Puberty 2

Causes, diagnosis, and treatment of central precocious puberty

Ana Claudia Latronico, Vinicius Nahime Brito, Jean-Claude Carel

Central precocious puberty results from the premature activation of the hypothalamic-pituitary-gonadal axis. It mimics physiological pubertal development, although at an inappropriate chronological age (before 8 years in girls and 9 years in boys). It can be attributable to cerebral congenital malformations or acquired insults, but the cause in most cases in girls remains unknown. *MKRN3* gene defects have been identified in familial disease, with important basic and clinical results. Indeed, genetic analysis of this gene should be included in the routine clinical investigation of familial and idiopathic cases of central precocious puberty. Gonadotropin-releasing hormone agonists are the gold-standard treatment. The assessment and management of this disease remain challenging for paediatric endocrinologists. In this Series paper, we describe current challenges involving the precise diagnosis and adequate treatment of this disorder.

Lancet Diabetes Endocrinol 2016; 4: 265–74

Published Online February 3, 2016 http://dx.doi.org/10.1016/S2213-8587(15)00380-0

This is the second in a Series of two papers about puberty

Disciplina de Endocrinologia e Metabologia, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil (Prof A C Latronico MD, V N Brito MD); **Univ Paris Diderot, Sorbonne Paris Cité, Paris, France** (Prof J-C Carel MD); **Department of Pediatric Endocrinology and Diabetology, Hôpital Robert Debré, and Centre de Référence des Maladies Endocriniennes Rares de la Croissance, Paris, France** (Prof J-C Carel); **and Institut National de la Santé et de la Recherche Médicale U1141, Paris, France** (Prof J-C Carel)

Correspondence to: Prof Ana Claudia Latronico, Disciplina de Endocrinologia e Metabologia, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, 05403-900, São Paulo, Brazil **anacl@usp.br**

Introduction

Puberty represents a complex biological process of sexual development that can be affected by genetic, nutritional, environmental, and socioeconomic factors. During this phase of development, individuals attain secondary sexual characteristics and reproductive capacity. In girls, the onset of puberty is defined clinically as the first appearance of breast buds, whereas in boys, testicular enlargement is the first pubertal sign.[1] In both sexes, pubic hair appearance can begin before, together with, or after the clinical onset of puberty.[1]

The normal age range for puberty onset refers to the time in which 95% of children attain initial pubertal signs (Tanner and Marshall stage 2 in both sexes).[2,3] In the 1960s, cross-sectional data led to designation of the normal age range of pubertal onset between ages 8 and 13 years in girls and between ages 9 and 14 years in boys. In the past two decades, cross-sectional data from the USA and Europe suggests that pubertal milestones are being reached earlier than previously thought in both sexes.[4–7] The putative decrease in age at the start of puberty has largely been attributed to improved health, nutrition, and sanitation.[8]

These findings guided recommendations to classify pubertal development as precocious when it occurs before age 6 years in black girls and before age 7 years in all other girls.[4] However, the validity of these initial recommendations was questioned because the Tanner staging of breast development was established mainly by inspection and not palpation.[3] In 2009, Roelants and colleagues[6] updated the reference charts for pubertal development in a large group of healthy Belgian children. The median age at menarche (13·0 years) had not advanced over the previous 50 years, despite the increasing prevalence of overweight and obesity in children older than 5 years in this period. However, about 10% of girls and boys in the study had initial pubertal development before age 9 years. In 2013, Biro and colleagues[7] reported that the onset of thelarche at younger ages is associated with ethnic origin and temporal changes in BMI, confirming and extending patterns seen in previous studies.[4–8] The lower age at thelarche in girls did not seem to be caused by gonadotropin-releasing hormone (GnRH) activation—but other potential mechanisms, such as endocrine disruptors and nutritional effects, might have had a role in this process.[9]

The most common mechanism of precocious puberty is the early activation of pulsatile GnRH secretion, known as gonadotropin-dependent precocious puberty or central precocious puberty. The estimated incidence in American girls is 1 in 5000–10 000.[10] However, the prevalence was 1 in 500 among Danish girls, based on national registries over a 9-year period (1993–2001).[11] The prevalence is sexually dimorphic, being higher in girls than in boys (15–20 girls for every boy).

The timing of puberty has substantial biological, psychosocial, and long-term health implications.[1,12] Concerns are associated with the diagnosis of precocious puberty, such as early menarche in girls, short adult stature because of early epiphyseal fusion, and adverse psychosocial outcomes. Evidence suggests an association between early timing of puberty and adverse health outcomes in later life.[8,12,13] Early age at menarche has been associated with increased risks of obesity, hypertension, type 2 diabetes, ischaemic heart disease, stroke, oestrogen-dependent cancer, and cardiovascular mortality.[12,13] Additionally, early age at menarche is a known risk factor for the development of breast cancer.[14,15] This association is largely attributed to high early exposure to oestrogen during the initial stages of breast development and throughout the reproductive years. Some evidence suggests that children with precocious puberty have increased sexual and delinquent behaviours in adulthood, or more psychological disturbances over and above general trends reported in children who undergo a normal puberty.[16,17] In this Series paper, we describe the known and new causes of central precocious puberty. We focus on the clinical assessment of central precocious puberty, and outline the challenges involved in the precise diagnosis and management of this common paediatric disorder.

Panel: **Causes of progressive central precocious puberty**

CNS lesions—congenital malformations
- Hypothalamic hamartoma
- Suprasellar arachnoid cysts
- Hydrocephalus
- Glioma or neurofibromatosis type 1
- Tuberous sclerosis
- Septo-optic dysplasia
- Chiari II malformations and myelomeningocele

CNS lesions—acquired insults
- Tumours: astrocytoma, ependymoma, pinealoma, hypothalamic or optic glioma, chraniopharyngioma, dysgerminoma (non-hCG secreting), meningioma
- Post-insults (perinatal, infection trauma, radiotherapy)
- Granulomatous disease
- Cerebral palsy

No CNS lesions
- Idiopathic
- Endocrine disruptors
- No CNS lesions—congenital causes
- Genetic changes: gain-of-function mutations in the genes encoding kisspeptin (*KISS1*) and kisspeptin receptor (*KISS1R* [formerly called *GPR54*]), loss-of-function mutation in makorin ring finger 3 (*MKRN3*)
- Chromosomal abnormalities

No CNS lesions—acquired conditions
- International adoption
- Early exposure to sex steroids (secondary central precocious puberty)

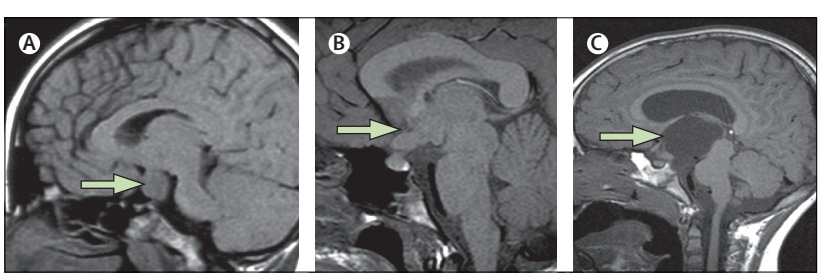

Figure 1: **Pathological brain MRI from three representative cases of central precocious puberty**
Hypothalamic hamartoma (A), optic glioma (neurofibromatosis type 1; B), and arachnoid cyst (C).

