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REVIEW

Diagnosis and management of precocious sexual maturation: an updated review

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Abstract

The classic definition of precocious sexual maturation is the development of secondary sexual characteristics before 8 years of age in girls and before 9 years of age in boys. It is classified as central precocious puberty when premature maturation of the hypothalamic-pituitary-gonadal axis occurs, and as peripheral precocious puberty when there is excessive secretion of sex hormones, independent of gonadotropin secretion. Precocious sexual maturation is more common in girls, generally central precocious puberty of idiopathic origin. In boys, it tends to be linked to central nervous system abnormalities. Clinical evaluation should include a detailed history and physical examination, including anthropometric measurements, calculation of growth velocity, and evaluation of secondary sexual characteristics. The main sign to suspect the onset of puberty is breast tissue development (thelarche) in girls and testicular enlargement (≥4 mL) in boys. Hormonal assessment and imaging are required for diagnosis and identification of the etiology. Genetic testing should be considered if there is a family history of precocious puberty or other clinical features suggestive of a genetic syndrome. Long-acting gonadotropin-releasing hormone analogs are the standard of care for central precocious puberty management, while peripheral precocious puberty management depends on the etiology.

Conclusion: The aim of this review is to address the epidemiology, etiology, clinical assessment, and management of precocious sexual maturation.

What is Known:

- *The main sign to suspect the onset of puberty is breast tissue development (thelarche) in girls and testicular enlargement (≥4 mL) in boys. The classic definition of precocious sexual maturation is the development of secondary sexual characteristics before 8 years of age in girls and before 9 years of age in boys.*
- *Long-acting gonadotropin-releasing hormone agonist (GnRHa) is the standard of care for CPP management, and adequate hormone suppression results in the stabilization of pubertal progression, a decline in growth velocity, and a decrease in bone age advancement.*

What is New:

- *Most cases of precocious sexual maturation are gonadotropin-dependent and currently assumed to be idiopathic, but mutations in genes involved in pubertal development have been identified, such as MKRN3 and DLK1.*
- *A different preparation of long-acting GnRHa is now available: 6-month subcutaneous injection.*

Keywords Precocious sexual maturation · Central precocious puberty · Peripheral precocious puberty · Sexual maturation · Long-acting GnRH analog

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Introduction

Puberty is a biological maturation process that represents the physical, hormonal, and psychological transition from childhood to adulthood, culminating in the development of secondary sexual characteristics and reproductive capacity. It is a complex process that involves genetic, metabolic, environmental, ethnic, geographic, and economic factors.

The exact mechanism underlying the onset of puberty remains unclear, but it is known to be influenced by factors such as adipose tissue, gastrointestinal function, adrenal androgen production, energy sensing, and physical and psychosocial stress [1]. The discovery of kisspeptin, neurokinin B, and dynorphin neuromodulators and their impact on the gonadotropin-releasing hormone (GnRH) pulse generator was very important for the understanding of the pubertal process [1]. A kisspeptin1-receptor loss-of-function mutation was first linked to idiopathic hypogonadotropic hypogonadism in 2003 [2]. Later research showed a pubertal increase in kisspeptin and kisspeptin receptor expression, accompanied by parallel changes in GnRH pulse [3]. Kisspeptin neurons of the arcuate nucleus express both dynorphin A and neurokinin B, and kisspeptin expression is highly sensitive to variations in the nutritional state or in serum leptin, which explains in part the association between overweight and early pubertal development [4].

Changes in pituitary gonadotropin secretion patterns serve as a hormonal trigger for puberty induction. Reactivation of the hypothalamic-pituitary-gonadal (HPG) axis leads to increased pulsatile secretion of GnRH, which stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn stimulate the secretion of gonadal steroids and promote gametogenesis [1, 5, 6]. The HPG axis is activated during the mid-gestation period in the fetus, turns off at the end of gestation, and is then reactivated soon after birth, with an increase in gonadotropin concentrations [7]. This transient postnatal activation of the HPG axis is called minipuberty and lasts up to about 6 months of age in boys and 3–4 years of age in girls [7].

The initial manifestation of puberty is usually breast development in girls (thelarche) and testicular enlargement in boys [8, 9]. The normal age range of onset is when 95% of children present with Tanner stage 2 (Fig. 1), which corresponds to 8–13 years of age in girls and 9–14 years of age in boys [10, 11]. Therefore, the classic definition of precocious sexual maturation is the development of secondary sexual characteristics before 8 years of age in girls and before 9 years of age in boys.

Although some studies have suggested that thelarche now occurs earlier than in the 1960s, the age of menarche has remained relatively stable over recent decades after a period of gradual decline until the mid-twentieth century in most industrialized countries [12, 13]. Therefore, the interval between thelarche and menarche appears to have increased [14]. A redefinition of the age limit for precocious sexual maturation in girls has been proposed in the USA, especially after epidemiological studies showed that clinical signs of puberty were present at 7 years of age in white girls and at 6 years of age in African-American girls [15, 16]. However, doubts have been raised about the reliability of these studies, as they estimated thelarche only by visual inspection (without palpation). In addition, a lowering of the age limit for evaluation of precocious sexual maturation may overlook some girls with true rapid progressive precocious puberty and possibly lead to the misdiagnosis of potentially treatable underlying pathology [13].

The aim of this review is to describe the clinical and laboratory features, diagnosis, advances in genetics, workup, and updated management of precocious sexual maturation.

