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Central precocious puberty, functional and tumor-related

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Precocious puberty is defined as the appearance of secondary sex characteristics before 8 years of age in girls and before 9 years of age in boys. Central precocious puberty (CPP) is diagnosed when activation of the hypothalamic–pituitary axis is identified. It is a rare disease with a clear female predominance. A background of international adoption increases its risk, with other environmental factors such as endocrine disruptors also being associated with CPP.

The causes of CPP are heterogeneous, with alterations of the CNS being of special interest. Physical injuries of the CNS are more frequent in boys, while idiopathic etiology is more prevalent among girls. However, in the last decade the number of idiopathic cases has diminished thanks to the discovery of mutations in different genes, including *KISS1*, *KISS1R*, *MKRN3*, and *DLK1* that cause CPP.

For the diagnosis of CPP, hormone studies are needed in addition to the clinical data regarding signs of pubertal onset. For this purpose, the GnRH test continues to be the gold standard. Imaging analyses, such as bone age and brain MRI, are also very useful. Furthermore, genetic testing must be incorporated in the diagnosis of CPP, especially in familial cases.

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Early puberty has been related to various consequences in the medium and long term such as behavioral problems, breast cancer, obesity, and metabolic comorbidities. However, there are few studies that have exclusively analyzed patients with CPP.
GnRH analogs are the most frequent treatment election with the main objective being to improve adult height. Currently, there are new formulations that are being investigated.

Introduction

Puberty is a very complex biological process, regulated by the dynamic interaction between genetic determinants and regulatory factors that include different endogenous elements and environmental signals such as the availability of nutrients, endocrine disruptors, light/dark cycles, and psychosocial status, among others [1]. Puberty is a transition period of somatic and behavioral changes by which the development of secondary sexual characteristics, complete reproductive capacity, and adult height will be achieved [2].

Control of puberty

To implement the best clinical approach to precocious puberty, it is necessary to know the main factors that can influence normal pubertal development, including neuroregulation, nutrition, and the environment. Even today, the exact mechanism controlling the onset of puberty continues to remain a mystery. However, in the last two decades, remarkable advances in our knowledge concerning the neuroregulation of puberty have been achieved. An increase in the number and amplitude of gonadotropin-releasing hormone (GnRH) secretory bursts by the hypothalamic neurons producing GnRH has been proposed as the final phenomenon that triggers puberty. This phenomenon, in turn, increases the production of gonadotropins [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] and sex steroids, favoring the development of secondary sexual characteristics [3,4]. However, what factors regulate this increase in the secretion and pulsatility of GnRH? *Ojeda and colleagues* [5,6] have postulated that the control of puberty depends on nodal networks of genes that encode different proteins and whose actions overlap and interact in both a hierarchical and independent ways. There are activity centers (hubs) and peripheral nodal network of genes encoding proteins that act as either stimulatory factors (glutamate, kisspeptin) or inhibitory factors (GABA, opioid substances). The current hypothesis postulates that a loss of transsynaptic inhibition and a rise in excitatory inputs might be responsible for the activation of increased GnRH release. Moreover, glial cells also appear to contribute to the activation of GnRH secretion through the release of growth factors that activate receptors on GnRH neurons and by changes in the coverage of GnRH neuronal bodies and terminals by glial cells, in particular by tanycytes. In short, puberty is not an event triggered by the action of a single gene.

Amongst the stimulating factors, it is necessary to highlight the role of the neurons producing kisspeptin, an essential peptide in the regulation of GnRH-producing neurons [7]. In the arcuate and infundibular region of the hypothalamus these neurons co-express neurokinin B and dynorphin (KDNy neurons) whose actions are to modulate the influence of kisspeptin on the control of puberty [8]. The discovery of the kisspeptin system has substantially contributed to improve our knowledge regarding the regulation of GnRH secretion. However, it is currently unknown whether this system is a trigger, amplifier or just a permissive factor for the onset of puberty [1].

For many years, nutritional status has been linked to the onset and maintenance of puberty. Initially, it was proposed that a minimum body weight was required for normal pubertal development to ensue [9]. Subsequently, the relevance of obtaining a minimum body fat mass was demonstrated [10] and the relationship between the onset and maintenance of puberty with peptides secreted by adipose tissue (e.g., leptin) and in the gastrointestinal tract (e.g., ghrelin) suggested [11]. From a clinical point of view

this is of great interest as childhood obesity is a nutritional disorder that can produce advanced/precocious puberty [12] as a result of changes in the synthesis and/or secretory patterns of peptides related to energy metabolism that can also act as stimulating factor of KNDy neurons [13].

There are various environmental factors that can affect normal pubertal development, such as changes in light and dark cycles [14] and endocrine disruptors [15], among others. One paradigm of the influence of environmental and nutritional factors on pubertal development it is well represented by internationally adopted children [16,17]. More recently, epigenetic studies have attempted to elucidate the influence of nutrition and environment on gene expression and how this might affect pubertal regulation [6,18]. In the coming years, this area of research will help to clarify, at least in part, idiopathic CPP cases in which no monogenic explanations are found.

Normal pubertal timing and precocious puberty definition

The normal age range for the onset of puberty is based on statistical criteria, that is, if the acquisition of secondary sexual characteristics is within the range of ± 2.5 SDS for sex and age of reference values. Historically, the standards for the normal ranges of pubertal timing came from the epidemiological studies performed by Tanner *and Marshall* [19,20]. These studies indicated that 95% of males started puberty between 9.5 and 13.5 years and, 95% of females initiated breast development between 8.5 and 13 years of age (Fig. 1). However, a subsequent epidemiological study conducted in the USA suggested that puberty had clearly advanced and, therefore, the normal limits of puberty should be redefined [21]. Nevertheless, this epidemiological study showed important methodological concerns. In effect, the main concern was that the estimation of thelarche stage was done by inspection and no palpation [22]. More recently, a surprising secular trend toward earlier thelarche development has been observed in contrast to menarche due to mechanisms that are not well understood [23]. Although this finding should be validated by prospective multicenter studies, it appears that the interval between thelarche and menarche has been prolonged and we should keep this in mind before launching predictions about the evolution of puberty and the time of first menstruation.

In summary, the current consensus indicates that precocious puberty is defined as the appearance of secondary sex characteristics (progressive thelarche in girls, increased testicular volume in boys) before eight years of age in girls and before nine years in boys [2,24,25]. Precocious puberty is traditionally classified as either [26]: a) Central precocious puberty (CPP) or gonadotropin-dependent where there is an early activation of the liberation of GnRH and secondarily of gonadotropins (LH

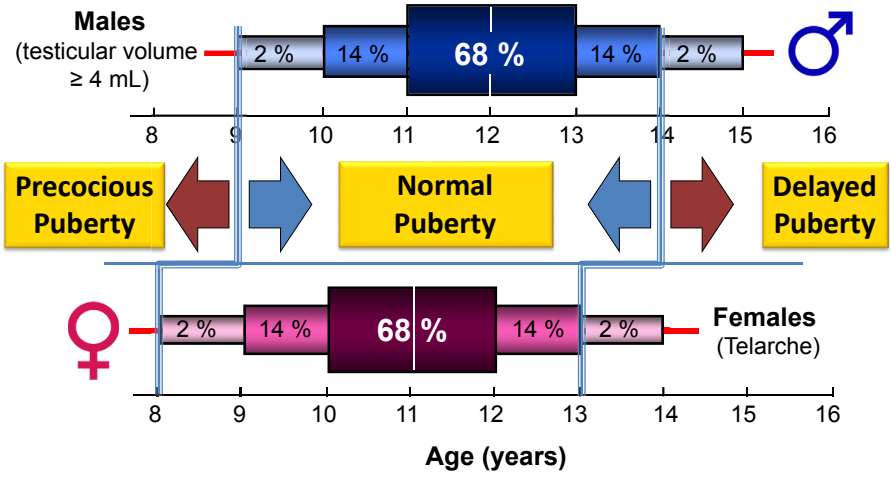

Fig. 1. Empirical concept of precocious puberty: start of secondary sex characteristics below 8 years of age in girls and 9 years in boys (pubertal onset around 2.5 SDS below the mean age for sex and population studied).

and FSH); b) Peripheral precocious puberty (PPP) or gonadotropin-independent that is produced by an increase in sex steroids without elevation of gonadotropins. In addition, patients with secondary CPP have been described very infrequently: children with PPP of long evolution in which the gonadotropin axis is abruptly activated when therapy arrest the negative feedback of sex steroids.

Physical characteristics of puberty

First, it is of relevance to clarify the difference between the concepts of gonadarche and adrenarche. Activation of the hypothalamic-pituitary-gonadal (HPG) axis is referred to "gonadarche" and is responsible for the actions of LH and FSH on ovaries and testes. Thus, gonadarche is responsible for the production of estradiol by the ovary and testosterone by the testes [27]. The term "adrenarche" refers to the increase in the secretion of adrenal androgens, mainly dehydroepiandrostendione-sulfate (DHEA-S), independently of the HPG axis.

The main physical characteristics related to gonadarche in girls [26,27] are as follows:

a) Thelarche: the main sign to suspect the onset of puberty.
b) Growth spurt: maximum before menarche. Total growth from the beginning to the end of puberty ranges between 20 and 25 cm.
c) Bone age (BA) advancement.
d) Menarche usually appears two years after the onset of thelarche.

The main physical characteristics related to gonadarche in boys [26,27] are as follows:

a) Testes enlargement ($\geq$4 ml): the main sign to suspect the onset of puberty. It should be determined whether only one or both testes are affected.
b) Pubarche and penile enlargement.
c) Growth spurt: total growth from the beginning to the end of puberty ranges between 25 and 30 cm.
d) BA advancement.
e) Breaking voice.
f) Others: acne, increasing muscle mass.