Causes

Several cerebral malformations and acquired insults have been associated with central precocious puberty (panel). The range of causes is similar in boys and girls, although idiopathic disease is much more common in girls—about 90% of cases in girls are idiopathic.[18,19] By contrast, 50–70% of the boys have identifiable pathological changes. The most frequently detected brain abnormalities associated with the disorder include hypothalamic hamartomas, encephalitis, hydrocephalus, neurofibromatosis type 1, meningomyelocele, and neonatal encephalopathy (figure 1).[20]

The hypothalamic hamartoma represents the most common organic cause in both sexes, usually manifesting before age 4 years.[21] This congenital mass is probably composed of GnRH neurons or transforming growth factor (TGF)α-producing astroglial cells that could cause premature activation of pulsatile GnRH release.[22] The disease phenotype caused by hamartomas can be associated with neurological abnormalities, such as gelastic, focal, or generalised tonic-clonic seizures, and cognitive impairment.[22,23]

Internationally adopted children seem to be at increased risk.[24] The reason for this finding is unclear, but it is postulated that nutritional deprivation in early life followed by increased adiposity after adoption triggers the endocrine and physical changes of puberty. Additionally, changing environmental effects, including possible roles of stress and early-life exposure to endocrine-disrupting factors, such as oestrogenic and antiandrogenic chemicals, can affect pubertal onset and tempo.[25,26] A quarter of the patients treated for sexual precocity in Belgium had migrated from abroad, particularly through international adoption, coming from malaria-endemic countries.[26] Additionally, most of these children had been exposed to the insecticide dichlorodiphenyltrichloroethane (DDT) during prenatal life and infancy.[26] DDT has prominently oestrogenic properties and its derivative dichlorodiphenyl-dichloroethylene (DDE) is regarded as antiandrogenic.[27] These findings initially suggested the potential involvement of DDT in the early pathogenesis of sexual precocity in exposed children. However, data for the timing of menarche after prepubertal exposure to DDE or DDT have been inconclusive, with menarche seen to occur early[28] or within the normal age range.[26,29,30] Additional animal and human studies are needed to establish the role of these chemicals in pubertal disorders.

Long-term exposure to sex steroids can result in maturation of CNS centres that are important for the initiation of puberty.[18,19,31] The decrease in sex steroids during treatment of the primary underlying disorder causes an activation of the precociously matured hypothalamic GnRH pulse generator via feedback mechanisms, resulting in what is referred to as secondary central precocious puberty. This form of puberty can occur after treatment of congenital adrenal hyperplasia, after removal of sex steroid-producing tumours, and in testotoxicosis.[19,31,32]

Studies[33–35] have implicated the activation of the genes *KISS1*, which encodes kisspeptin, and *KISS1R* (formerly called *GPR54*), which encodes the kisspeptin receptor, and the inactivation of the *MKRN3* gene, which encodes makorin ring finger protein 3, in the premature reactivation of GnRH secretion, which was previously deemed idiopathic. In 2008, a heterozygous activating mutation of *KISS1R* (p.Arg386Pro) was identified in association with central precocious puberty.[33] This mutation was identified in an adopted girl who had progressive thelarche from birth, suggesting early, persistent, and slightly increased oestrogen secretion. Accelerated growth, skeletal maturation, and progression of breast development were noticed at age 7 years. Data

from in-vitro studies showed that the p.Arg386Pro mutation, located in the C-terminal tail of the receptor, led to prolonged activation of intracellular signalling pathways in response to kisspeptin, resulting in much higher inositol phosphate accumulation for as long as 18 h.[33]

In view of the description of an activating mutation in *KISS1R* causing premature activation of the gonadotropic axis, *KISS1* was another obvious natural candidate gene for genetic central precocious puberty. One rare kisspeptin variant, p.Pro74Ser, was identified in the heterozygous state in a boy who developed sporadic disease at age 1 year, with high concentrations of basal luteinising hormone (LH) and testosterone.[34] His mother and maternal grandmother, both of whom had normal pubertal development, also carried the p.Pro74Ser mutation in the heterozygous state, suggesting incomplete sex-dependent penetrance. Results of in-vitro studies showed that the capacity to stimulate signal transduction was significantly greater for p.Pro74Ser than for the wild type, suggesting that this variant might be more resistant to degradation, resulting in greater kisspeptin bioavailability.[34] Although these cases contribute to the elucidation of the fundamental role of the kisspeptin pathway in the physiological regulation of pubertal development, no other cases with activating *KISS1R* or *KISS1* mutations have been reported, suggesting that these genetic abnormalities are very rare.

MKRN3, an imprinted gene located on the long arm of chromosome 15 (Prader-Willi region), encodes makorin ring finger protein 3, which is involved in gene transcription and ubiquitination. The MKRN3 protein is derived only from RNA transcribed from the paternally inherited copy of the gene, because of maternal imprinting.[35] Segregation analysis of families with central precocious puberty caused by *MKRN3* mutations clearly shows an autosomal dominant inheritance with complete penetrance. Inherited *MKRN3* defects have been identified in children with apparently sporadic disease.[36] Because of the imprinting pattern (maternal silencing) of *MKRN3*, the disease phenotype can be inherited from an asymptomatic father who carries an *MKRN3* mutation. Indeed, genotype analysis of patients who have *MKRN3* mutations and no family history of premature sexual development showed that paternal inheritance was present in all studied cases;[36] no de-novo mutation of *MKRN3* has been described in these patients so far. Findings from these initial studies suggested that the familial nature of this disorder is probably under-recognised, because of the difficulty of obtaining a precise family history from the father and the likelihood of under-diagnosis of early testicular enlargement.[36] A growing list of loss-of-function mutations of *MKRN3* has been identified in several affected families from different ethnic groups.[35–42] Remarkably, patients with *MKRN3* mutations had typical clinical and hormonal features of premature activation of the reproductive axis, including early pubertal signs such as breast, testis, and pubic hair development, accelerated linear growth, advanced bone age, and raised basal or GnRH-stimulated LH concentrations. A few patients with loss-of-function mutations in *MKRN3* had mild, non-specific syndromic features, including two related patients with esotropia and one girl with a high-arched palate, dental abnormalities, clinodactyly, and hyperlordosis.[40] No significant difference was noted in the median age of pubertal onset, clinical features, or basal and GnRH-stimulated LH concentrations between patients with and without *MKRN3* mutations.[40]