Epidemiology

Precocious sexual maturation occurs most frequently in girls (15–20 girls for every boy), with an estimated incidence of 1 case per 5000–10,000 girls in the USA [17, 18]. A Danish study found a prevalence of 0.2% for girls and <0.05% for boys [19]. A Spanish study reported a prevalence of 37 cases per 100,000 girls and 0.46 per 100,000 boys, while in Korea the prevalence was 55.9 cases per 100,000 girls and 1.7 per 100,000 boys [20, 21].

Precocious sexual maturation is classified as central precocious puberty (CPP) when premature maturation of the HPG axis occurs, and as peripheral precocious puberty (PPP) when there is excessive secretion of sex hormones from a tumoral or exogenous source, or secondary to a genetic disease, independent of gonadotropin secretion [5]. In 80% of cases, sexual precocity is central and, therefore, gonadotropin-dependent [11].

In approximately 75–90% of girls and 25–60% of boys with CPP, the cause is idiopathic [12, 22]. The identifiable causes are similar in girls and boys, as shown in Table 1 [17, 23–31]. The most commonly involved brain disorders are hypothalamic hamartoma, encephalitis, hydrocephalus, neurofibromatosis type 1, meningomyelocele, and neonatal encephalopathy [32]. These causes are much more frequent in boys [33]. The main risk factors for a central nervous system (CNS) etiology are younger age and male sex [21, 32].

PPP is much less frequent than CPP and can be congenital or acquired. Congenital causes include McCune-Albright syndrome (MAS), familial male-limited precocious puberty (FMPP), and congenital adrenal hyperplasia. Acquired causes include sex steroid-secreting tumors or cysts, profound primary hypothyroidism, and exogenous hormone exposure [34]. Congenital and acquired causes are summarized in Table 2, along with their prevalence in both sexes [25, 34–46].

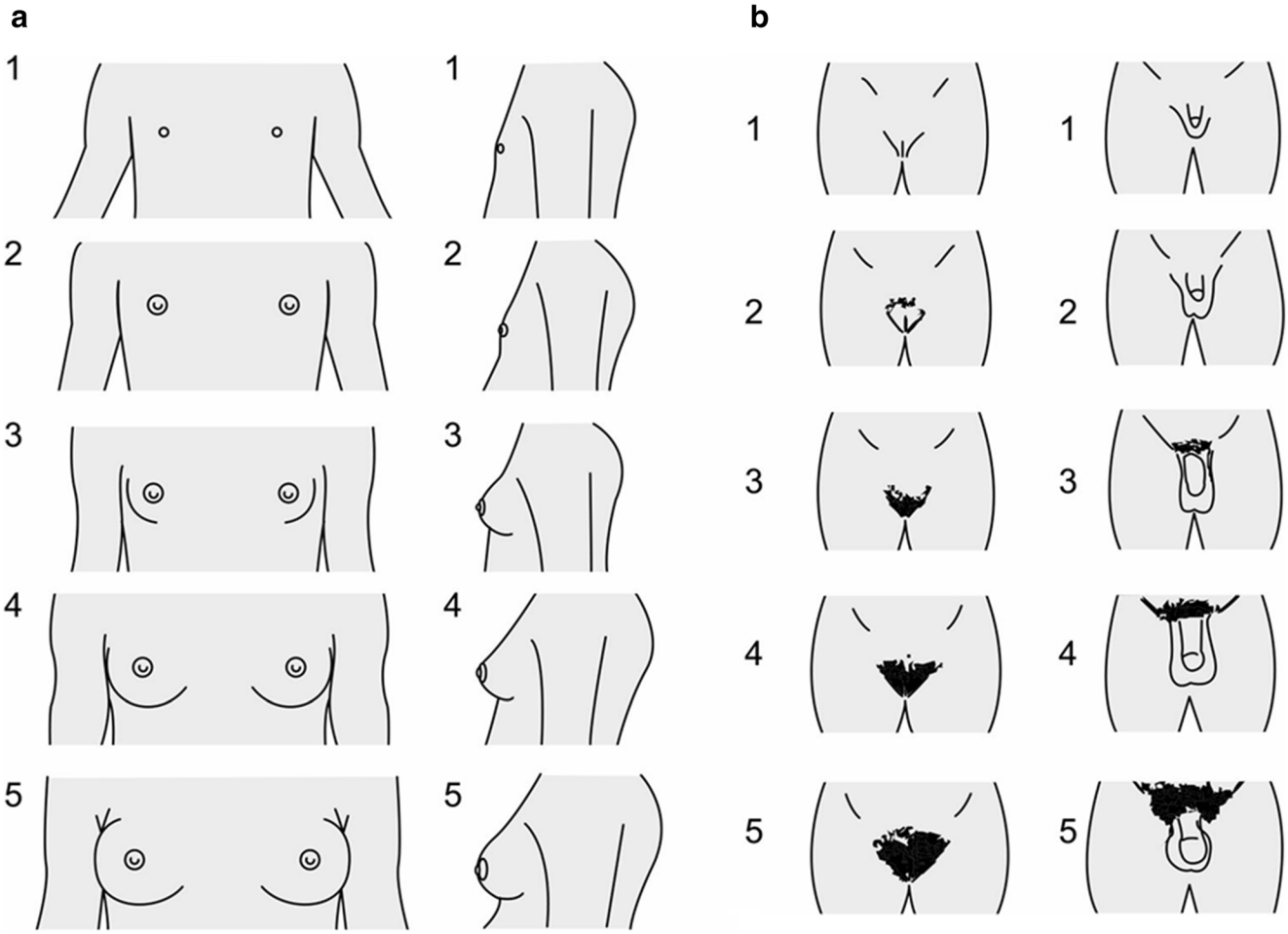

Fig. 1 Pubertal rating according to Tanner stages in girls (panel **a**) and boys (panel **b**)