Adrenarche is responsible for pubic/axillary hair in girls and adult apocrine adult odor in boys and girls [26].

Epidemiology

To date, there are very few studies that have analyzed the incidence and prevalence of CPP. To our understanding, there are several factors that may have contributed to this lack of data: 1) The diagnosis of CPP does not depend on a single variable; 2) There are different criteria to define the age cut-off for diagnosis of CPP; 3) The terminology is confusing such that in many occasions patients are classified as variants of normality instead of true CPP; 4) The use of different radiological and biochemical criteria; and 5) There are different national registration models for obtaining data.

In a Danish study, the prevalence of CPP and PPP and common variants of puberty (premature adrenarche and premature thelarche) were estimated to be 0.2% in girls and less than 0.05% in boys [28]. Afterwards, a Spanish epidemiological study referring exclusively to CPP ("A National Registry for Central Precocious Puberty —Pubere-) showed an estimated global prevalence of 19 per 100,000 (girls, 37; boys, 0.46). The annual incidence for the period analyzed (1997—2009) ranged between 0.02 and 1.07 new cases per 100,000 persons (boys, 0—0.23; girls, 0.13—2.17) with a remarkable increase from 2000 onwards, mainly among girls. Likewise, a clear female predominance (10:1) was observed [17]. Subsequently, a Korean epidemiological study, using very similar criteria for CPP as that of the Spanish registry, was published [29]. These researchers collected data from the Korean Health Insurance Review during the period from 2004 to 2010 and the prevalence of CPP in 2010 was found to be 55.9 per

100.000 children in girls and 1.7 in boys. The most relevant finding of this study is the notable increase in the annual incidence, from 3.3 to 50.4 per 100,000 girls and 0.3 to 1.2 per 100,000 boys, during the period analyzed (from 2004 to 2010). Once again, girls were 25-times more likely to develop CPP than boys.

More recently, a nationwide study was performed in France [30]. The authors designed an epidemiological study of the incidence of idiopathic CPP by using drug treatment data from the French National Health Insurance Information System. They recruited girls under nine years of age and boys less than ten years, taking into account a period of one year of interval from clinical debut until treatment was started. The study period was 2011–2013 and they observed an annual incidence of 2.68 per 10,000 girls <9 yr and 0.24 per 10,000 boys <10 yr. Furthermore, they found marked geographic patterns in the incidence of idiopathic CPP.

Etiology

Several conditions causing CPP are listed in Table 1. It is very important to highlight that there is a clear sexual dimorphism regarding the prevalence of central nervous system (CNS) pathology. Thus, the prevalence of CNS lesions ranges from 30% to 70% among boys while this percentage diminishes to around 10% in girls. Hence, idiopathic CPP is more frequent among girls [25,26,31].

Functional

The term idiopathic refers to unknown etiology after ruling out other pathologies. This is the most prevalent etiology of CPP in girls. However, in the last decade, we have observed a notable progress in the molecular basis of CPP, which will lead to a decrease in the number of idiopathic cases.

The first suggestion of a possible genetic etiology of CPP was reported in 2004 by *De Vries and colleagues* [32] who observed a frequency of family cases of 27.5% among all those diagnosed with

Table 1
Etiology of central precocious puberty.

CNS lesions
• Congenital
✓ Hypothalamic hamartoma.
✓ Arachnoid cyst.
✓ Hydrochephalus.
✓ Septo-optic displasia.
✓ Chiari malformations.
✓ Myeolomeningocele.
• Acquired
✓ Tumors: low grade gliomas, ependymoma, pinealoma, craniopharyngioma, germinoma.
✓ Cranial irradiation.
✓ Traumatic brain injury.
✓ CNS infection.
✓ Granulomatous disease.
✓ Intracranial bleeding.
✓ Cerebral palsy secondary to perinatal hypoxic-ischemic encephalopathy.
No documented CNS lesions
• Idiopathic
• Genetic
✓ *KISS1* gain of function mutations.
✓ *KISS1R* gain of function mutations.
✓ *MKRN3* loss of function mutations.
✓ *DLK1* loss of function mutations.
✓ Chromosomal abnormalities.
• Environmental
✓ International adoption.
✓ Endocrine disruptors.
• Secondary central precocious puberty
✓ Previously PPP after withdrawal of chronic sex homone exposure.

idiopathic CPP, suggesting an autosomal dominant pattern of inheritance with incomplete penetrance. Then, in 2008, the first genetic disturbance producing CPP due to an activating mutation in heterozygosis in the kisspeptin receptor (*KISS1R*) in an adopted patient was reported [33]. In 2010, three new cases of mutations in the kisspeptin gene (*KISS1*), with different inheritance patterns, were described in patients with idiopathic CPP [34].

In 2013, mutations with loss of function in the makorin ring finger protein 3 (*MKRN3*) were reported to be causative of idiopathic CPP in five patients from 15 different families included in the study. *MKRN3* is a maternally imprinted gene located in the Prader–Willi syndrome critical region (chromosome 15q11–q13) and only subjects who inherit the mutation from their father develop CPP [35].

Finally, in 2017 a new mutation causing idiopathic CPP was described in four girls of the same family. A deletion of the first exon of *the DLK1* gene (Delta-Like 1 Homolog) was reported to be the cause of CPP in this family. Once again, this gene presents a phenomenon of maternal genomic imprinting, so the mutated allele is inherited from the father [36].

To date, *MKRN3* gene mutations are the most prevalent genetic etiology of monogenic CPP. Nevertheless, the prevalence of *MKRN3* mutations varies significantly depending on the selected criteria. Among sporadic cases, a prevalence that ranges from 0.4 to 5% can be found [37–40], while among familial cases this percentage increases to 33–46% [41,42].

Some chromosomal abnormalities, mainly deletions, causing different complex syndromes have been infrequently associated with CPP. These abnormalities include: 1p, 7q (Williams-Beuren syndrome), 9p, 14q (Temple syndrome), 15q (Prader Willi syndrome) and Xp22 (Rett syndrome) [25].

Several epidemiological studies agree in the importance of highlighting the increased risk of CPP among internationally adopted girls compared to native girls [16,17,43]. The exact mechanism explaining the relationship between adoption and CPP remains unknown, and the current hypothesis includes the influence of racial, emotional, nutritional and environmental factors. Indeed, it is important to establish follow-up programs for these children beginning at the time of their arrival to host countries. Special emphasis should be placed on adequate nutrition, avoiding excess weight gain during short periods of time.

Endocrine disruptors are defined by WHO as "*exogenous compounds or mixtures that alter function(s) of the endocrine system and consequently cause adverse effects in an intact organism, or its progeny, or (sub)populations*" [44]. Krstevska-Konstantinova *and colleagues* [45] were the first to raise the possibility of a relationship between precocious puberty and exposure to endocrine disruptors. Specifically, these authors observed higher levels of p.p'-DDE in foreign adopted and non-adopted children with precocious puberty compared with native Belgian girls suffering CPP. Nevertheless, it is difficult to clarify the exact mechanism that could activate the onset of puberty after leaving the source of pesticides in their original countries. More recently, a French epidemiological study has shown notable regional variations in the incidence of CPP with the highest incidence in the Midi-Pyrénes and Rhône-Alpes regions. These areas are eminently dedicated to farming where the use of pesticides is widespread [30]. In summary, these epidemiological studies show a possible causal relationship that will need to be demonstrated through the design of new studies where the main objective is to detect endocrine disruptors clearly implicated in this pathology. Consequently, with this new information public health authorities will be able to legislate so that these chemical products can be avoided [46].

Although the term early puberty is very broad, and the object of this review is focused on CPP, scientific evidence from several epidemiologic studies has shown a clear relationship between earlier puberty and being overweight in girls [47]. This evidence is not as strong in boys. Moreover, the early activation of puberty is reported to be especially sensitive to changes in body mass index in girls from six to eight years [48]. Therefore, programs addressed to monitor weight gain in pre-pubertal schoolgirls could contribute to avoiding early puberty.

Central nervous system lesions

Lesions or malformations of the CNS must first be considered in the differential diagnosis of CPP (Figs. 2 and 3). Main risk factors for a physical CNS etiology include a young age and male sex [17,49]. The most common CNS lesion associated with CPP is hypothalamic hamartoma (HH), a congenital, nonneoplastic, heterotopic collection of neural tissue located at the base of the third ventricle. The

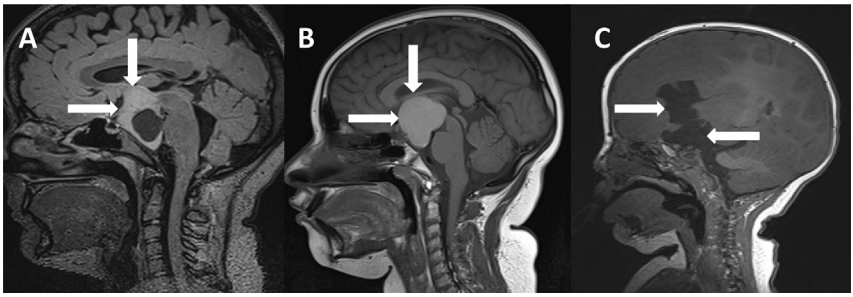

Fig. 2. Central nervous system (CNS) lesions causing CPP. A) Hypothalamic hamartoma. B) Craniopharyngioma. C) Arachnoid cyst.