Distinct chromosomal abnormalities have been associated with complex syndromic phenotypes that could include premature sexual development caused by activation of the hypothalamic-pituitary-gonadal axis. Among these syndromes are the 1p36 deletion, 7q11.23 microdeletion (Williams-Beuren syndrome),[43] 9p deletion,[44] maternal uniparental disomy of chromosomes 7 (Silver-Russell syndrome) and 14 (Temple syndrome),[45] inversion duplication of chromosome 15,[46] de-novo interstitial deletion and maternal uniparental disomy of chromosome 15 (Prader-Willi syndrome),[47] and a de-novo deletion in cyclin-dependent kinase-like 5 gene (*CDKL5*; located in the Xp22 region),[48] with a phenotype reminiscent of Rett syndrome. Notably, maternal uniparental disomy of chromosomes 7 and 14 are genomic imprinting disorders.[45]

Assessment

Clinical assessment

The first step in assessing a child with precocious puberty is to obtain a detailed personal and family history.[18,31] The age of onset and the time velocity of physical changes, development of secondary sexual characteristics, sex steroid exposure, and evidence of possible CNS dysfunction (such as headache, large head circumference, visual abnormalities or seizures, trauma, or infections) are important information. The physical examination includes the assessment of secondary sexual features—ie, breast development in girls and testis measurement in boys, and pubic hair development in both sexes, classifying them on the basis of the Marshall and Tanner criteria.[31] Careful assessment is desirable, particularly in overweight and obese girls, to avoid overestimation of breast development. In boys, testicular volume greater than 4 mL or length greater than 2·5 cm usually suggests gonadotropin stimulation. Advanced height, bone age, and accelerated growth velocity are usually present in patients with central precocious puberty and should be checked for. Other physical characteristics, such as axillary hair and body composition, should also be documented. Skin examination is strongly recommended for detection of facial acne or oily skin and cutaneous pigmentation (café au lait spots) and lesions, which could be associated with McCune-Albright syndrome, neurofibromatosis, or tuberous sclerosis.

Hormonal profile

The gold-standard biochemical diagnosis is based on the assessment of gonadotropins, mainly LH, after stimulation with exogenous GnRH or GnRH agonists.[18,31] With the development of laboratory methods that make use of monoclonal antibodies such as immunofluorometric, immunochemiluminometric, and electrochemiluminometric assays, which have higher sensitivity and specificity than radioimmunoassay methods, it has been suggested that baseline random LH could be used to assess the activation of the gonadotropic axis, avoiding the need for testing of the GnRH-stimulated LH concentration.[49] However, several studies[49–54] have shown that the diagnostic value of basal LH is variable, with sensitivity ranging from 60% to 100%. Different cutoff values for basal LH, ranging from 0·1 to 1·5 IU/L, showed different diagnostic sensitivities and specificities (table). Caution should be used when interpreting gonadotropin concentrations in children younger than 2 or 3 years, because baseline gonadotropin concentrations are usually high in this age group.[18]

In patients with clinical sexual precocity and basal prepubertal LH, the GnRH stimulation test is indicated to establish the level of activation of the gonadotropic axis.[18,31] Generally, the several protocols that have been produced suggest blood sampling at one or more timepoints for gonadotropin measurement, ranging from 30 min to 180 min after intravenous or subcutaneous GnRH administration.[49,54] Some investigators have suggested that a simplified test with a single measurement 30 or 40 min after GnRH is sufficient to confirm activation of the gonadotropic axis.[55,56] Cutoff concentrations for an LH peak higher than 5 IU/L, assessed by ultrasensitive immunoassays, are usually indicative of an activated gonadotropic axis.[18,50] However, several cutoffs for GnRH-stimulated LH concentrations have been suggested, particularly for girls, ranging from 5 to 8 IU/L.[49,50,54] Basal and GnRH-stimulated follicle-stimulating hormone (FSH) concentrations do not adequately differentiate children with and without central precocious puberty because of a substantial overlap between prepubertal and pubertal healthy children.[31,49] However, evidence of suppressed GnRH-stimulated FSH concentrations strongly suggests peripheral precocious puberty. A GnRH-stimulated peak LH-to-FSH ratio of 0·6–1·0 has been suggested for use in diagnosis.[57] However, its sensitivity and specificity are not greater than the GnRH-stimulated peak LH alone.[49]

In boys, testosterone is an excellent marker for sexual precocity, because prepubertal concentrations of this hormone exclude the diagnosis of precocious puberty.[31] In girls, low oestradiol concentrations do not rule out the diagnosis of precocious puberty. In fact, many girls (about 40%) with central precocious puberty have prepubertal concentrations of oestradiol.[16,18,31] Nevertheless, high concentrations of oestradiol in the presence of suppressed or low concentrations of gonadotropins strongly suggest a peripheral cause.[19] Reference values for testosterone and oestradiol vary with the method and assay used for assessment.

Some challenges in the hormonal assessment of children with sexual precocity at the time of diagnosis and during depot GnRH agonist therapy still remain. First, the adequate and standardised determination of normal hormonal concentrations in healthy children on the basis of sex, chronological age, and pubertal stage for each laboratory method is difficult. However, novel laboratory techniques such as tandem mass spectrometry might improve the sensitivity and specificity of oestradiol assays.[58]

Serum concentrations of MKRN3 were assessed in a population-based longitudinal study of healthy Danish girls.[59] MKRN3 concentrations declined before pubertal onset, and circulating MKRN3 concentrations were negatively associated with gonadotropin concentrations in prepubertal girls.[59] Undetectable or low MKRN3

	Number of patients	Method	Basal LH concentration (IU/L)	Sensitivity for basal LH concentration (%)	Specificity for basal LH concentration (%)	GnRH stimulated peak LH concentration (IU/L)	Sensitivity for GnRH stimulated peak LH concentration (%)	Specificity for GnRH stimulated peak LH concentration (%)
Neely et al (1995)[50]	26	ICMA	0·1	94	88	5·0	NA	NA
Brito et al (1999)[49]	58	IFMA	0·6	62·7 (girls)	100	6·9 (girls)	92·2 (girls)	100
				71·2 (boys)		9·6 (boys)	100 (boys)	100
Houk et al (2009)[51]	14	ICMA	0·83	93	100	NA	NA	NA
	20	IFMA	1·05	100				
Pasternak et al (2012)[53]	42	ICMA	0·1	94·7	64·4	4·9	78	79
Lee et al (2013)[52]	147	ECLIA	0·1	56·4	88·4	5·0	56·4	88·4
Freire et al (2013)[54]	46	IFMA	NA	NA	NA	7·0	76	100
		ECLIA				8·0		

GnRH=gonadotropin-releasing hormone. LH=luteinising hormone. ICMA=immunochemiluminometric assay. NA=not available. IFMA=immunofluorometric assay. ECLIA=electrochemiluminometric assay.