Diagnosis

Clinical assessment

If precocious sexual maturation is suspected, clinical evaluation should begin with a detailed history including age of onset, rate of progression of physical changes, exposure to sex steroids, medication use, symptoms related to CNS disease (headache, visual impairment, polyuria or polydipsia, and personality change), history of traumatic brain injury or CNS infection, and family and neonatal history. Accidental ingestion of combined oral contraceptive pills, transfer of testosterone gel by skin contact, and skin exposure to substances containing estrogens or androgens are potential sources of exogenous sex steroid exposure [25]. It is also important to obtain information on puberty onset in parents and siblings (age at menarche, voice breaking, first shave, and growth spurt), as well as in other family members with precocious puberty (or height below the mid-parental height when data on puberty onset are inaccurate).

Physical examination consists of anthropometric measurements, calculation of growth velocity, and evaluation of secondary sexual characteristics according to the Tanner classification (breast development in girls, testicular volume and penile development in boys, and presence of pubic hair) (Fig. 1). The main sign to suspect the onset of puberty is thelarche in girls and testicular enlargement (≥4 mL) in boys. Testicular volume should be assessed using an orchidometer, distinguishing between unilateral vs. bilateral enlargement and checking for the presence of lumps. It may be difficult to discriminate between increased fatty tissue in breasts (lipomastia) and true glandular breast tissue in overweight and obese girls. Firm glandular tissue under the areolae is indicative of thelarche. Skin examination should also be performed to search for café-au-lait spots, which may suggest MAS or neurofibromatosis type 1 (Fig. 2).

Heights should be plotted over time on a growth chart, since a height increase crossing one or more full centile spaces supports a diagnosis of precocious puberty [12]. Moreover, the child's height should be compared to the mid-parental height, calculated according to the following equations: for girls, ([father's height cm − 13 cm] + mother's height cm)/2; for boys, ([mother's height cm + 13 cm] + father's height cm)/2 [47].

Table 1 Central precocious puberty: etiologies and prevalence in girls and boys (%)

Etiology	Central precocious puberty	
	Female	Male
Idiopathic	75–90%	25–60%
Genetic causes		
Activating mutations in the KISS1R and KISS1 genes	Rare	Rare
Inactivating mutations in the MKRN3 gene (familial central precocious puberty)	Up to 43%	Up to 43%
Chromosomal abnormalities	Unknown	Unknown
Secondary to chronic exposure to sex steroid hormones or endocrine disruptors	Unknown	Unknown
McCune-Albright syndrome[a]	85%	15%
Poorly controlled congenital adrenal hyperplasia[b]	Up to 30%	Up to 30%
CNS abnormalities	8–33%	40–90%
Tumors: hypothalamic hamartoma, astrocytoma, craniopharyngioma, ependymoma, luteinizing hormone-secreting adenoma, neurofibroma, non-human chorionic gonadotropin secreting dysgerminoma, optic or hypothalamic glioma, pinealoma	8.2–15%	40–75%
Hypothalamic hamartoma[c]	33–85%	33–85%
Congenital malformations: arachnoid cyst, ectopic posterior pituitary lobe, hydrocephalus, myelomeningocele, pituitary duplication, septo-optic dysplasia, spina bifida, suprasellar cyst, tuberous sclerosis complex	Unknown	Unknown
Hydrocephalus[b]	10–11%	10–11%
Myelomeningocele[b]	5–18%	5–18%
Acquired diseases: inflammatory processes (abscess, encephalitis, meningitis, sarcoidosis, tuberculosis), perinatal asphyxia, radiation, trauma	Unknown	Unknown
Neonatal encephalopathy	4.3%	Unknown

[a] Prevalence of central precocious puberty in McCune-Albright syndrome patients with classical signs

[b] Prevalence of central precocious puberty in patients with referred disease

[c] Prevalence of central precocious puberty in younger patients with hypothalamic hamartoma

It is important to distinguish between CPP, isolated premature thelarche (IPT), and premature adrenarche. IPT is defined as the appearance of breast tissue without other findings indicative of puberty, such as accelerated growth velocity, rapid breast development, and advanced skeletal maturation; it usually regresses over months to years [48]. IPT is a benign, self-limited condition that only rarely progresses to CPP [49]. Premature adrenarche is characterized by an increase in adrenal androgen levels independent of the HPG axis in the absence of or after ruling out other pathologic causes of androgen excess, traditionally before 8 years of age in girls and 9 years of age in boys [50]. It is generally regarded as a benign condition, but the child should be monitored for other signs of pubertal progression [51]. Premature adrenarche is clinically identified as pubarche and includes the presence of pubic and axillary hair, apocrine body odor, and acne [52].

Clinical presentation, rate of progression, and sequence of pubertal events in PPP may differ from CPP, since the onset of pubertal development may be sudden or intermittent and involve estrogens, androgens, or both [25]. Testicular volume <4 mL associated with pubic hair development and penile growth suggests PPP, whereas increased testicular volume associated with other features of puberty suggests CPP [12]. The exceptions are human chorionic gonadotropin-secreting germ-cell tumors and FMPP, which are characterized by mild testicular enlargement. FMPP, also called testotoxicosis, is a form of PPP caused by an activating mutation of the LH receptor, resulting in autonomous Leydig cell secretion of testosterone [53].