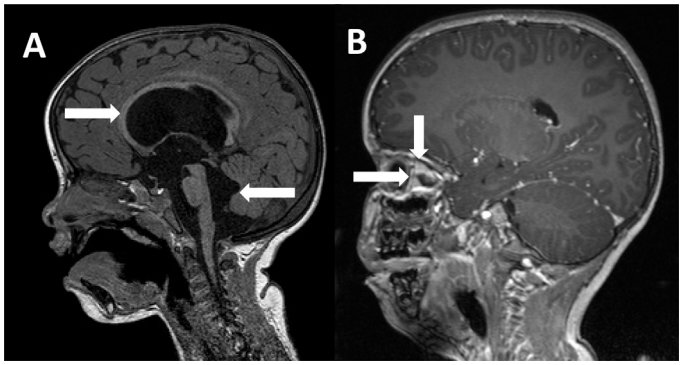

Fig. 3. Central nervous system (CNS) lesions causing CPP. A) Hydrochephalus and Dandy–Walker malformation. B) Optic nerve glioma in a patient with neurofibromatosis type 1.

diagnosis is usually established before 4 years of age. It is a very rare abnormality with an estimated prevalence of 1:50,000–1:100,000 children [49]. To date, the pathophysiology of how HH produces the premature initiation of puberty is not well established; however, several hypotheses have been postulated in recent years [26]: 1) It functions as an ectopic GnRH-pulse generator; 2) It produces physical pressure on the adjacent normal hypothalamus that contributes to diminishing the action of inhibitory regulatory factors on GnRH neurons. What we do know is that the location of the HH is predictive of the clinical spectrum as parahypothalamic or pedunculated lesions are associated with CPP and intrahypothalamic or sessile lesions are related with gelastic seizures. Of course, there are lesions of intermediate location that clinically present with CPP and gelastic seizures at the same time (40% of patients) [50]. Surgical treatment is reserved for intractable epilepsy by using a transcallosal approach [49,50].

Although CNS tumors are a prevalent cause of childhood cancer, their clinical presentation as precocious puberty is relatively unusual. Symptomatology of CNS tumors is linked to the tumor expansion velocity, its location and the age of the child. Infratentorial tumors can occur in the posterior fossa (medulloblastomas, cerebellar astrocytomas, brain stem gliomas, and ependymomas) and their clinical presentation consists in signs of increased intracranial pressure (headache, emesis), ataxia and neuropathy. Supratentorial tumors (craniopharyngiomas, gliomas, germinomas, pineal tumors, ependymomas) display visual disturbances, signs of increased intracranial pressure and neuroendocrine dysfunction such as growth failure or diabetes insipidus [49,51,52].

Juvenile pilocytic astrocytomas (JPA) are low-grade gliomas (Fig. 4) located in the cerebellar region, hypothalamic/optic pathway or the spinal cord. The average age at diagnosis is between 6 and 9 years with a predominance in boys. The clinical spectrum related to this tumor consists of headache, seizures and precocious puberty. It should be noted that it is relatively common to find low-grade gliomas in the optic pathway of patients with type 1 neurofibromatosis. In this regard, lesions close to or in the chiasm optic due to the existence of a foreign mass could contribute to triggering precocious puberty [49,51].

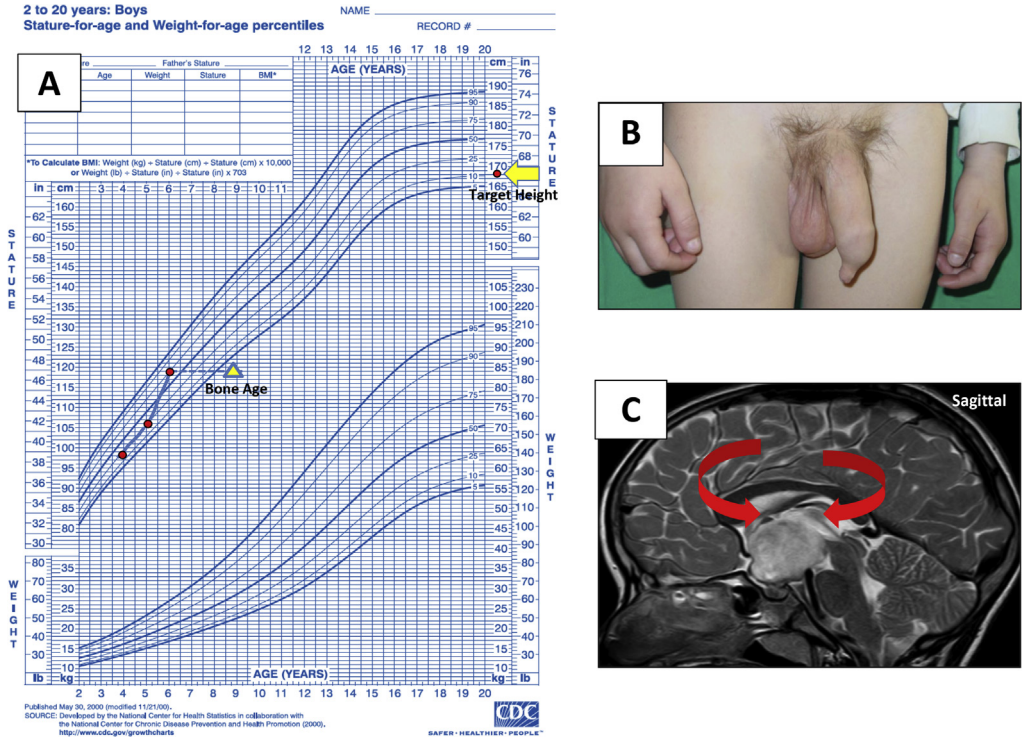

Fig. 4. A boy with CPP diagnosed at 5 years and 11 months. At this moment, he had a BA of 8 years and 8 months and he was in Tanner stage IV. A) Growth chart: height of 116 cm (+0.2 SDS) higher than target height (−1.6 SDS). It is relevant to check the increase of growth velocity. B) Tanner stage IV: testes of 15 cc of Prader, P3 and penis enlargement. Testosterone levels were 5.2 ng/ml and the LH peak after GnRH stimulation test was 15.5 IU/L. C) Brain MRI: juvenil pilocityc astrocitoma.

Ependymoma is a slow and well-circumscribed tumor commonly located in the lateral posterior fossa. The mean age at diagnosis is 3 years with male predominance. Clinical signs and symptoms of this tumor are related to obstructive hydrocephalus, including precocious puberty. As the pineal gland is located near the cerebral aqueduct, tumors rising in this location may also produce obstructive hydrocephalus and, subsequently, precocious puberty. Although infrequent, patients affected with suprasellar arachnoid cysts that develop precocious puberty have also been reported. Finally, it should be noted that precocious puberty is not the endocrine disturbance most frequently associated with craniopharyngioma, but it may appear. At times, this finding constitutes a diagnostic challenge, since growth hormone deficiency may be associated and the typical pubertal growth spurt of precocious puberty is not displayed [49].

Cranial irradiation is largely employed for the treatment of specific childhood malignancies including primary CNS tumors. This modality of treatment might cause damage to γ-aminobutyric-acid secreting neurons, which could lead to premature activation of GnRH neurons [53]. The risk of precocious puberty increases with an irradiation of ≥18 Gy, female sex and a younger age at cancer treatment. Once again, the pubertal growth spurt may be absent due to a concomitant GH deficiency. Conversely, the risk of gonadotropin deficiency is related to the dose of irradiation ≥30 Gy [49,53].

Diagnostic approach

It is a diagnostic challenge to discriminate common normal pubertal variants (e.g., premature thelarche and premature adrenarche) from CPP. For this purpose, both careful clinical data together with thorough physical examination are essential. After this, additional testing must be selected in an individualized manner (Table 2 and Figs. 5 and 6).

Table 2
Diagnostic approach to Central Precocious Puberty.

Clinical data	Physical examination	Diagnostic procedures
Recent clinical history		**First step**
Thelarche: for how long?	Phenotype	Boys and
Bilateral? Progressive?	Weight (SDS)	girls:
With or without vaginal	Height (SDS, to compare	BA and
bleeding?	with target height)	GnRH test
Penis enlargement and/or	BMI (SDS)	Boys:
pubarche: for how long?	Growth velocity (SDS)	testosterone levels
Testicular increased: for	Abdominal palpation	Girls: 17-β-estradiol
how long? Symmetrical?	Tanner stage (I to V):	levels and pelvic
Growth velocity	✓ Thelarche from 1 to 5	ultrasound
Data of CNS dysfunction: headache,	(palpation in supine position)	
emesis, visual impairment, seizures	✓ Pubarche from 1 to 5	
Personal antecedents	✓ Axillary hair	**Second step**
Pregnancy	✓ Testicular size	Brain MRI
Birth (type and gestational age)	(Prader orchidometer)	
Birth weight (SDS)	Skin:	
Birth length (SDS)	✓ Acne	
Neonatal period	✓ Excess body hair	
Chronic diseases	✓ Café au lait spots	
Psychomotor development	✓ Striaes	
Family antecedents	✓ Acanthosis	**Third step**
Mother: adult height, menarche	Eye fundus.	Genetic
age, growth spurt age	Neurological examination	studies:
Father: adult height, breaking voice age,		*MKRN3* and *DLK1*
first shaved age, growth spurt age		analysis in familial cases.
Target height calculation		Chromosomal
Idiopathic CPP cases in the family		abnormalities suspected:
		consider CGH-arrays.

Differential diagnosis				
Peripheral precocious puberty	**Premature thelarche**	**Premature adrenarche**	**Premature menarche**	**Lipomastia**
Prepubertal GnRH test	Growth velocity within normal percentiles	Absence of thelarche in girls neither testicular	Absence of thelarche	Careful breast palpation
Boys: testicular size < 4 ml except for testotoxicosis	BA similar to CA or not too advanced	increased in boys. Diagnosis	Normal growth velocity	
	Prepubertal GnRH test	of exclusion.	BA similar to CA	

Adapted from reference [22].