Table: **Diagnostic values of basal and GnRH-stimulated LH concentrations in the diagnosis of central precocious puberty, by study**

concentrations were reported in a subgroup of patients with early onset of puberty. These findings support MKRN3 as a major regulator of hypothalamic GnRH secretion during childhood and suggest that the assessment of serum MKRN3 concentrations might be useful for the assessment of pubertal development.[59]

Imaging studies

The bone age of patients with precocious puberty is generally advanced by 2 years or more, or by more than 2·5 SDs, in relation to chronological age.[18,32] However, the absence of advanced bone age is not a reason to discontinue follow-up assessment when increased growth velocity and other clinical symptoms of progressive puberty are present. Bone age is often used to predict adult height, although this prediction tends to overestimate adult height and is not very reliable.[60,61]

In girls, pelvic ultrasonography can be useful initially in the differential diagnosis of premature sexual development to assess the presence of ovarian tumours or cysts, particularly if oestradiol concentrations are high.[62] Uterine changes due to oestrogen exposure can also be used as an index of progressive puberty in patients.[18] Sathasivam and colleagues[63] compared the use of ovarian and uterine volumes measured by ultrasonography with the use of baseline and leuprolide-stimulated LH and oestradiol concentrations for diagnostic assessment in 50 girls (aged 3·1–9·5 years) with suspected precocious puberty. They reported a substantial overlap in ovarian and uterine volumes among girls from prepubertal (baseline and stimulated LH and oestradiol in prepubertal range) and pubertal (baseline or leuprolide-stimulated LH in pubertal range) groups, suggesting that pelvic ultrasonography alone cannot distinguish between prepubertal girls and those in the early stages of puberty.

MRI of the brain should be done to find out if a hypothalamic lesion is present in cases of progressive central precocious puberty. The prevalence of such lesions is higher in boys (40–90%) than in girls (8–33%) with precocious puberty and is much lower when puberty starts after age 6 years in girls (about 2% in case series).[16,18,64,65] MRI should be done in all cases for diagnosis of brain abnormalities associated with central precocious puberty. Notably, young age, rapid progression, and high oestradiol concentrations are factors that might predict increased risk of brain abnormalities.

Mogensen and colleagues[64] showed that 13 (6%) of 208 girls with central precocious puberty had an abnormal brain MRI. All of the girls were older than 6 years and half were aged 8–9 years. Moreover, the brain abnormalities were not predicted by clinical or biochemical parameters in this study.[64] Pedicelli and colleagues[65] showed the presence of an abnormal MRI in 13 (14%) of 182 girls with central precocious puberty. Girls with hypothalamic hamartomas were younger than 6 years and had significantly higher mean baseline and stimulated LH concentrations, LH-to-FSH ratios, serum oestradiol concentration, and uterine lengths. However, all the parameters overlapped widely in girls with and without brain lesions.

Incidental findings on brain MRI, which were not thought to be related to early pubertal development, were seen in up to 11% of cases.[64,65] These findings usually result in parental and medical concern, and can lead to repeated and potentially harmful procedures. Among the most frequent incidental findings are pituitary abnormalities (enlargement of the gland and microadenomas) and pineal cysts.[64,65]

MKRN3 loss-of-function mutations are a frequent cause of familial disease. Whole-exome sequencing of 15 families (40 members) with central precocious puberty revealed 15 children (eight girls and seven boys) belonging to five families with *MKRN3* defects (33% of the affected families).[35] This genetic disorder has been associated with normal MRI scans of the hypothalamic-pituitary region in all affected patients from both sexes. These genetic findings should affect the clinical decision about the use of MRI. In fact, routine screening with brain MRI does not seem to be useful in patients with a clear family history, such as two affected siblings, or a father and one or more of his children having the disorder. In these cases, genetic studies could precede the brain MRI, which might be postponed (in non-mutant cases) or even avoided completely in patients who carry *MKRN3* mutations. The financial costs of the genetic analysis of *MKRN3*, an intronless gene, are much lower than the costs of a brain MRI in children, who usually need anaesthesia for the scan. We propose a diagnostic procedure that includes clinical, hormonal, CNS imaging, and potential genetic investigation of patients with suspected central precocious puberty (figure 2). A reliable family history is a key element for driving the medical decision of whether to do a brain MRI or a genetic test first.

Differential diagnosis of precocious puberty

It is very important to distinguish between central precocious puberty and common variants of precocious puberty, such as premature thelarche or premature adrenarche.[18,19,49] Premature thelarche is defined by isolated development of breast tissue, without other pubertal findings, such as accelerated linear growth, rapid progression of breast development, or advanced skeletal maturation. It often occurs in toddler girls and usually regresses over several months.[66] Premature adrenarche is characterised by gradually progressive pubic or axillary hair growth secondary to mildly increased concentrations of adrenal-derived androgens.[67] Advanced bone age might be present, but breast development is absent in this disorder. Therefore, girls with pubic hair or axillary hair and no breast development, or boys with pubic hair or axillary hair and no testicular enlargement,

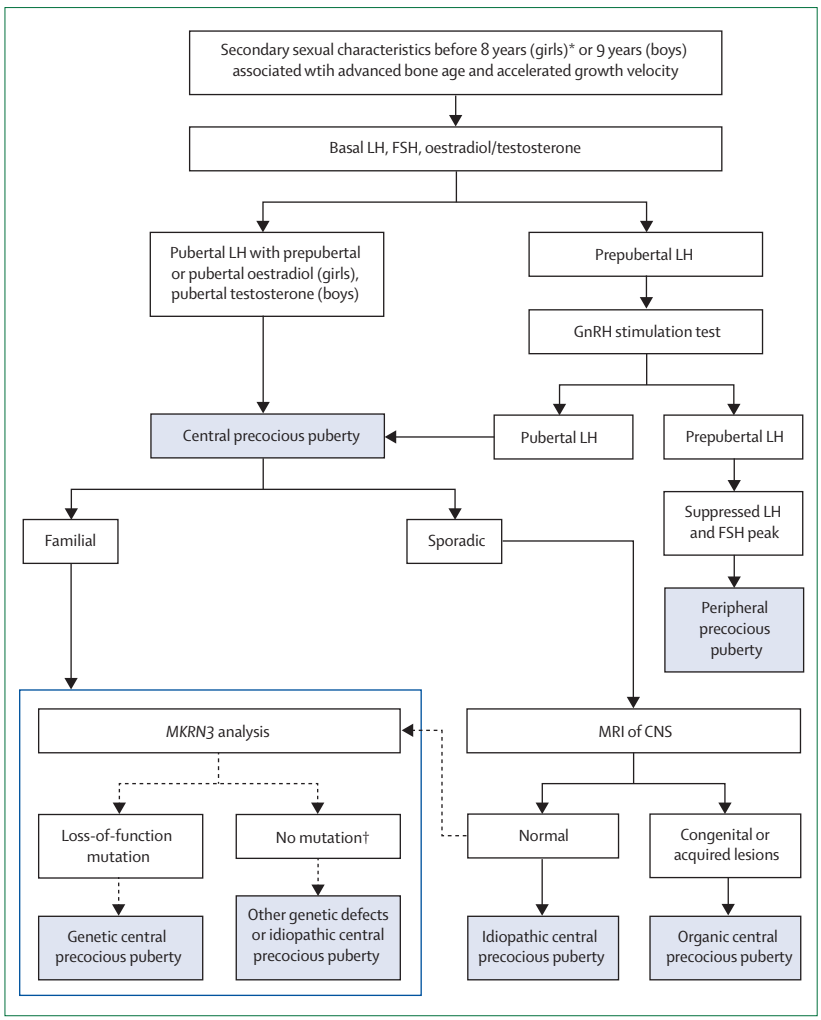

***Figure 2*: Flow diagram for investigation of precocious puberty in girls and boys**
Measured values of pubertal basal and GnRH-stimulated LH concentrations are dependent on the laboratory method used for assessment. For ultrasensitive assays (immunochemiluminometric and electrochemiluminometric assays), basal LH concentration greater than 0·2 IU/L and GnRH-stimulated LH concentrations greater than 8 IU/L are usually deemed pubertal concentrations in both sexes.[49–54] Basal oestradiol concentrations have low sensitivity for diagnosis of central precocious puberty.[49] The left side of diagram with dashed lines indicates a potential strategy for identification of the most frequent genetic cause of central precocious puberty. LH=luteinising hormone. FSH=follicle-stimulating hormone. *MKRN3*=makorin ring finger protein 3 gene. *The limits of chronological age for pubertal development can vary for different ethnic groups (eg, earlier in black girls).[4] †Patients with no genetic mutations should undergo CNS imaging.