Adrenal tumors can manifest with signs of virilization due to androgen excess, such as clitoromegaly and pubic hair in girls, as well as with signs of glucocorticoid excess, such as rapid weight gain, round face, facial plethora, striae, hypertension, and hirsutism [53]. Sudden onset of vaginal bleeding along with minimal or no breast development may suggest MAS, a disease caused by a postzygotic, somatic, activating mutation of the α-subunit of the G-protein [34]. PPP in girls with MAS is caused by estrogen secreted by autonomously functioning ovarian cysts [54]. Vaginal bleeding results from withdrawal of estrogen when the cyst resolves [53]. The classic triad of MAS includes polyostotic fibrous dysplasia of bone, café-au-lait spots, and precocious sexual maturation [54] (Fig. 2).

Hormonal assessment

The initial laboratory evaluation of precocious sexual maturation includes the measurement of serum gonadotropins (LH

Table 2 Peripheral precocious puberty: prevalence and treatment

Etiology	Peripheral precocious puberty		Main treatment	Dose	Effect
	Female	Male			
Primary hypothyroidism	18%	6%	Levothyroxine	According to TSH	Regression of symptoms
Chronic exposure to sex steroid hormones	9.2%	23.1%	Exposure cessation		Regression of symptoms
Endocrine disruptors	Unknown	Unknown			
Adrenal tumors or congenital adrenal hyperplasia[a]	16.9%	38.5%	Tumors: complete surgical resection		Curative[b]
			Congenital adrenal hyperplasia: hydrocortisone	10–15 mg/m^2/day in 3 divided doses	Increases final adult height If salt-wasting, mineralocorticoid replacement If clinical central precocious puberty, consider GnRHa
McCune-Albright syndrome[a]	72%	15–21%	Letrozole	2.5 mg/day or progressive increase	Decreases rate of bone maturation; increases final adult height
			Tamoxifen	20 mg/day	Decreases frequency of menses; improves predicted adult height, lowers growth velocity Decreases bone maturation rate
Aromatase excess	Rare	Very rare	Histrelin acetate (GnRHa)	10–15 μg/kg/day	Improves final adult height; combined with an aromatase inhibitor
			Testolactone	40 mg/kg/day	Improves final adult height Combined with a GnRHa
Ovarian cysts	37%	-	Observation	-	Spontaneous regression
Ovarian tumors	1.5%	-	Complete surgical resection	-	Regression of symptoms[b]
Leydig cell tumors	-	1.25–4%	Orchiectomy	-	Curative surgery[b]
HCG-secreting germ-cell tumors	Very rare	Rare	Complete surgical resection	-	Regression of symptoms; may require chemotherapy or radiation therapy
Familial glucocorticoid resistance	-	Rare	Dexamethasone	1–3 mg/day	Regression of symptoms
Familial male-limited precocious puberty	-	0.0001%	Cyproterone acetate	70–130 mg/m^2/day	Decreases growth velocity Lowers testosterone levels
			Ketoconazole	10 mg/kg	Decreases growth velocity Lowers testosterone levels
			Spironolactone	5.7 mg/kg/day; up to 450–500 mg per day	Combined with testolactone Decreases growth velocity and bone maturation rate
			Anastrozole	1 mg/day	Combined with spironolactone Decreases growth velocity and bone maturation rate

[a] Prevalence of peripheral precocious puberty in patients with reported disease

[b] Possible later progression to central precocious puberty

HCG, human chorionic gonadotropin

and FSH) and sex steroids (estradiol in girls and testosterone in boys).

Suppressed FSH secretion associated with elevated sex steroid levels suggests the presence of PPP [27, 52]. LH should preferably be collected in the morning using an ultrasensitive assay with a detection limit of 0.1 IU/L [27]. The available high-sensitivity assays are immunofluorometric assay (IFMA), immunochemiluminescent assay (ICMA), and electrochemiluminescence (ECL). Second-generation immunoradiometric assays (IRMA) have sensitivities in the range of 0.1 to 0.5 lU/L [55]. Several studies have evaluated the use of basal LH to rule out CPP, with basal LH cutoffs ranging from 0.1 to 1 IU/L [55–59]. The sensitivity of morning basal LH for the diagnosis of CPP ranges from 56 to 100%, with a specificity of 64 to 100%, depending on the cutoff point and assay used [17]. Basal LH levels above 0.6 IU/L (IFMA) or 0.3 IU/L (ICMA, ECL) are considered pubertal, although values below these levels do not exclude CPP