Clinical assessment

First, it is a priority to obtain data of the onset and progression of puberty [22,24,25]:

- For girls this data should include: time of thelarche onset, if it is progressive or oscillating, uni- or bilateral, with or without additional local pain and with or without darkening of the areola. In addition, information regarding the presence of pubic and/or axillary hair must be collected. Menarche is a late sign that suggests a long period of evolution.
- In boys the data collected should include: information regarding the presence of pubarche and/or penis enlargement, which is usually the occurrence that motivates the clinical visit. Information about the time of evolution of these signs should be obtained. It is difficult to detect an increase in the size of testicles by simple inspection and this should be precisely evaluated. As with menarche in girls, a breaking voice is a late sign of puberty in boys.
- In both boys and girls data the evaluation should include: growth velocity, sex steroid exposure, suggestive signs and symptoms of CNS dysfunction (such as headache, emesis, visual impairment, seizures). In addition, data about birth (gestational age, weight, and length), chronic diseases and psychomotor development must be obtained.

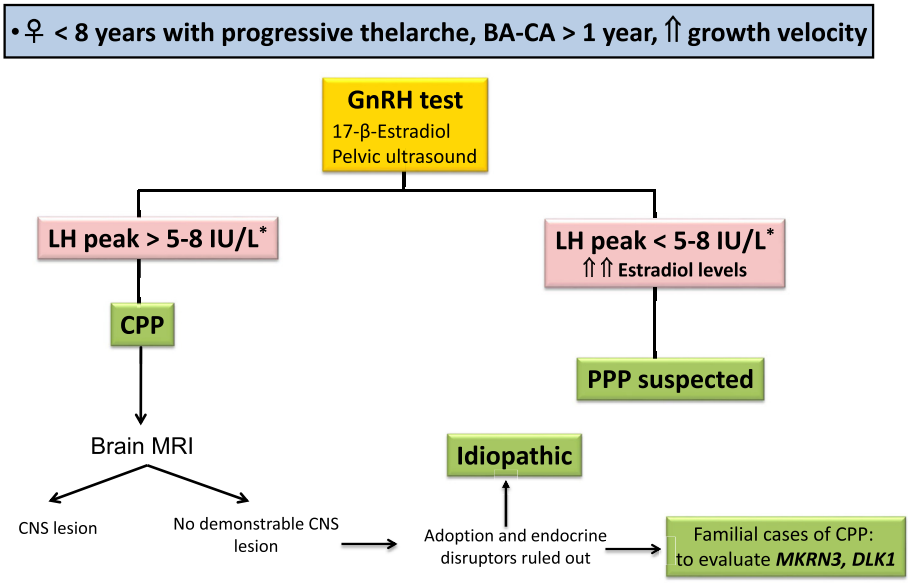

Fig. 5. Diagnostic algorithm of CCP in girls. **Depending on the method employed to measure LH values.

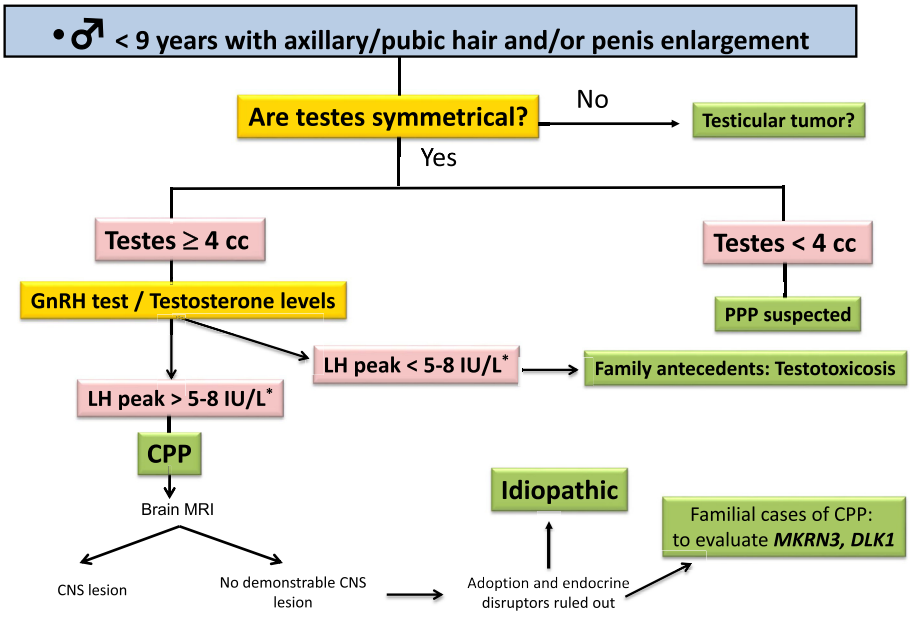

Fig. 6. Diagnostic algorithm of CCP in boys. **Depending on the method employed to measure LH values.

Second, information regarding the onset of puberty in parents (age at menarche, breaking voice, first shaved, and growth spurt) and siblings is needed. It is also of interest to know the parental anthropometric data to calculate the target height. In addition, family members (first and second-degree relatives) with precocious puberty should be gathered [22,24,25].

Third, a physical examination that includes the assessment of sexual features should be performed and classified according to Tanner stage (breast development, testicular size, pubic and axillary hair).

Careful thelarche evaluation is advisable in overweight and obese girls to distinguish lipomastia *versus* true thelarche. In boys, testicles must be explored to determine their size and if they are symmetrical. If the testicular volume is $\geq$ 4 ml it suggests central activation of puberty. Additionally, skin evaluation is highly recommended to find the presence of acne, oily skin and/or pigmented cutaneous lesions [24,25].

Hormonal profile

Traditionally, CPP has been characterized by the increase of estradiol (girls), testosterone (boys) and an LH peak after stimulation with GnRH or GnRH agonist (GnRHa) testing in both sexes [26]. During the last two decades, new laboratory methods such as immunofluorometric (IFMA), immunochemiluminometric (ICMA) and electrochemiluminometric (ECLIA) assays that employ monoclonal antibodies have been developed. With these methods, the sensitivity (0.1 UI/L) and accuracy have improved significantly compared with traditional ultrasensitive assays [25,26]. As a result, several studies have evaluated the use of basal LH to rule out CPP instead of GnRH testing. Thus, different basal LH cutoff values have been proposed, ranging from 0.1 to 1 IU/L, with remarkable differences of sensitivity [54–59]. Hence, using basal LH levels it is still very complex to distinguish prepubertal children with common variants of puberty (such as premature thelarche) from those with true CPP, especially in initial stages (Tanner II), due to the existence of a large overlap of basal LH levels [22]. In addition, data should be evaluated with caution in children <2 years because the elevation in gonadotropins may be physiological [24].

Even today, analysis of LH peaks after GnRH testing is the gold-standard in the biochemical diagnosis of CPP. For this purpose, several protocols have been proposed using synthetic GnRH (not available in some countries) or GnRH analogs (leuprolide acetate) [25,31]. However, the problem emerges regarding the LH peak cut-off point after which the existence of a central activation of puberty should be considered. Currently, regardless of the protocol employed, the threshold of LH peak to consider activation of puberty ranges between 5 and 8 IU/L [22,24,25].

A LH/FSH ratio greater than 0.66 after stimulation has been recently postulated as an indicator of pubertal activation [60]. Nevertheless, its sensitivity and specificity do not reach that of the GnRH-stimulated LH peak [25]. Testosterone is a useful tool in the diagnosis of precocious puberty in boys and testosterone values in the prepubertal range rule out CPP. Conversely, low estradiol levels in girls do not reject the diagnosis of CPP [22,25]. In addition, in our opinion, although the analysis of pulsatile secretion of estradiol could be more sensitive than that of isolated estradiol determinations, this test does not achieve the utility of GnRH test in the diagnosis of CPP. In addition, it also has the inconveniences derived from performing multiple blood extractions.

Imaging studies

Bone age (BA) is a traditional complementary tool in the evaluation of a patient with suspicion of precocious puberty. The BA of patients with precocious puberty is notably greater than their chronological age (CA) compared to normal variants of puberty [22,24]. Notwithstanding, in the early phases of CPP this advance may not be very striking [25]. Although, BA has been also employed to predict adult height, the reliability of this prediction is low [61].

The main utility of **pelvic ultrasound** is to detect ovarian tumors or cysts that can cause an increase in estradiol production [22,26]. In addition, in recent years, changes in uterine and ovarian dimensions due to estrogen exposure have also been included in pelvic ultrasound evaluations (Fig. 7). For some authors, these changes could be useful to distinguish between girls with CPP and those with isolated premature thelarche [62,63]. Contrariwise, a more recent study questions such utility due to the great overlap of the ovarian and uterine measurements observed between prepubertal and pubertal girls [64].