are likely to have premature adrenarche or a peripheral cause of precocious puberty. Additionally, the distinction of central precocious puberty from GnRH-independent or peripheral precocious puberty is necessary. Central precocious puberty in boys is typically associated with symmetrically increased testicular volumes, by contrast with most forms of peripheral precocious puberty, which are characterised by asymmetrical or prepubertal testes.[19,31] Boys with testotoxicosis or adrenal rest tumours—very rare GnRH-independent forms of precocious puberty—have symmetrically enlarged testes.[31]

Therefore, early breast or testicular development are not always manifestations of central precocious puberty, and clinical and laboratory investigation can help to resolve the diagnosis. Clinical indicators of pubertal progression should be given priority over hormonal tests and imaging. A period of clinical observation is highly recommended before any pharmacological interventions.[9,16] In an elegant study, 13% of premature thelarche cases were subsequently diagnosed as having progressive central precocious puberty (independent of the age of initial clinical presentation), which suggests the need for long-term follow-up.[66,68]

Additional challenges have arisen from confusion over the terminology used to describe precocious puberty. Atypical forms of sexual precocity, mainly when progressive central precocious puberty occurs without evidence of pubertal LH activation, have been described as early puberty.[8] The same term has been used when the onset of puberty begins within the normal age range, but at the inferior limits (8–9 years in girls and 9–10 years in boys).[69] The use of such terminology results in confusion and should be avoided, as terms are often overlapping. The benefits of the GnRH agonists in patients with these atypical forms of early or accelerated puberty are not defined.[8] Indeed, it seems that these atypical forms might just show the extremes of normal pubertal development.

Management

GnRH agonist treatment

Long-acting GnRH agonists have been the gold-standard treatment since the mid-1980s. Questions remain about their optimum use—an international consensus statement published in 2009 summarised the available information and the areas of uncertainty.[16] GnRH agonists continuously stimulate the pituitary gonadotrophs, leading to desensitisation and decreases in release of LH and, to a lesser extent, FSH.[70] Several GnRH agonists are available in various depot forms, and their approval for use and recommended doses in precocious puberty vary in different countries. Use of GnRH agonist results in the regression or stabilisation of pubertal symptoms, lowering of growth velocity to normal prepubertal values, and decrease of bone-age advancement.[16] Progression of breast or testicular development usually indicates poor compliance, treatment failure, or incorrect diagnosis, demanding further assessment. All well controlled cases should have prepubertal oestradiol and testosterone concentrations monitored during GnRH agonist therapy. Routine biochemical monitoring of basal LH concentration has been questioned.[16,71] Prepubertal or suppressed serum GnRH-stimulated LH concentrations are expected in patients on GnRH agonist therapy. The classic GnRH stimulation test with short-acting GnRH or, alternatively, a single LH sample 30–120 min after long-acting GnRH agonist administration can be used to monitor therapy.[72,73] Suppression of LH to less than 4·5 IU/L is an adequate target in patients on GnRH agonist therapy.[74]

The optimum time to discontinue treatment has not been formally established. Factors that could affect the decision of when to stop GnRH agonists include synchronising puberty with peers, or in some cases, facilitating care of the developmentally delayed child. Treatments are usually interrupted at age 10–11 years, with the goal of having menarche occur near the population norms.[16] The optimum time for interruption of treatment should be based on the combination of chronological age and bone maturation. The best outcomes for final height were obtained with GnRH-agonist treatment withdrawal between 12·0 and 12·5 years of bone age in girls and between 13·0 and 13·5 years of bone age in boys.[75] Pubertal manifestations generally reappear within months of GnRH agonist treatment being stopped, with a mean time to menarche of 16 months for depot GnRH agonists, and seemingly less for histrelin implants.[76,77]

The addition of growth hormone[78] or oxandrolone[79] when growth velocity decreases (<4 cm/year) or if height is impaired has been proposed, but data are scarce regarding the efficacy and safety of these drugs in children with precocious puberty, and thus they cannot be recommended.

Outcomes after GnRH agonist treatment

No randomised controlled trials have assessed long-term outcomes after GnRH agonist treatment. Height outcomes have been assessed mainly by comparisons between achieved adult height and predicted height before treatment. In a meta-analysis of about 400 girls treated until a mean age of 11 years, the mean adult height was about 160 cm and mean gains over predicted height varied from 3 to 10 cm.[61] Factors affecting height outcome included initial patient characteristics (lower achieved adult height if bone age is substantially advanced and if predicted height was lower at initiation of treatment) and, in some case series, duration of treatment (greater height gains in patients starting treatment at a younger age and with longer duration of treatment). The effect of age at discontinuation of treatment on achieved height has been considered and the use of variables such as chronological age, duration of therapy, bone age, height, target height, and growth velocity have been proposed, alone or in combination, to help decide when to stop treatment. However, these closely interrelated variables cannot be considered independently. Findings from retrospective analyses suggest that continuing treatment beyond age 11 years in girls is associated with no further gain in height.[75]

The newest form of therapy includes a subcutaneous implant of the GnRH agonist histrelin, which leads to gonadotropin suppression for 12–24 months.[80,81] Results from a long-term, phase 3, prospective, open-label study[80] of 36 children with central precocious puberty who had once-yearly histrelin subcutaneous implant therapy were reported in 2015. Over the 72-month treatment phase, sequential histrelin implant therapy provided sustained gonadotropin suppression in these children. 6 months after removal of the final implant, peak LH and FSH concentrations had risen to pubertal concentrations in all patients assessed, suggesting recovery of the hypothalamic-pituitary-gonadal axis after long-term gonadotropin suppression.[80] Oestradiol and testosterone concentrations were consistently in the prepubertal range over the course of long-term histrelin implant therapy and rose above suppression thresholds in the follow-up period. In girls, predicted adult height increased from 151·9 cm at baseline to 166·5 cm at month 60, with a 10·7 cm height gain. These data were not available for boys. No adverse effect on growth or recovery of the hypothalamic-pituitary-gonadal axis was reported with hormonal suppression. These findings suggest that long-term histrelin implant therapy provided sustained gonadotropin suppression safely and effectively, and improved predicted adult height in children with central precocious puberty.[80]

