LA. A review of the genetics and epigenetics of central precocious puberty. Front Endocrinol 2022;13:1029137.
64. Tajima T. Genetic causes of central precocious puberty. Clin Pediatr Endocrinol 2022;31(3):101–9.