Brain Magnetic Resonance Imaging (MRI) should be performed in all boys < 9 yr and girls < 6 yr with documented CPP. Likewise, girls <8 years of age with CPP and findings of neurological dysfunction also require brain MRI [26,65]. However, it is controversial whether all girls who develop CPP between 6 and 8 years of age require brain MRI taking into account the low prevalence of CNS lesions in this age range and because MRI is a procedure with some limitations. These limitations include the need for sedation and the intravenous administration of contrast agents, not to forget the fact that it is

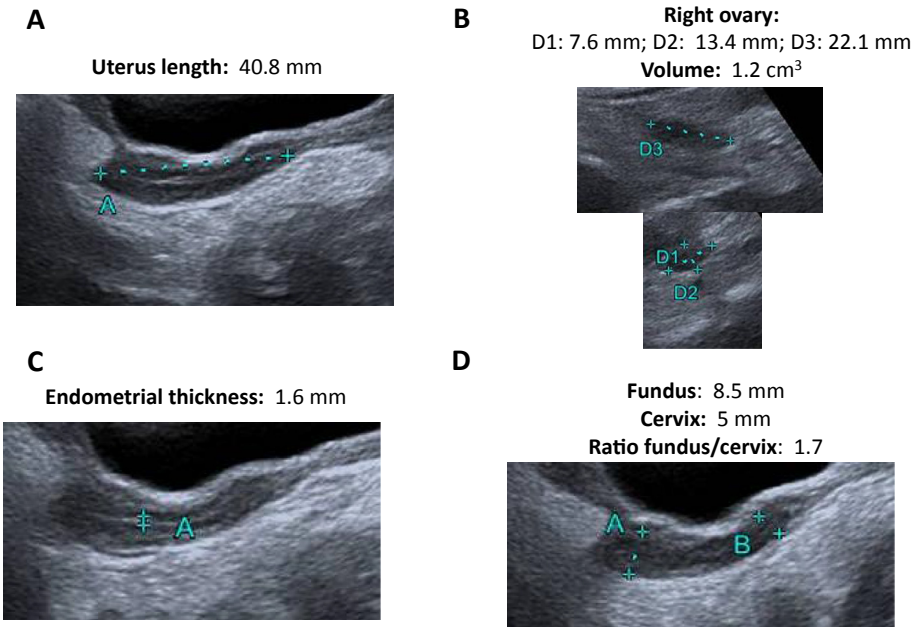

Fig. 7. Pubertal pelvic ultrasound changes in a girl with CPP. A 7 year 5 month old Caucasian girl with bilateral progressive thelarche and acceleration of growth velocity; a) Height 128 cm (+0.5 SDS compared to target height); b) Bilateral thelarche of 4 × 3 cm with increased sensitivity of areola without axillary or pubic hair; c) A BA of 8 years and 10 months; d) The hormonal profile was: 17-β-estradiol 14.5 pg/ml, basal LH 0.2 IU/L and LH peak after GnRH test of 17.9 IU/L. A) Uterus length (prepubertal values: <35 mm). B) Ovarian volume (prepubertal values: <2 $cm^{3)}$. C) Endometrial thickness visible. D) Fundus to cervix ratio (prepubertal values: 1).

expensive. In addition, the decision to request a brain MRI could increase parental anxiety [65]. On the contrary, there are some European reports that show relevant percentages of CNS lesions in girls between 6 and 8 years of age with CPP that could not be predicted from any clinical or biochemical parameters [17,66]. In summary, our position is that girls with precocious pubertal development of central origin before 8 years of age should continue to be examined by a brain MRI after explaining meticulously both the benefits and risks to the family.

Genetic studies

In an excellent review performed by *Latronico and colleagues* [25], the authors propose an algorithm for sequencing of *MKRN3* in familial cases. Indeed, the employment of genetic testing in CPP is a developing area of research.

Differential diagnosis

The important dilemma is that precocious puberty is a heterogeneous pathology, of plural etiology, in many cases unknown, where genetic testing is starting to shed some light. The differential diagnosis is complex, with only one observation in common: the increased levels of sex steroids, arbitrarily limited to before 8 years of age in girls and before 9 years of age in males.

In order to perform a correct diagnosis of CPP it is necessary that the following elements concur: a) girls: bilateral progressive thelarche before 8 years of age; b) boys: symmetrical testicular size increased (≥4 ml) before 9 years of age; c) advanced BA compared to CA (>1 yr); d) accelerated growth rate according to reference charts; and d) LH peak > 5–8 IU/L, according to the method employed, after GnRH test.

The distinction of CPP from PPP is mandatory. For girls, in most cases, the clinical evaluation is not enough and a GnRH test is necessary to determine if there is central activation of puberty. In contrast,

CCP in boys is related to symmetrical increased testicular volumes (≥4 ml), while PPP is characterized by asymmetrical or prepubertal testes (<4 ml). Interestingly, we can also be confronted with an exceptional form of PPP characterized by symmetrical enlarged testes: testotoxicosis [25,26,67].

Overall, common variants of pubertal development are characterized by growth velocity within the percentiles of reference growth charts and no significantly advanced BA. *Premature thelarche* consists of isolated breast development in the absence of any other clinical signs of pubertal maturation in girls younger than age 8 years, predominantly in the first 2 years of life. This clinical entity is a benign, self-limited condition of unknown etiology that rarely progresses to CPP (9–14%, especially in girls > 2 yr). If the LH peak after GnRH testing is evaluated, it will be < 5 UI/L [68]. *Premature adrenarche* is defined as the appearance of pubic hair and/or axillary hair, sometimes accompanied of increased apocrine body odor, before 8 years in girls and before 9 years in boys. There is no thelarche in girls or an increase in testicular volume in boys. It is a diagnosis of exclusion after ruling out other causes of overproduction of androgens such as adrenal or gonadal tumors, congenital adrenal hyperplasia or exogenous administration of androgens. This condition is more commonly seen in girls than in boys, with a ratio of 9:1. It is necessary to emphasize that this condition is more disturbing and requires an early approach among boys [69].

Isolated premature menarche or benign prepubertal vaginal bleeding is an uncommon, benign condition characterized by isolated or recurrent menstrual bleeding in the absence of secondary sex characteristics, such as breast development, and with normal growth. Once again, it requires a diagnosis by exclusion of traumas, foreign bodies, infection, sexual abuse, and vaginal/uterine tumor, among others. Over time, it tends to complete remission [27].

Sometimes, it is difficult to distinguish lipomastia from true progressive thelarche in overweight and obese girls. For this purpose, it is important to examine the patient in a supine position and careful palpation of the breast must be done to confirm the existence of firm glandular tissue [27]. In addition, darkening of nipples and areola could suggest estrogenic stimulation.

In this section of differential diagnosis, it is advisable to clarify certain terminology that leads to some confusion. For some authors, there is usually no distinction between rapidly progressive CPP *versus* slowly progressive CPP. As previously mentioned, the diagnosis of CPP focuses on the observation of changes in secondary sex characteristics along with accelerated growth and BA and is complemented by a hormonal profile. If these criteria are not met, it will not be a true CPP and it will probably be a common variant of pubertal development. In addition, another term that produces some confusion is that of “early puberty”. To our knowledge, the appropriate term would be “early normal variant of puberty”, a purely statistical definition, that should refer to girls who start puberty between 8 and 9 years of age and boys who begin between 9 and 10 years [22,70].

Consequences

Adult height

Loss of potential adult height caused by rapid advancement of skeletal maturation is the most prevalent consequence associated with CPP. Notably, in series of untreated patients mean heights around 150–154 cm in girls and 151–156 cm in boys were reported [71]. Nonetheless, this information should be interpreted with caution for several reasons, including: a) A limited sample size; b) The data are from CPP patients who were more severely affected (CNS lesions) than the average patient treated today; and c) Some of the untreated patients with organic CPP may have other endocrinopathies that could affect normal growth [72].

Behavioral and psychological problems

Puberty is a dynamic process that includes not only physical, but also emotional changes. In short, it is a period of life of maximum vulnerability [22]. Thus, parents often express concerns about the emotional issues of a child achieving puberty at an age that is unfit for their society and/or culture. In this regard, a higher prevalence of behavioral and psychological affections has been described among girls experiencing early normal pubertal timing [73]. However, can we extrapolate these associations to

children with CPP? To date, very few studies have evaluated behavioral and psychological function in CPP patients and the few results available are contradictory [74–80]. The design of these studies has been very heterogeneous in terms of selection criteria, transversal/prospective evaluation, the inclusion of a control group and the type of test for psychological assessment. Moreover, the sample size of these reports has been relatively small.

Considering all the above, there is limited scientific evidence to affirm that patients with CPP exhibit more prevalence of behavioral and psychological disturbances than the normal population [73,81]. In addition, these girls have a very close follow-up in hospital consultations where, among other things, the emergence of behavioral changes is tightly monitored. Nonetheless, we should pay close attention to family concerns about behavior changes.

Cancer risk

An international case-control study (3993 breast cancer cases and 11,783 controls) in 1990 described that age at menarche was a risk factor for breast cancer among both pre-menopausal and post-menopausal women. Namely, a delay of 2 years in menarche produced a decline of 10% in breast cancer risk. In addition, women with menopause at each 5-year age difference had a 17% higher risk of breast cancer [82].

In 2012, a meta-analysis that included 117 epidemiological studies (118,964 women) showed that breast cancer risk increased by 5% when menarche was 1 year early. Likewise, when menopause was delayed by 1 year the risk was increased by 2.9% [83]. This causal relationship reinforces the hypothesis that earlier menarche and later menopause produces a longer period of higher estrogen levels, increasing the length of breast mitotic activity [84]. Nevertheless, early menarche has a greater effect on the risk of breast cancer than late menopause [83].

In 2015, a meta-analysis that included eight prospective studies involving 4553 subjects with endometrial cancer was published [85]. This study showed that the risk of endometrial cancer increases significantly in the group with the lowest menarcheal age. In addition, endometrial cancer risk decreased by 4% when menarche was delayed by 2 years. It is speculated that the number and length of ovulatory cycles plays a role in the etiopathogenesis of endometrial cancer.

A British study involving 15,807 women revealed that cancer mortality was 1.25 higher (95% CI: 1.03–1.51) in women with a menarcheal age < 12 yr [86]. Conversely, a Korean study that includes 443,909 women evaluated the risk of several cancers (uterine cervix, ovary and thyroid) other than breast-cancer and the age at menarche without finding higher risk among women with an earlier menarcheal age [87]. Again, these studies are referring to the pathology associated with early puberty and not specifically to CPP. To our knowledge, there is only one report that has evaluated 142 women aged from 27 to 50 years with the antecedent of CPP. The authors did not find an increased risk of cancer compared to the control group [88].