Other outcomes to consider include bone mineral density, risk of obesity, and psychosocial outcomes. Bone mineral density can decrease during GnRH agonist therapy, but subsequent bone mass accrual is preserved, and peak bone mass does not seem to be negatively affected by treatment.[16] There have been concerns that use of GnRH agonists might affect BMI, but the available data suggest that long-term GnRH agonist treatment does not seem to cause or aggravate obesity, as assessed by BMI.[16] Nonetheless, the risk of obesity is a concern in girls with precocious puberty, and BMI should be closely monitored. Psychosocial assessment data are scarce in patients with premature sexual maturation, and there is little evidence to show whether treatment with GnRH agonists is associated with improved psychological outcome.[16]

Tolerance to GnRH agonist treatment

Tolerance to GnRH agonists is generally judged to be good. Treatment can be associated with headaches, rash, gastrointestinal complaints, or menopausal symptoms such as hot flushes. These adverse effects are generally transient and resolve spontaneously or with symptomatic treatment. Local complications (seen in 3–13% of cases in several case series) such as sterile abscesses can result in a loss of efficacy, and anaphylaxis has been described in rare cases.[82,83] Vaginal bleeding after the first injection of a GnRH agonist can occur in girls with advanced pubertal development (Tanner stage IV) and has been attributed to a transient increase in oestradiol secretion. However, persistent vaginal bleeding during treatment suggests poor suppression of gonadotropin. Long-term fertility has not been fully assessed, but preliminary data showed normal reproduction function in both sexes.[76,84]

Search strategy and selection criteria

Data for this Series paper were identified by searches of PubMed and references from relevant articles using the search terms "precocious puberty" or "central precocious puberty". Articles in English published between Jan 1, 1995, and July 20, 2015 were included.

Management of causal lesions

When precocious puberty is caused by a hypothalamic lesion (such as mass or malformation), management of the causal lesion generally has no effect on the course of pubertal development.[18] Hypothalamic hamartomas should not be treated by surgery for the management of precocious puberty. Surgical treatment is only indicated for large hamartomas with neurological symptoms, such as refractory epilepsy and intracranial hypertension.[85] An alternative diagnosis caused by a different type of hypothalamic lesion should be considered when unexpected enlargement occurs. Precocious puberty associated with the presence of a hypothalamic lesion might progress to gonadotropin deficiency with hypogonadism.

Conclusions

Despite great advances in knowledge regarding the assessment and management of central precocious puberty, several challenges remain. Among these challenges are to distinguish normal pubertal development (benign variants or non-progressive forms of sexual precocity) from pathological disorders and to recognise the underlying mechanisms involved. During the investigation, it is important to establish the appropriate time to do additional assessments in a cost-effective way.

Recent progress in the identification of new causes of the disorder has opened many avenues of research for understanding the mechanisms of pubertal timing in human beings. However, laboratory diagnosis remains a challenge in view of the absence of uniform laboratory criteria for diagnosis and standardised methods for gonadotropin and sex steroid measurement. Finally, more research needs to be done to investigate long-term outcomes after GnRH agonist treatment, which could be used as the basis for standard guidelines to support clinicians in the diagnosis and treatment of central precocious puberty.

Contributors

All authors contributed to the preparation of the Series paper content, and to critical reading and revision of the draft report.

Declaration of interests

J-CC has received research grants from Ipsen. VNB has received lecture fees from Abbvie. ACL declares no competing interests.

Acknowledgments

ACL thanks Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq # 302825/2011-8) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP # 13/03236–5) for research funding. We thank Dr Ursula B Kaiser for her contributions to the text editions and suggestions.

References

1 Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocr Rev* 2003; **24:** 668–93.

2 Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970; **45:** 13–23.

3 Marshall WATJ, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969; **44:** 291–303.

4 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:** 505–12.

5 Aksglaede L, Sørensen K, Petersen JH, Skakkebaek NE, Juul A. Recent decline in age at breast development: the Copenhagen Puberty Study. *Pediatrics* 2009; **123:** e932–39.

6 Roelants M, Hauspie R, Hoppenbrouwers K. References for growth and pubertal development from birth to 21 years in Flanders, Belgium. *Ann Hum Biol* 2009; **36:** 680–94.

7 Biro FM, Greenspan LC, Galvez MP, et al. Onset of breast development in a longitudinal cohort. *Pediatrics* 2013; **132:** 1019–27.

8 Willemsen RH, Elleri D, Williams RM, Ong KK, Dunger DB. Pros and cons of GnRHa treatment for early puberty in girls. *Nat Rev Endocrinol* 2014; **10:** 352–63.

9 Kaplowitz P. Update on precocious puberty: girls are showing signs of puberty earlier, but most do not require treatment. *Adv Pediatr* 2011; **58:** 243–58.

10 Partsch CJ, Sippell WG. Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens. *Hum Reprod Update* 2001; **7:** 292–302.

11 Teilmann G, Pedersen CB, Jensen TK, Skakkebaek NE, Juul A. Prevalence and incidence of precocious pubertal development in Denmark: an epidemiologic study based on national registries. *Pediatrics* 2005; **116:** 1323–28.

12 Lakshman R, Forouhi NG, Sharp SJ, et al. Early age at menarche associated with cardiovascular disease and mortality. *J Clin Endocrinol Metab* 2009; **94:** 4953–60.

13 Prentice P, Viner RM. Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis. *Int J Obes (Lond)* 2013; **37:** 1036–43.

14 Ritte R, Lukanova A, Tjønneland A, et al. Height, age at menarche and risk of hormone receptor-positive and -negative breast cancer: a cohort study. *Int J Cancer* 2013; **132:** 2619–29.

15 Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol* 2012; **13:** 1141–51.

16 Carel JC, Eugster EA, Rogol A, et al, and the ESPE-LWPES GnRH Analogs Consensus Conference Group. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics* 2009; **123:** e752–62.

17 Xhrouet-Heinrichs D, Lagrou K, Heinrichs C, et al. Longitudinal study of behavioral and affective patterns in girls with central precocious puberty during long-acting triptorelin therapy. *Acta Paediatr* 1997; **86:** 808–15.

18 Carel JC, Léger J. Precocious puberty. *N Engl J Med* 2008; **358:** 2366–77.

19 Partsch CJ, Heger S, Sippell WG. Management and outcome of central precocious puberty. *Clin Endocrinol (Oxf)* 2002; **56:** 129–48.

20 Stephen MD, Zage PE, Waguespack SG. Gonadotropin-dependent precocious puberty: neoplastic causes and endocrine considerations. *Int J Pediatr Endocrinol* 2011; **2011:** 184502.

21 de Brito VN, Latronico AC, Arnhold IJ, et al. Treatment of gonadotropin dependent precocious puberty due to hypothalamic hamartoma with gonadotropin releasing hormone agonist depot. *Arch Dis Child* 1999; **80:** 231–34.

22 Jung H, Ojeda SR. Pathogenesis of precocious puberty in hypothalamic hamartoma. *Horm Res* 2002; **57** (suppl 2)**:** 31–34.