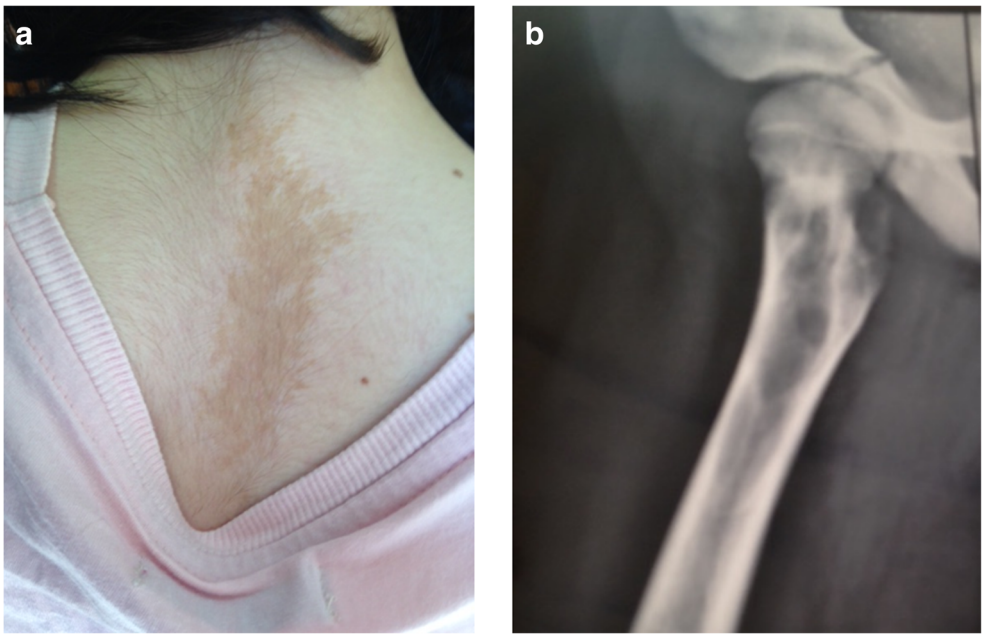

Fig. 2 Girl with McCune-Albright syndrome. **a** Café-au-lait spot. **b** Femur with fibrous dysplasia

[27, 52, 56, 60]. Gonadotropin concentrations should be interpreted with caution in children younger than 2 years because elevated LH and FSH levels could be physiological due to minipuberty [7, 10]. Clinical monitoring of pubertal progression and growth is recommended, as it helps differentiate premature thelarche from CPP in most cases [61].

When CPP is suspected in the presence of non-diagnostic basal LH, a GnRH stimulation test is indicated, with LH measurement in a single blood sample at 30–40 min after intravenous injection of a short-acting GnRH (gonadorelin 100 μg) [62]. A stimulated peak LH of at least 5 IU/L suggests that puberty is activated [10, 56]. It is important to emphasize that, in early puberty, LH pulses initially occur only during certain sleep stages [63]. For example, an association has been found between slow-wave sleep and nocturnal increase in LH pulses during puberty [64]. In the unavailability of a short-acting GnRH, a long-acting GnRH agonist (GnRHa), leuprorelin 3.75 mg, can be used, with LH measurement in a single blood sample at 30–180 min (or at more time points, depending on the protocol used) after intramuscular injection. We perform a single LH measurement 2 h after leuprorelin injection due to its simplicity and high accuracy. A response >5 IU/L is suggestive of puberty [5, 22, 55, 65, 66], but other cutoff points, ranging from 4 to 8 IU/L, have also been suggested [17]. A GnRHa-stimulated peak LH-to-FSH ratio of 0.6 to 1.0 has been proposed as an indicator of pubertal activation, but its sensitivity and specificity are not greater than those of GnRHa-stimulated peak LH alone [11]. Girls with IPT may have a FSH-predominant response [67]. The main disadvantages of the GnRHa stimulation test are the high cost and risk of injection-site reaction.

In boys, morning testosterone concentration is a useful marker of sexual precocity, since prepubertal concentrations rule out precocious puberty [52]. On the other hand, low estradiol levels do not exclude the diagnosis of precocious sexual maturation in girls [17, 68]. Nevertheless, high estradiol concentrations in the presence of suppressed gonadotropins strongly suggest PPP [69].

Thyroid function should also be assessed, since precocious pseudopuberty due to long-standing hypothyroidism, although rare, is possible [44]. In addition, insulin-like growth factor-1 (IGF-1) levels usually increase in early puberty, more commonly in girls, which may be helpful in diagnosing CPP [63]. IGF-1 levels might also be correlated with higher insulin levels [70].

Imaging assessment

Bone age assessment with a radiograph of the left hand and wrist is indicated. The most commonly used methods are the Greulich and Pyle atlas and the Tanner-Whitehouse 3 (TW3) method [71, 72]. The use of automated measurement systems with artificial intelligence has increased [73]. Bone age is often advanced in patients with precocious sexual maturation; when the advancement exceeds either 1 year or 2 standard deviations the chronological age, it is considered a significant advance in maturation [74]. However, in the early stages of CPP, bone age advancement may not be remarkable [14]. Intra- and inter-observer variability is another limitation. Bone age can be used to predict adult height, but its reliability is low and tends toward overestimation [75–78]. It is also

worth noting that, in the presence of glucocorticoid excess or hypothyroidism, there may be no bone age advancement.

Magnetic resonance imaging (MRI) of the brain is recommended for all boys with CPP and for girls under 6 years of age. Performing MRI in girls aged 6–8 years without symptoms of CNS disease is controversial, since the prevalence of CNS lesions is lower in this age group (25% in girls <6 years of age vs. 3% in 6–8 years of age in a meta-analysis); also, the test is expensive, requiring intravenous administration of contrast agents and possibly sedation [14, 22, 25, 79]. Therefore, it has been suggested that, in otherwise asymptomatic girls, the pros and cons of imaging should be discussed with the parents [22]. Nevertheless, most authors recommend performing MRI in all girls younger than 8 years with CPP [5, 14, 17, 80].