In summary, it appears that there is a relationship between early age at menarche and breast cancer documented by epidemiological studies. We do not have enough data to extrapolate these results to women with a history of CPP. Likewise, a distinction should be made between CPP patients who have been treated with GnRH analogs (GnRHa) compared with those who have not received this treatment.

Obesity and cardiometabolic risk

Obese girls tend to begin puberty earlier than other girls, and in turn, early menarche has been associated with increased adult body mass index [84,86]. In addition, earlier menarcheal age has also been reported to be involved with increased metabolic syndrome and diabetes in middle-aged women. However, it is not clear if the increased diabetes risk is more related to the BMI and degree of adiposity than the early menarche itself [73,84].

The largest prospective study that has examined coronary heart disease, cerebrovascular disease, and hypertensive disease risks by menarcheal age was recently published [89]. This epidemiological study included 1.2 million women 50–64 years with no previous disease and a mean of 11.6 years of follow-up. Surprisingly, they found that the relationship between age at menarche to vascular disease risk was U-shaped. Namely, women with menarcheal age $\leq$10 years or $\geq$17 years had a mainly higher

risk of coronary heart disease. The associations were weaker for the cerebrovascular and hypertensive disease. When the population was divided into different subgroups according to BMI, socioeconomic status or tobacco consumption, the U-shaped relationship with menarcheal age remained unchanged.

Once again, data about CPP are scarce. A prospective Danish study [90] evaluated glucose metabolism, lipid profile and body composition of CPP girls compared with a group of control girls with normal pubertal timing. At diagnosis, girls with CPP had a worse lipid profile as well as lower insulin sensitivity compared with controls. Interestingly, metabolic disturbances remained altered after one year with GnRH analogue treatment. More recently, a case-control study of a historical cohort of CPP patients in Israel [88] showed that at young adulthood, the BMI of treated and untreated CPP women was similar to their respective controls. Similarly, the metabolic comorbidities prevalence was equal in CPP patients and their controls.

In brief, there is a close relationship between metabolism and reproduction. Thus, it is difficult to distinguish whether obesity has conditioned pubertal advancement or, maybe, pubertal advancement contributes to the excess of weight gain. Likewise, it is also very difficult to determine whether the cardiometabolic risk at later ages is due only to pubertal advancement or whether the excess weight and adiposity also contributes to this risk. Thus, we should ask whether a genetic disorder might contribute to both the pubertal advancement and metabolic alterations. In other words, obesity, metabolic comorbidities and precocious puberty could be different clinical expressions of the same genetic syndrome. In this regard, the recent discovery of *DLK1* mutations has been very relevant. These mutations have been related to familial CPP cases, but also to the later appearance of obesity and metabolic complications such as type 2 diabetes [91].

Treatment

In cases of CPP secondary to CNS lesions, the etiological treatment, such as surgery, would not have any effect on the course of pubertal development [22,24]. In addition, the organic lesion most frequently associated with CPP, HH, has a very difficult access and surgery should be reserved for those patients with refractory epilepsy [49,50].

Since the 1980s, GnRH analogues (GnRHa) are the medical treatment selected for CPP. This compound stems from a chemical substitution at position 6 and 10 of the native GnRH molecule. This product has a decreased enzymatic degradation and in parallel it has an increased affinity for the GnRH–pituitary receptor resulting in desensitization of the receptor. Consequently, this action produces an inhibition of gonadotropin secretion [92].

GnRHa depot formulations

Although the form of presentation, as well as the route and interval of administration has changed over time GnRHa has been shown to be effective in stopping puberty progression. Nowadays, the most commonly used formulations are monthly intramuscular triptorelin and leuprolide acetate depot forms [26]. The newest GnRHa depot forms are in a very exciting research phase [93–96]. These include leuprolide acetate 3-month depot, triptorelin 3-month depot, triptorelin 6-month depot, and histrelin subcutaneous implant replaced annually. These forms are reported to be safe and provide sustained gonadotropin suppression, slowing puberty progression and improve predicted adult height (PAH). However, we should be very cautious until data of AH including a relevant number of patients is published. Another consideration to keep in mind is the high cost of these preparations compared with monthly depot forms [31].

Outcomes

Optimal treatment results in stabilization of pubertal progression, a decline of growth velocity and a decrease of BA advancement. However, there is no uniform consensus of the best way for monitoring CPP treatment through auxological parameters, periodic BA and/or basal or stimulated LH levels [25,31]. The evaluation of AH is the main outcome of GnRHa treatment. Nevertheless, there are some important concerns when evaluating this effect [72,92] including the lack of well-designed,

randomized, controlled studies, and the fact that the majority of studies have evaluated the effectiveness of GnRHa comparing AH with PAH at initiation of treatment.

The evaluation of BA is influenced by a notable intra- and inter-observer variance. In addition, the Greulich-Pyle method is the most widespread method to calculate BA and this method uses radiographs from children recruited in Cleveland (USA) more than six decades ago. Moreover, Bayley-Pinneau is the most commonly used method for estimating AH based on BA and this model has a 95% confidence interval of about 6 cm below to 6 cm above the predicted value. Another handicap of BA interpretation is the absence of unanimity at the time of selecting average or advanced options in the Bayley-Pinneau height prediction table [72].

A consensus statement of the use of GnRHa was published in 2009 [97]. This report analyzed long-term outcome data published between 1990 and 2007 and they observed that the best results have been observed in girls with CPP diagnosed <6 years with an average gain in AH respected to PAH of 9–10 cm (exceeding the 95% confidence interval of ± 6 cm of the PAH). However, this evident benefit was not observed in girls with pubertal onset between 6 and 8 years. In this group, the average gain ranged from 4.5 to 7.2 cm (within the 95 CI interval of the PAH). Likewise, the authors of this consensus focused on the lack of data of height outcomes in boys. Afterwards, Guaraldi *and colleagues* [92] published an exhaustive review analyzing long-term outcomes of CPP. In this report, the authors again discuss the lack of randomized controlled trials and they agree with the consensus mentioned above in highlighting the major benefit in height gain after GnRHa treatment in girls <6 years. To date, several factors have been positively associated with better AH including an earlier age at the start of puberty, a younger BA at diagnosis, a short interval between pubertal onset and starting treatment, an elevated height (SDS) at diagnosis and a greater target height. Controversial data exist related to the treatment duration and its influence on AH [73,92,97]. In an exhaustive recent review [72] that includes the results of 29 studies of GnRHa treatment of CPP, some relevant information could be ascertained. This study indicated that: a) AH was ≈4 cm higher than PAH (ranging 2–10.5 cm); b) FH was ≈1 cm shorter than TH (ranging from 5.2 shorter to 4.2 taller than TH); and c) the difference of AH of treated patients compared with untreated patients ranges from −3 to + 11 (included only 4 studies).

There is no consensus on the optimal age to withdraw the GnRH analogue treatment. Taking into account the views of the parents and patients and with the aim of menarche emerging near to the age of the normal population, we agree with Kaplowitz *and colleagues* [81] that we should evaluate whether to discontinue GnRHa in girls around 10 years of CA. In this regard, spontaneous menses appears around 12 months after GnRH withdrawal [92,98]. Moreover, as a result of the scarcity of data related to CPP in boys it is not easy to determine the most appropriate age to remove treatment. Nonetheless, we propose that in CPP boys we should make a decision around 11–11.5 years of CA.

Adverse effects

With more than 30 years of experience, we can affirm that GnRHa treatment is safe. The most frequently documented side effects are headaches and hot flushes. Less than 15% of skin reactions are reported, with a rare presentation of an abscess. Vaginal bleeding after the first injection is possible but rare [25,31,73]. Long-term data support the lack of negative influence on body mineral density and on reproductive potential [92]. However, new prospective studies with inclusion of treated and untreated patients are needed to elucidate the possible association of GnRHa with the increase of BMI [98] and with the higher prevalence of polycystic ovarian syndrome [92].

Making decisions

When graded, the quality of the scientific evidence mentioned in previous sections (consequences & treatment) is found to be low to moderate [99]. Due to the lack of high quality data, our recommendations should be classified as suggestions. Hence, in the treatment of CPP, we suggest:

✓ The use of intramuscular GnRHa depot preparations (triptorelin or leuprolide) every 28 days as the first option outside of preparations that are under research.

✓ To treat all boys <9 yr with GnRHa.
✓ To treat all girls <6 yr with GnRHa.
✓ To individualize the treatment decision in girls between 6 and 8 yr. We have to take into consideration the prediction of menarcheal age, PAH (taking into account the low 95% CI), target height, parent's opinion, and patient's psychosocial maturity.

Practice points

- The definition of Precocious Puberty is still arbitrary.
- Central Precocious Puberty is a rare disease with clear female predominance.
- Central Precocious Puberty is the most common form of precocious puberty
- International adoption increases the risk of Central Precocious Puberty.
- In males a younger age increases the risk of CNS lesions.
- The diagnosis of Central Precocious Puberty needs detailed clinical information and a thorough physical examination along with the support of imaging and hormonal tests.
- The GnRH test continues to be the reference hormonal test in the diagnosis of Central Precocious Puberty.
- Genetic testing plays an emerging role in the diagnosis of Central Precocious Puberty.
- The differential diagnosis of Central Precocious Puberty includes Peripheral Precocious Puberty and common variants of normal puberty such as premature thelarche and premature adrenarche.
- Early puberty is related to a higher risk of behavioral/psychological problems, breast cancer and cardiometabolic comorbidities. There are few data to extrapolate these consequences to Central Precocious Puberty patients.
- GnRHa is the choice treatment in Central Precocious Puberty with different types of formulations. It is a safe treatment with more than 30 years of experience.
- GnRHa particularly improves PAH in girls <6 yr.