23 Cukier P, Castro LH, Banaskiwitz N, et al. The benign spectrum of hypothalamic hamartomas: infrequent epilepsy and normal cognition in patients presenting with central precocious puberty. *Seizure* 2013; **22:** 28–32.

24 Teilmann G, Pedersen CB, Skakkebaek NE, Jensen TK. Increased risk of precocious puberty in internationally adopted children in Denmark. *Pediatrics* 2006; **118:** e391–99.

25 Mouritsen A, Aksglaede L, Sørensen K, et al. Hypothesis: exposure to endocrine-disrupting chemicals may interfere with timing of puberty. *Int J Androl* 2010; **33:** 346–59.

26 Parent AS, Franssen D, Fudvoye J, Gérard A, Bourguignon JP. Developmental variations in environmental influences including endocrine disruptors on pubertal timing and neuroendocrine control: revision of human observations and mechanistic insight from rodents. *Front Neuroendocrinol* 2015; **38:** 12–36.

27 Rasier G, Parent AS, Gérard A, et al. Mechanisms of interaction of endocrine-disrupting chemicals with glutamate-evoked secretion of gonadotropin-releasing hormone. *Toxicol Sci* 2008; **102:** 33–41.

28 Deng F, Tao FB, Liu DY, et al. Effects of growth environments and two environmental endocrine disruptors on children with idiopathic precocious puberty. *Eur J Endocrinol* 2012; **166:** 803–09.

29 Denham M, Schell LM, Deane G, Gallo MV, Ravenscroft J, DeCaprio AP, and the Akwesasne Task Force on the Environment. Relationship of lead, mercury, mirex, dichlorodiphenyldichloroethylene, hexachlorobenzene, and polychlorinated biphenyls to timing of menarche among Akwesasne Mohawk girls. *Pediatrics* 2005; **115:** e127–34.

30 Ozen S, Darcan S, Bayindir P, Karasulu E, Simsek DG, Gurler T. Effects of pesticides used in agriculture on the development of precocious puberty. *Environ Monit Assess* 2012; **184:** 4223–32.

31 Brito VN, Latronico AC, Arnhold IJ, Mendonça BB. Update on the etiology, diagnosis and therapeutic management of sexual precocity. *Arq Bras Endocrinol Metabol* 2008; **52:** 18–31.

32 Kumar M, Mukhopadhyay S, Dutta D. Challenges and controversies in diagnosis and management of gonadotropin dependent precocious puberty: an Indian perspective. *Indian J Endocrinol Metab* 2015; **19:** 228–35.

33 Teles MG, Bianco SD, Brito VN, et al. A *GPR54*-activating mutation in a patient with central precocious puberty. *N Engl J Med* 2008; **358:** 709–15.

34 Silveira LG, Noel SD, Silveira-Neto AP, et al. Mutations of the *KISS1* gene in disorders of puberty. *J Clin Endocrinol Metab* 2010; **95:** 2276–80.

35 Abreu AP, Dauber A, Macedo DB, et al. Central precocious puberty caused by mutations in the imprinted gene *MKRN3*. *N Engl J Med* 2013; **368:** 2467–75.

36 Macedo DB, Abreu AP, Reis AC, et al. Central precocious puberty that appears to be sporadic caused by paternally inherited mutations in the imprinted gene *makorin ring finger 3*. *J Clin Endocrinol Metab* 2014; **99:** E1097–103.

37 Settas N, Dacou-Voutetakis C, Karantza M, Kanaka-Gantenbein C, Chrousos GP, Voutetakis A. Central precocious puberty in a girl and early puberty in her brother caused by a novel mutation in the *MKRN3* gene. *J Clin Endocrinol Metab* 2014; **99:** E647–51.

38 Schreiner F, Gohlke B, Hamm M, Korsch E, Woelfle J. *MKRN3* mutations in familial central precocious puberty. *Horm Res Paediatr* 2014; **82:** 122–26.

39 de Vries L, Gat-Yablonski G, Dror N, Singer A, Phillip M. A novel *MKRN3* missense mutation causing familial precocious puberty. *Hum Reprod* 2014; **29:** 2838–43.

40 Bulcao Macedo D, Nahime Brito V, Latronico AC. New causes of central precocious puberty: the role of genetic factors. *Neuroendocrinology* 2014; **100:** 1–8.

41 Neocleous V, Shammas C, Phelan MM, Nicolaou S, Phylactou LA, Skordis N. In silico analysis of a novel *MKRN3* missense mutation in familial central precocious puberty. *Clin Endocrinol (Oxf)* 2015; published online July 15. DOI:10.1111/cen.12854.

42 Lee HS, Jin HS, Shim YS, et al. Low frequency of *MKRN3* mutations in central precocious puberty among Korean girls. *Horm Metab Res* 2015; published online May 4. DOI: 10.1055/s-0035-1548938

43 Partsch CJ, Japing I, Siebert R, et al. Central precocious puberty in girls with Williams syndrome. *J Pediatr* 2002; **141:** 441–44.

44 Cisternino M, Della Mina E, Losa L, et al. Idiopathic central precocious puberty associated with 11 mb de novo distal deletion of the chromosome 9 short arm. *Case Rep Genet* 2013; **2013:** 978087.

45 Hoffmann K, Heller R. Uniparental disomies 7 and 14. *Best Pract Res Clin Endocrinol Metab* 2011; **25:** 77–100.

46 Grosso S, Balestri P, Anichini C, et al. Pubertal disorders in inv dup(15) syndrome. *Gynecol Endocrinol* 2001; **15:** 165–69.

47 Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader–Willi syndrome. *Genet Med* 2012; **14:** 10–26.

48 Saletti V, Canafoglia L, Cambiaso P, Russo S, Marchi M, Riva D. A *CDKL5* mutated child with precocious puberty. *Am J Med Genet A* 2009; **149A:** 1046–51.

49 Brito VN, Batista MC, Borges MF, et al. Diagnostic value of fluorometric assays in the evaluation of precocious puberty. *J Clin Endocrinol Metab* 1999; **84:** 3539–44.

50 Neely EK, Hintz RL, Wilson DM, et al. Normal ranges for immunochemiluminometric gonadotropin assays. *J Pediatr* 1995; **127:** 40–46.

51 Houk CP, Kunselman AR, Lee PA. Adequacy of a single unstimulated luteinizing hormone level to diagnose central precocious puberty in girls. *Pediatrics* 2009; **123:** e1059–63.

52 Lee DS, Ryoo NY, Lee SH, Kim S, Kim JH. Basal luteinizing hormone and follicular stimulating hormone: is it sufficient for the diagnosis of precocious puberty in girls? *Ann Pediatr Endocrinol Metab* 2013; **18:** 196–201.

53 Pasternak Y, Friger M, Loewenthal N, Haim A, Hershkovitz E. The utility of basal serum LH in prediction of central precocious puberty in girls. *Eur J Endocrinol* 2012; **166:** 295–99.

54 Freire AV, Escobar ME, Gryngarten MG, et al. High diagnostic accuracy of subcutaneous triptorelin test compared with GnRH test for diagnosing central precocious puberty in girls. *Clin Endocrinol (Oxf)* 2013; **78:** 398–404.