Pelvic ultrasound is considered a rapid, noninvasive, and low-cost method to assess uterine development and ovarian volume and to detect ovarian cysts and tumors (Fig. 3). The size and morphology of the uterus and ovaries are relatively stable during childhood: the volume of each ovary is less than 2 cm^3, with follicles less than 9 mm; uterine length is less than 4 cm, with a diameter less than 1.5 cm [81]. The uterine fundus and cervix have a similar width, arranged in a tubular configuration with a fundus-to-cervix ratio of approximately 1. During puberty, the uterus progressively increases in size, becoming wider than the cervix and assuming the typical pear shape found in adults [81, 82]. Many studies have shown increased ovarian and uterine volume in girls with CPP compared with prepubertal controls [83–85]. Although uterine volume cutoff points range from 1.8 to 4 cm^3 [82], they show low sensitivity for differential diagnosis due to the large overlap of values between groups [86–88]. Doppler ultrasound facilitates the assessment of utero-ovarian blood flow and flow impedance measurement in this vascular tree (Fig. 4). The pulsatility index, defined as the difference between peak systolic flow and end-diastolic flow divided by the mean maximum flow velocity, reflects the impedance to blood flow in the vessel distal to the sampling point [89]. Two studies assessing flow velocity in the uterine artery of healthy women in different age groups identified an increase in the pulsatility index in the prepubertal stage and a decrease during puberty, which could reflect a progressive increase in blood flow to the uterus [90, 91]. A further increase in the pulsatility index occurs in adulthood, when the uterus is fully developed and angiogenesis is complete. It has been determined that a low pulsatility index at the uterine artery level has a high diagnostic value for precocious sexual maturation [92, 93].

Genetic assessment

Familial precocious puberty is typically defined as the occurrence of more than one affected family member [94]. The identification of *MKRN3* and *DLK1* mutations in familial CPP highlights the important role of genetic factors in the

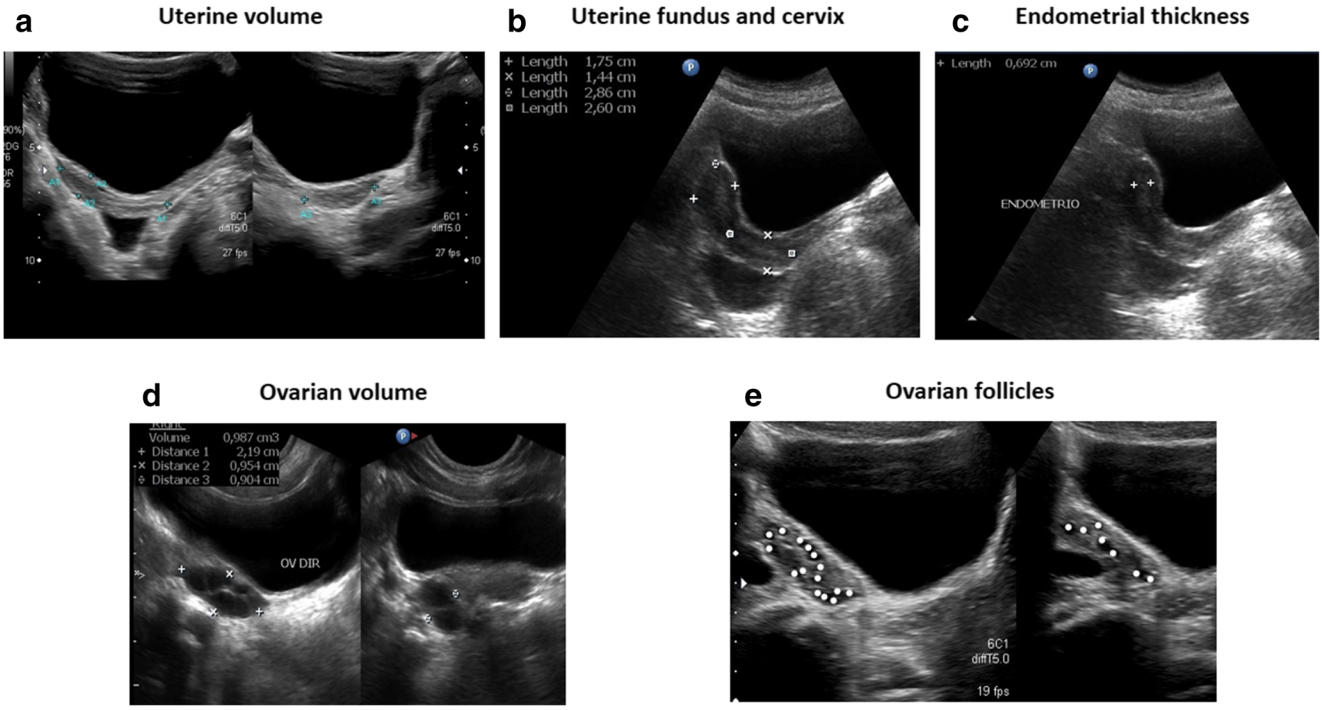

Fig. 3 Pelvic ultrasound. **a** Uterine volume calculated according to the formula for ellipsoid volume: longitudinal diameter × anteroposterior diameter × transverse diameter × 0.5233. **b** Diameters of the uterine fundus and cervix, to calculate the fundus-to-cervix ratio. **c** Endometrial thickness. **d** Ovarian volume in a prepubertal girl. **e** Normal pubertal ovary with 22 follicles with a diameter smaller than 0.6 cm. Courtesy of Iara Lucena, MD