Research agenda

- It is necessary to design prospective epidemiological studies that include a significant number of subjects from different countries and different ethnic groups with the purpose of assessing normal pubertal development. With these data, we will be able to reevaluate the definition of precocious puberty.
- Genetic testing will help pediatric endocrinologists to decrease the number of cases of idiopathic Central Precocious Puberty, by increasing the number of monogenic cases.
- It will be of interest to measure DLK1 protein levels in plasma of CPP patients with obesity and/or diabetes mellitus type 2.
- It is feasible that in the coming years epigenetic studies will help to clarify, at least partially, the pathogenesis of idiopathic Central Precocious Puberty.
- More multicenter higher sample size studies are needed to evaluate the usefulness of basal LH levels in the diagnosis of Central Precocious Puberty.
- Large international databases of Central Precocious Puberty would allow us to analyze in more detail the prevalence of CNS lesions. In addition, international registers would contribute to detecting predictor variables of CNS lesions, which in turn could assist to select candidates for brain MRI.
- These databases also could contribute to obtaining more information about boys with Central Precocious Puberty.
- The design of prospective studies including treated and untreated patients with Central Precocious Puberty is needed to assess the emergence of behavioral/psychological problems, obesity, as well as cardiometabolic comorbidities and breast cancer.
- In the years to come, we will obtain adult height data of the different GnRHa formulations under research. Apart from the adult height data, it would be advisable that these studies provide information about cost-benefit analysis.

Summary

The diagnosis of CPP is based on clinical and hormonal requirements without unanimity in the international community. First, there is a permanent debate about age from which to consider precocious puberty and about confusing terminology such as slowly versus rapidly progressive CPP and early puberty. Second, there is no extended criterion of the best hormonal profile (basal LH, LH peak, method employed) to detect CPP. On top of this, the controversy on the request of cranial MRI of girls with CPP between 6 and 8 years must be added. Finally, there is also uncertainty about the long-term consequences of CPP that could be mitigated in the future with the design of large-scale follow up treated and untreated CPP patients.

There are some certainties such as the higher risk of CPP among internationally adopted girls, as well as the higher prevalence of CNS lesions among boys of younger age. In addition, genetic studies have and will contribute to reduce the number of idiopathic CPP cases. Moreover, GnRHa is a safe and effective treatment that particularly improves PAH in girls <6 yr.

Conflicts of interest

LS and JA have nothing to declare.

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References

*[1] Avendaño MS, Vazquez MJ, Tena-Sempere M. Disentangling puberty: novel neuroendocrine pathways and mechanisms for the control of mammalian puberty. Hum Reprod Update 2017;23(6):737–63.
[2] Parent AS, Teilmann G, Juul A, et al. 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(5):668–93.
*[3] Ojeda SR, Lomniczi A, Mastronardi C, et al. Minireview: the neuroendocrine regulation of puberty: is the time ripe for a systems biology approach? Endocrinology 2006;147(3):1166–74.
[4] Herbison AE. Control of puberty onset and fertility by gonadotropin-releasing hormone neurons. Nat Rev Endocrinol 2016;12(8):452–66.
*[5] Ojeda SR, Dubay C, Lomniczi A, et al. Gene networks and the neuroendocrine regulation of puberty. Mol Cell Endocrinol 2010;324:3–11.
*[6] Lomniczi A, Wright H, Ojeda SR. Epigenetic regulation of female puberty. Front Neuroendocrinol 2015;36C:90–107.
[7] Pinilla L, Aguilar E, Díeguez C, et al. Kisspeptins and reproduction: physiological roles and regulatory mechanisms. Physiol Rev 2012;92:1235–316.
[8] Uenoyama Y, Tsukamura H, Maeda K. KNDy neuron as a gatekeeper of puberty onset. J Obstet Gynaecol Res 2014;40(6):1518–26.
[9] Frisch RE, Revelle R. Height and weight at menarche and a hypothesis of critical body weights and adolescent events. Science 1970;169:377–9.
[10] Frisch RE. Body fat, menarche, fitness and fertility. Hum Reprod 1987;2:521–33.
[11] Comninos AN, Jayasena CN, Dhillo WS. The relationship between gut and adipose hormones, and reproduction. Hum Reprod Update 2014;20(2):153–74.
[12] Burt Solorzano CM, McCartney CR. Obesity and the pubertal transition in girls and boys. Reproduction 2010;140(3):399–410.
[13] Sultan C, Gaspari L, Maimoun L, et al. Disorders of puberty. Best Pract Res Clin Obstet Gynaecol 2018;48:62–89.
[14] Smith JT, Clarke IJ. Seasonal breeding as a neuroendocrine model for puberty in sheep. Mol Cell Endocrinol 2010;324(1–2):102–9.
[15] Bourguignon JP, Juul A, Franssen D, et al. Endocrine disruptors. Contribution of the endocrine perspective in the evaluation of endocrine disrupting chemical effects: the case study of pubertal timing. Horm Res Paediatr 2016;86(4):221–32.
[16] Teilmann G, Pedersen CB, Skakkebaek NE, et al. Increased risk of precocious puberty in internationally adopted children in Denmark. Pediatrics 2006;118(2):e391–9.
[17] Soriano-Guillén L, Corripio R, Labarta JI, et al. Central precocious puberty in children living in Spain: incidence, prevalence, and influence of adoption and immigration. J Clin Endocrinol Metab 2010;95(9):4305–13.

[18] Toro CA, Aylwin CF, Lomniczi A. Hypothalamic epigenetics driving female puberty. J Neuroendocrinol 2018 Jul;30(7): e12589. https://doi.org/10.1111/jne.
[19] Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child 1969;44:291–303.
[20] Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970;45:13–24.
[21] Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the pediatric research in office settings network. Pediatrics 1997;99(4):505–12.
[22] Soriano-Guillén L, Argente J. Central precocious puberty: epidemiology, etiology, diagnosis and treatment. An Pediatr 2011;74(5). 336.e1–336.e13.
[23] Sorensen K, Mouritsen A, Aksglaede L, et al. Recent secular trends in pubertal timing: implications for evaluation and diagnosis of precocious puberty. Horm Res 2012;77(3):137–45.
[24] Carel JC, Léger J. Precocious puberty. N Engl J Med 2008;358:2366–77.
*[25] Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diabetes Endocrinol 2016;4(3):265–74.
[26] Soriano-Guillén L, Sarafoglou K, Argente J, et al., editors. Textbook pediatric endocrinology and inborn errors of metabolism. 2nd ed. New York: Editorial Mc Graw Hill; 2017. p. 643–61.
[27] Kaplowitz P, Bloch C. Section on endocrinology, American academy of pediatrics. Evaluation and referral of children with signs of early puberty. Pediatrics 2016;137(1):e20153732.
[28] Teilmann G, Pedersen CB, Jensen TK, et al. Prevalence and incidence of precocious pubertal development in Denmark: an epidemiologic study based on national registries. Pediatrics 2005;116(6):1323–8.
[29] Kim SH, Huh K, Won S, et al. A significant increase in the incidence of central precocious puberty among Korean girls from 2004 to 2010. PLoS One 2015 Nov 5;10(11), e0141844.
[30] Le Moal J, Rigou A, Le Tertre A, et al. Marked geographic patterns in the incidence of idiopathic central precocious puberty: a nationwide study in France. Eur J Endocrinol 2018 Jan;178(1):33–41.
*[31] Aguirre RS, Eugster EA. Central precocious puberty: from genetics to treatment. Best Pract Res Clin Endocrinol Metab 2018;32(4):343–54.
[32] de Vries L, Kauschansky A, Shohat M, et al. Familial central precocious puberty suggests autosomal dominant inheritance. J Clin Endocrinol Metab 2004;89(4):1794–800.
[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(5):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(26):2467–75.
[36] Dauber A, Cunha-Silva M, Macedo DB, et al. Paternally inherited DLK1 deletion associated with familial central precocious puberty. J Clin Endocrinol Metab 2017;102(5):1557–67.
[37] Känsäkoski J, Raivio T, Juul A, et al. A missense mutation in MKRN3 in a Danish girl with central precocious puberty and her brother with early puberty. Pediatr Res 2015;78(6):709–11.
[38] Lee HS, Jin HS, Shim YS, et al. Low frequency of *MKRN3* mutations in central precocious puberty among Korean girls. Horm Metab Res 2016;48(2):118–22.
[39] Bessa DS, Macedo DB, Brito VN, et al. High frequency of MKRN3 mutations in male central precocious puberty previously classified as idiopathic. Neuroendocrinology 2017;105(1):17–25.
[40] Ortiz-Cabrera NV, Riveiro-Álvarez R, López-Martínez MÁ, et al. Clinical exome sequencing reveals *MKRN3* pathogenic variants in familial and nonfamilial idiopathic central precocious puberty. Horm Res Paediatr 2017;87(2):88–94.
[41] Schreiner F, Gohlke B, Hamm M, et al. MKRN3 mutations in familial central precocious puberty. Horm Res Paediatr 2014; 82(2):122–6.
[42] Simon D, Ba I, Mekhail N, et al. Mutations in the maternally imprinted gene MKRN3 are common in familial central precocious puberty. Eur J Endocrinol 2016;174(1):1–8.
[43] Baron S, Battin J, David A, et al. Precocious puberty in children adopted from foreign countries. Arch Pediatr 2000;7(8):809–16.
[44] WHO. Global assessment of the state-of-the-science of endocrine disruptors. WHO/PCS/EDC/02.2. 2002. http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/.
[45] Krstevska-Konstantinova M, Charlier C, Craen M, et al. Sexual precocity after immigration from developing countries to Belgium: evidence of previous exposure to organochlorine pesticides. Hum Reprod 2001;16(5):1020–6.
[46] Bourguignon JP, Slama R, Bergman A, et al. Science-based regulation of endocrine disrupting chemicals in Europe: which approach? Lancet Diabetes Endocrinol 2016;4(8):643–6.
[47] Kaplowitz PB. Link between body fat and the timing of puberty. Pediatrics 2008;121(3):S208–17.
[48] Gavela-Pérez T, Garcés C, Navarro-Sánchez P, et al. Earlier menarcheal age in Spanish girls is related with an increase in body mass index between pre-pubertal school age and adolescence. Pediatr Obes 2015;10(6):410–5.
[49] Stephen MD, Zage PE, Waguespack SG. Gonadotropin-dependent precocious puberty: neoplastic causes and endocrine considerations. Int J Pediatr Endocrinol 2011;2011:184502.
[50] Harrison VS, Oatman O, Kerrigan JF. Hypothalamic hamartoma with epilepsy: review of endocrine comorbidity. Epilepsia 2017;58(Suppl 2):50–9.
[51] Packer RJ, MacDonald T, Vezina G. Central nervous system tumors. Pediatr Clin N Am 2008;55(1):121–45.
[52] Wilne S, Koller K, Collier J, et al. The diagnosis of brain tumours in children: a guideline to assist healthcare professionals in the assessment of children who may have a brain tumour. Arch Dis Child 2010;95(7):534–9.
[53] Rose SR, Home VE, Howell J, et al. Late endocrine effects of childhood cancer. Nat Rev Endocrinol 2016;12(6):319–36.
[54] Neely EK, Hintz RL, Wilson DM, et al. Normal ranges for immunochemiluminometric gonadotropin assays. J Pediatr 1995; 127:40–6.
[55] Wu FC, Butler GE, Kelnar CJ, et al. Ontogeny of pulsatile gonadotropin releasing hormone secretion from midchildhood, through puberty, to adulthood in the human male: a study using deconvolution analysis and an ultrasensitive immunofluorometric assay. J Clin Endocrinol Metab 1996;81(5):1798–805.