55 Cavallo A, Richards GE, Busey S, Michaels SE. A simplified gonadotrophin-releasing hormone test for precocious puberty. *Clin Endocrinol (Oxf)* 1995; **42:** 641–46.

56 Lawson ML, Cohen N. A single sample subcutaneous luteinizing hormone (LH)-releasing hormone (LHRH) stimulation test for monitoring LH suppression in children with central precocious puberty receiving LHRH agonists. *J Clin Endocrinol Metab* 1999; **84:** 4536–40.

57 Carretto F, Salinas-Vert I, Granada-Yvern ML, et al. The usefulness of the leuprolide stimulation test as a diagnostic method of idiopathic central precocious puberty in girls. *Horm Metab Res* 2014; **46:** 959–63.

58 Ketha H, Kaur S, Grebe SK, Singh RJ. Clinical applications of LC-MS sex steroid assays: evolution of methodologies in the 21st century. *Curr Opin Endocrinol Diabetes Obes* 2014; **21:** 217–26.

59 Hagen CP, Sørensen K, Mieritz MG, Johannsen TH, Almstrup K, Juul A. Circulating MKRN3 levels decline prior to pubertal onset and through puberty: a longitudinal study of healthy girls. *J Clin Endocrinol Metab* 2015; **100:** 1920–26.

60 Brito VN, Latronico AC, Cukier P, et al. Factors determining normal adult height in girls with gonadotropin-dependent precocious puberty treated with depot gonadotropin-releasing hormone analogs. *J Clin Endocrinol Metab* 2008; **93:** 2662–69.

61 Carel JC, Lahlou N, Roger M, Chaussain JL. Precocious puberty and statural growth. *Hum Reprod Update* 2004; **10:** 135–47.

62 de Vries L, Phillip M. Pelvic ultrasound examination in girls with precocious puberty is a useful adjunct in gonadotrophin-releasing hormone analogue therapy monitoring. *Clin Endocrinol (Oxf)* 2011; **75:** 372–77.

63 Sathasivam A, Rosenberg HK, Shapiro S, Wang H, Rapaport R. Pelvic ultrasonography in the evaluation of central precocious puberty: comparison with leuprolide stimulation test. *J Pediatr* 2011; **159:** 490–95.

64 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:** e29829.

65 Pedicelli S, Alessio P, Scirè G, Cappa M, Cianfarani S. 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:** 4455–61.

66 de Vries L, Guz-Mark A, Lazar L, Reches A, Phillip M. Premature thelarche: age at presentation affects clinical course but not clinical characteristics or risk to progress to precocious puberty. *J Pediatr* 2010; **156:** 466–71.

67 Williams RM, Ward CE, Hughes IA. Premature adrenarche. *Arch Dis Child* 2012; **97:** 250–54.

68 Léger J, Reynaud R, Czernichow P. Do all girls with apparent idiopathic precocious puberty require gonadotropin-releasing hormone agonist treatment? *J Pediatr* 2000; **137:** 819–25.

69 Lazar L, Padoa A, Phillip M. Growth pattern and final height after cessation of gonadotropin-suppressive therapy in girls with central sexual precocity. *J Clin Endocrinol Metab* 2007; **92:** 3483–89.

70 Lahlou N, Carel JC, Chaussain JL, Roger M. Pharmacokinetics and pharmacodynamics of GnRH agonists: clinical implications in pediatrics. *J Pediatr Endocrinol Metab* 2000; **13** (suppl 1)**:** 723–37.

71 Lewis KA, Eugster EA. Random luteinizing hormone often remains pubertal in children treated with the histrelin implant for central precocious puberty. *J Pediatr* 2013; **162:** 562–65.

72 Brito VN, Latronico AC, Arnhold IJ, Mendonca BB. A single luteinizing hormone determination 2 hours after depot leuprolide is useful for therapy monitoring of gonadotropin-dependent precocious puberty in girls. *J Clin Endocrinol Metab* 2004; **89:** 4338–42.

73 Bhatia S, Neely EK, Wilson DM. Serum luteinizing hormone rises within minutes after depot leuprolide injection: implications for monitoring therapy. *Pediatrics* 2002; **109:** E30.

74 Badaru A, Wilson DM, Bachrach LK, et al. Sequential comparisons of one-month and three-month depot leuprolide regimens in central precocious puberty. *J Clin Endocrinol Metab* 2006; **91:** 1862–67.

75 Carel JC, Roger M, Ispas S, et al, and the French study group of Decapeptyl in Precocious Puberty. Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. *J Clin Endocrinol Metab* 1999; **84:** 1973–78.

76 Heger S, Müller M, Ranke M, et al. Long-term GnRH agonist treatment for female central precocious puberty does not impair reproductive function. *Mol Cell Endocrinol* 2006; **254–255:** 217–20.

77 Gillis D, Karavani G, Hirsch HJ, Strich D. Time to menarche and final height after histrelin implant treatment for central precocious puberty. *J Pediatr* 2013; **163:** 532–36.

78 Pasquino AM, Pucarelli I, Segni M, Matrunola M, Cerroni F. Adult height in girls with central precocious puberty treated with gonadotropin-releasing hormone analogues and growth hormone. *J Clin Endocrinol Metab* 1999; **84:** 449–52.

79 Vottero A, Pedori S, Verna M, et al. Final height in girls with central idiopathic precocious puberty treated with gonadotropin-releasing hormone analog and oxandrolone. *J Clin Endocrinol Metab* 2006; **91:** 1284–87.

80 Silverman LA, Neely EK, Kletter GB, et al. Long-term continuous suppression with once-yearly histrelin subcutaneous implants for the treatment of central precocious puberty: a final report of a phase 3 multicenter trial. *J Clin Endocrinol Metab* 2015; **100:** 2354–63.

81 Lewis KA, Goldyn AK, West KW, Eugster EA. A single histrelin implant is effective for 2 years for treatment of central precocious puberty. *J Pediatr* 2013; **163:** 1214–16.

82 Carel JC, Lahlou N, Jaramillo O, et al. Treatment of central precocious puberty by subcutaneous injections of leuprorelin 3-month depot (11·25 mg). *J Clin Endocrinol Metab* 2002; **87:** 4111–16.

83 Johnson SR, Nolan RC, Grant MT, et al. Sterile abscess formation associated with depot leuprorelin acetate therapy for central precocious puberty. *J Paediatr Child Health* 2012; **48:** E136–39.

84 Lazar L, Meyerovitch J, de Vries L, Phillip M, Lebenthal Y. Treated and untreated women with idiopathic precocious puberty: long-term follow-up and reproductive outcome between the third and fifth decades. *Clin Endocrinol (Oxf)* 2014; **80:** 570–76.

85 Castaño De La Mota C, Martín Del Valle F, Pérez Villena A, Calleja Gero ML, Losada Del Pozo R, Ruiz-Falcó Rojas ML. Hypothalamic hamartoma in paediatric patients: clinical characteristics, outcomes and review of the literature. *Neurologia* 2012; **27:** 268–76 (in Spanish).