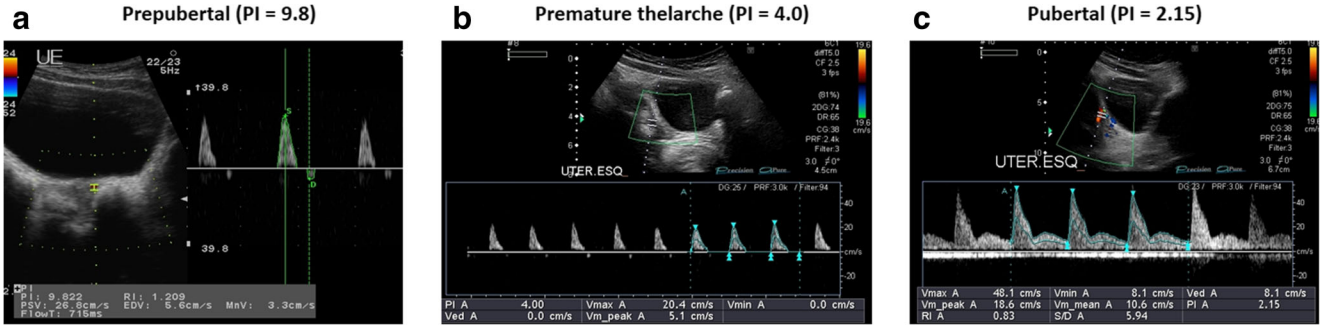

Fig. 4 Color Doppler ultrasound of the uterine arteries. **a** Prepubertal girl. **b** Girl with premature thelarche. **c** Girl with pubertal response to GnRH stimulation test. GnRH, gonadotropin-releasing hormone. PI, pulsatility index. Courtesy of Iara Lucena, MD

pathophysiology of precocious sexual maturation [95]. Currently, *MKRN3* mutations are the most common genetic etiology of monogenic CPP, with a prevalence ranging from 33 to 46% in familial cases and from 0.4 to 5% in sporadic cases [96–101]. The *MKRN3* gene is located in the critical region of Prader-Willi and Angelman syndromes (locus 15q11-q13) and has maternal imprinting (silencing); therefore, patients develop CPP only when they inherit the mutated allele from their fathers [95, 102]. The clinical features of CPP due to mutations that inactivate *MKRN3* are similar to those of idiopathic CPP [82]. Comparable to *MKRN3*, carriers of *DLK1* defects only manifest CPP if the defect is inherited from their fathers [103]. In addition, CPP is part of the clinical manifestations of some genetic syndromes, such as Temple syndrome, Silver-Russell syndrome, and Williams-Beuren syndrome. Therefore, genetic testing should be considered if there is a family history of precocious puberty or other clinical features [94].

Management

CPP

Long-acting GnRHa is the standard of care for CPP management. The action of GnRHa relies on sustained high concentrations of GnRH that result in a paradoxical downregulation and subsequent suppression of the HPG axis, thus inhibiting gonadotropin secretion [104].

Management with adequate hormone suppression results in the stabilization of pubertal progression, a decline in growth velocity, and a decrease in bone age advancement [14]. As shown in Table 3, different preparations are available: intramuscular 4-week, 12-week, or 6-month depot forms; 6-month subcutaneous injection; and subcutaneous implant [105–109]. Although marketed to be replaced annually, the implant can suppress puberty for at least 2 years [110].

The main goals of treatment are the preservation of adult height, synchronization of puberty with peers, alleviation of psychosocial distress, and, in girls, avoiding menarche at an early age [27]. No randomized controlled trials have examined the effects of GnRHa treatment on height or other outcomes. Height outcomes have been mainly assessed by using historical controls and differences between achieved and predicted adult height based on bone age before treatment, which are highly imprecise. For girls, the increase in final height ranges from 2 to 10 cm [111]. Girls who begin GnRHa treatment before 6 years of age obtain the greatest benefit, while those who begin treatment between 6 and 8 years of age have variable outcomes [75, 112]. On the other hand, girls treated after 8 years of age show no increase in adult height [113, 114]. Factors associated with increased adult height are earlier age at the start of puberty, younger bone age at diagnosis, prompt treatment, greater height at diagnosis, and greater target height [14]. For boys, a recent study reported that the predicted adult height significantly increased by approximately 4.1 cm after GnRHa treatment [115]. There is currently insufficient evidence to establish an age parameter for treatment in boys.

The most common side effects of GnRHa treatment are headaches, hot flashes, and injection-site reactions, which are usually mild [105]. Rarely, a sterile abscess develops with intramuscular injection or implant and may result in loss of efficacy [21, 116–118]. Vaginal bleeding can occur after the first injection, usually in girls with advanced pubertal development and possibly due to a transient increase in estradiol secretion [17]. A negative influence on long-term reproductive potential or bone mineral density has not been observed [108]. Weight gain can also be a side effect of GnRHa treatment in patients with normal body mass index; however, it is unclear whether overweight or obese patients experience significant weight gain after treatment [119–122]. The implant is typically inserted into the upper inner arm under local anesthesia and promotes a rapid and profound suppression of the HPG axis for 1 year after insertion [123]. One concern is the risk of device fracture during extraction, which may rarely require ultrasound-guided removal of the remaining fragments [93].

Treatment monitoring is based on clinical parameters such as linear growth, Tanner staging, and skeletal maturation. Breast or testicular development, bone age advancement, and high growth velocity are suggestive of treatment failure

Table 3 Pharmacokinetics of extended-release preparations of GnRH analogs

Generic name	Route of administration	Available doses (mg)	Duration of action
Leuprolide acetate	Intramuscular	3.75	4 weeks
	Intramuscular	7.5	4 weeks
	Intramuscular	11.25	12 weeks
	Intramuscular	22.5	12 weeks
	Intramuscular	30	12 weeks
	Subcutaneous	45	6 months
Triptorelin	Intramuscular	3.75	4 weeks
	Intramuscular	11.25	12 weeks
	Intramuscular	22.5	24 weeks
Goserelin	Subcutaneous injection	3.6	24–28 days
	Subcutaneous injection	10.8	3 months
Histrelin implant	Subcutaneous implant	50	1 year

[27, 124]. When treatment fails, after confirming adherence to GnRHa administration, the dose can be increased or the dosing interval can be reduced as an option [124].