[56] Resende EA, Lara BH, Reis JD, et al. Assessment of basal and gonadotropin-releasing hormone-stimulated gonadotropins by immunochemiluminometric and immunofluorometric assays in normal children. J Clin Endocrinol Metab 2007;92(4):1424–9.
[57] Houk CP, Kunselman AR, Lee PA. Adequacy of a single unstimulated luteinizing hormone level to diagnose central precocious puberty in girls. Pediatrics 2009;123(6):e1059–63.
[58] Pasternak Y, Friger M, Loewenthal N, et al. The utility of basal serum LH in prediction of central precocious puberty in girls. Eur J Endocrinol 2012;166(2):295–9.
[59] Lee DS, Ryoo NY, Lee SH, et al. Basal luteinizing hormone and follicular stimulating hormone: is it sufficient for the diagnosis of precocious puberty in girls? Ann Pediatr Endocrinol Metab 2013;18(4):196–201.
[60] 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(13):959–63.
[61] Bar A, Linder B, Sobel EH, et al. Bayley-Pinneau method of height prediction in girls with central precocious puberty: correlation with adult height. J Pediatr 1995;126(6):955–8.
[62] de Vries L, Horev G, Schwartz M, et al. Ultrasonographic and clinical parameters for early differentiation between precocious puberty and premature thelarche. Eur J Endocrinol 2006;154(6):891–8.
[63] Badouraki M, Christoforidis A, Economou I, et al. Evaluation of pelvic ultrasonography in the diagnosis and differentiation of various forms of sexual precocity in girls. Ultrasound Obstet Gynecol 2008;32(6):819–27.
[64] Sathasivam A, Rosenberg HK, Shapiro S, et al. Pelvic ultrasonography in the evaluation of central precocious puberty: comparison with leuprolide stimulation test. J Pediatr 2011;159(3):490–5.
[65] Kaplowitz PB. Do 6–8 year old girls with central precocious puberty need routine brain imaging? Int J Pediatr Endocrinol 2016;2016:9.
[66] Mogensen SS, Aksglaede L, Mouritsen A, et al. Pathological and incidental findings on brain MRI in a single-center study of 229 consecutive girls with early or precocious puberty. PLoS One 2012;7(1), e29829.
[67] Soriano Guillén L, Argente J. Peripheral precocious puberty: clinical, diagnostic and therapeutical principles. An Pediatr 2012;76(4). 229.e1–10.
[68] Khokhar A, Mojica A. Premature thelarche. Pediatr Ann 2018;47(1):e12–5.
[69] Novello L, Speiser PW. Premature adrenarche. Pediatr Ann 2018;47(1):e7–11.
[70] Mogensen SS, Aksglaede L, Mouritsen A, et al. Diagnostic work-up of 449 consecutive girls who were referred to be evaluated for precocious puberty. J Clin Endocrinol Metab 2011;96(5):1393–401.
[71] Carel JC, Lahlou N, Roger M, et al. Precocious puberty and statural growth. Hum Reprod Update 2004;10:135–47.
[72] Bereket A. A critical appraisal of the effect of gonadotropin-releasing hormone analog treatment on adult height of girls with central precocious puberty. J Clin Res Pediatr Endocrinol 2017;9(Suppl 2):33–48.
[73] Willemsen RH, Elleri D, Williams RM, et al. Pros and cons of GnRHa treatment for early puberty in girls. Nat Rev Endocrinol 2014;10(6):352–63.
[74] Sonis WA, Comite F, Blue J, et al. Behavior problems and social competence in girls with true precocious puberty. J Pediatr 1985;106(1):156–60.
[75] 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(8):808–15.
[76] Mul D, Versluis-den Bieman HJ, Slijper FM, et al. Psychological assessments before and after treatment of early puberty in adopted children. Acta Paediatr 2001;90(9):965–71.
[77] Schoelwer MJ, Donahue KL, Bryk K, et al. Psychological assessment of mothers and their daughters at the time of diagnosis of precocious puberty. Int J Pediatr Endocrinol 2015;2015(1):5.
[78] Schoelwer MJ, Donahue KL, Didrick P, et al. One-year follow-up of girls with precocious puberty and their mothers: do psychological assessments change over time or with treatment? Horm Res Paediatr 2017;88(5):347–53.
[79] Wojniusz S, Callens N, Sütterlin S, et al. Cognitive, emotional, and psychosocial functioning of girls treated with pharmacological puberty blockage for idiopathic central precocious puberty. Front Psychol 2016;7:1053.
[80] Menk TAS, Inácio M, Macedo DB, et al. Assessment of stress levels in girls with central precocious puberty before and during long-acting gonadotropin-releasing hormone agonist treatment: a pilot study. J Pediatr Endocrinol Metab 2017;30(6):657–62.
*[81] Kaplowitz PB, Backeljauw PF, Allen DB. Toward more targeted and cost-effective gonadotropin-releasing hormone analog treatment in girls with central precocious puberty. Horm Res Paediatr 2018;90(1):1–7.
[82] Hsieh CC, Trichopoulos D, Katsouyanni K, et al. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. Int J Cancer 1990;46(5):796–800.
[83] 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(11):1141–51.
[84] Yoo JH. Effects of early menarche on physical and psychosocial health problems in adolescent girls and adult women. Korean J Pediatr 2016;59(9):355–61.
[85] Gong TT, Wang YL, Ma XX. Age at menarche and endometrial cancer risk: a dose-response meta-analysis of prospective studies. Sci Rep 2015;5:14051.
[86] Lakshman R, Forouhi NG, Sharp SJ, et al. Early age at menarche associated with cardiovascular disease and mortality. J Clin Endocrinol Metab 2009;94(12):4953–60.
[87] Shin A, Song YM, Yoo KY, et al. Menstrual factors and cancer risk among Korean women. Int J Epidemiol 2011;40(5):1261–8.
*[88] Lazar L, Lebenthal Y, Yackobovitch-Gavan M, et al. Treated and untreated women with idiopathic precocious puberty: BMI evolution, metabolic outcome, and general health between third and fifth decades. J Clin Endocrinol Metab 2015;100(4):1445–51.
*[89] Canoy D, Beral V, Balkwill A, et al. Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. Circulation 2015;131(3):237–44.

[90] Sørensen K, Mouritsen A, Mogensen SS, et al. Insulin sensitivity and lipid profiles in girls with central precocious puberty before and during gonadal suppression. J Clin Endocrinol Metab 2010;95(8):3736–44.
[91] Gomes LG, Cunha-Silva M, Crespo RP, et al. DLK1 is a novel link between reproduction and metabolism. J Clin Endocrinol Metab 2018. https://doi.org/10.1210/jc.2018-02010.
*[92] Guaraldi F, Beccuti G, Gori D, et al. Long-term outcomes of the treatment of central precocious puberty. Eur J Endocrinol 2016;174(3):R79–87.
[93] Lee PA, Klein K, Mauras N, et al. 36-month treatment experience of two doses of leuprolide acetate 3-month depot for children with central precocious puberty. J Clin Endocrinol Metab 2014;99(9):3153–9.
[94] Durand A, Tauber M, Patel B, et al. Meta-analysis of paediatric patients with central precocious puberty treated with intramuscular triptorelin 11.25 mg 3-month prolonged-release formulation. Horm Res Paediatr 2017;87(4):224–32.
[95] Klein K, Yang J, Aisenberg J, et al. Efficacy and safety of triptorelin 6-month formulation in patients with central precocious puberty. J Pediatr Endocrinol Metab 2016 Nov 1;29(11):1241–8.
[96] 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(6):2354–63.
[97] Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123(4):e752–62.
[98] Corripio R, Soriano-Guillén L, Herrero FJ, et al. Changes in body mass index in girls with idiopathic central precocious puberty under gonadotropin-releasing hormone analogue therapy: the Spanish registry. Horm Res Paediatr 2016;86(3):154–60.
[99] Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.