There is no agreement about the need for biochemical measurements to assess treatment effectiveness. In children receiving GnRHa therapy, random ultrasensitive LH levels can remain in the pubertal range, despite apparent puberty suppression [125]. Stimulated LH levels using GnRH, aqueous GnRHa, or the free GnRHa contained in depot preparations can be used to evaluate treatment if the clinical results are poor [22, 27, 105]. Suppression of LH secretion to less than 2.5–4.5 IU/L (the cutoff point varies in the literature) according to IFMA, ICMA, or ECL is an adequate target in patients on monthly or trimonthly GnRHa therapy [126–128]. A recent study found first-void urinary LH measured with ECL useful in assessing puberty suppression during GnRHa treatment, with a cutoff of 1.01 IU/L for the highest sensitivity (92%) and specificity (100%) [129].

Patients with familial precocious puberty show adequate clinical and laboratory responses to long-acting GnRH analogs, similar to patients with idiopathic CPP [95]. There is no consensus on the optimal age to discontinue GnRHa therapy. The decision should be individualized and consider factors such as actual and predicted height, synchronization of puberty with peers, and psychological distress [27]. Treatment withdrawal should be evaluated at 12 to 12.5 years of bone age in girls and at 13 to 13.5 years of bone age in boys [17, 105]. Spontaneous menses occur approximately 12 months after interruption of GnRH treatment [107].

PPP

PPP management depends on the etiology, as shown in Table 2 [36, 41, 53, 54, 130–139]. Management of congenital adrenal hyperplasia is aimed at suppressing adrenal androgen production with glucocorticoids [140].

In MAS, girls with rapidly progressive puberty, frequent menses, accelerated growth, and bone age advancement may benefit from treatment [141]. Aromatase inhibitors have been used in the management of PPP in girls with MAS as they bind to the cytochrome P450 portion of aromatase, thus inhibiting the conversion of androgens to estrogens [28]. Third-generation aromatase inhibitors, such as anastrozole and letrozole, are more potent and better tolerated than earlier-generation agents, but only letrozole has been shown to be effective in the management of MAS [45]. Tamoxifen and fulvestrant are used as second-line or adjuvant therapy [141]. Treatment may include letrozole at a single daily dose of 2.5 mg for the entire treatment period or in escalating doses, starting with 0.5 mg/m^2/day for 7 days, then 1 mg/m^2/day on days 8–14, and then 1.5 mg/m^2/day thereafter. However, if there is any progression of PPP, a dose of 2 mg/m^2/day is suggested [139]. Ovarian surgery for cysts should be avoided, as disease is usually bilateral [141]. In boys with MAS, however, PPP has not been extensively studied because of its very low frequency, and all available treatment information is derived from case reports. Bisphosphonates (pamidronate and zoledronate) are proposed for persistent, moderate-to-severe bone pain. It remains unclear whether bisphosphonates can reduce fibrous dysplasia lesion size or progression [141]. Evidence for the efficacy and safety of denosumab is currently scarce, and its use is not recommended outside the context of a clinical trial [141].

For boys with FMPP, the most frequent approach involves the combination of an antiandrogen with a third-generation aromatase inhibitor [53]. The most common combination is spironolactone (5.7 mg/kg/day, up to 450–500 mg/day) plus anastrozole (1 mg/day), which has been shown to improve final adult height and to reduce the rate of bone maturation [132, 142, 143]. Ketoconazole and cyproterone acetate have also been suggested as alternative therapies [131].

Surgical resection is the first-line therapy for sex steroid-secreting tumors, with the exception of functioning follicular

ovarian cysts, because they tend to regress spontaneously [53, 144]. It should be noted that CPP and PPP can occur concomitantly in children due to early activation of the HPG axis, especially in those with significant bone age advancement; in this case, additional GnRHa treatment may be necessary [25].

Conclusion and perspectives

Puberty is a complex process that marks the transition from childhood to adulthood, and its mechanisms are not fully understood. Most cases of CPP are currently assumed to be idiopathic, but the recent identification of genes involved in pubertal development shows that genetic factors play a role in its pathophysiology. PPP is a heterogeneous disorder resulting from a wide range of gonadal and extragonadal conditions that involve diverse clinical manifestations, which requires accurate etiological investigation for correct management. Some questions remain unanswered, such as whether CNS imaging should be considered in all girls with CPP, the best method for monitoring hormone suppression, and optimal timing of treatment discontinuation. Future clinical trials should compare different drugs and dosages in GnRHa therapy, particularly in boys.

Abbreviations CNS, Central nervous system; CPP, Central precocious puberty; ECL, Electrochemiluminescence; FMPP, Familial male-limited precocious puberty; FSH, Follicle-stimulating hormone; GnRH, Gonadotropin-releasing hormone; GnRHa, Gonadotropin-releasing hormone agonist; HPG, Hypothalamic-pituitary-gonadal; ICMA, Immunochemiluminescent assay; IFMA, Immunofluorometric assay; IGF-1, Insulin-like growth factor-1; IPT, Isolated premature thelarche; LH, Luteinizing hormone; MRI, Magnetic resonance imaging; MAS, McCune-Albright syndrome; PPP, Peripheral precocious puberty; TW3, Tanner-Whitehouse 3

Code availability N/A

Authors' contributions Sandra Pinho Silveiro had the idea for the article. Amanda Veiga Cheuiche and Leticia Guimarães da Silveira performed the literature search and data analysis. Amanda Veiga Cheuiche wrote the first draft of the manuscript. Leila Cristina Pedroso de Paula, Iara Regina Siqueira Lucena, and SandraPinho Silveiro critically revised the work.

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Data Availability N/A

Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

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