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Clinical Expression of Precocious Puberty in Girls

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Abstract

Premature development of breast and/or pubic hair in a prepubertal girl used to raise questions and concerns from the families. There is actually a wide range of clinical expressions of precocious puberty in girls and not all presentations are considered to be true precocious puberty. Central precocious puberty occurs in 10–20% of girls, but beside the typical forms other clinical presentations have been identified. In 50–60% of the cases, only one secondary sex characteristic shows premature development and raises the diagnosis of premature thelarche, premature pubarche or isolated metrorrhagia. In 10% of the cases, autonomous ovarian overproduction of estrogens causes peripheral precocious puberty. Lastly, hyperestrogenism may have exogenous causes, such as exposure to environmental chemical pollutants. A decision on therapeutic management is based on clinical, biological and radiologic examinations, and LHRH analogous treatment should be limited to central precocious puberty before the age of 8 years.

The premature appearance of secondary sexual characteristics like breast development and pubic hair is upsetting and prompts many families to consult in pediatric endocrinology. Yet the management of precocious puberty is not always straightforward, especially given the unusually wide range of clinical expression: not all presentations of precocious puberty are true precocious puberty [1]!

- Ten to twenty percent of all cases are instances of central precocious puberty (CPP) [2]. The course of its development needs to be carefully assessed and a central tumor must be eliminated. In its typical form, CPP progresses rapidly and the accelerated bone maturation leads to early fusion of the bone plates, thus compromising final adult height. Other clinical presentations have been identified and will be discussed further on.
- In 50–60% of the cases, only one secondary sexual characteristic shows premature development and the diagnosis is premature thelarche (breast development) [3],
premature pubarche (appearance of pubic hair) [4] or metrorrhagia. In these cases, the etiology should be sought, and clinical, biological and radiographic management is devoted to preventing the precocious onset of puberty.

- In 10% of the cases, the development of secondary sexual characteristics has an adrenal or ovarian cause, with an autonomous hyperproduction of estrogens causing precocious pseudopuberty independently of gonadotropin activation. In these cases, it has become increasingly evident that the hyperestrogenism may have an exogenous cause, such as environmental chemical pollutants in the air, water, and food chain. These xenoestrogens have a chemical structure that mimics the actions of natural estrogens by stimulating the activity of target tissues.

In all cases, the initial step is to evaluate the level of estrogen secretion, in terms of both its impact on target organs (breasts, growth rate, bone maturation, etc.) and its course over time. A good understanding of the various ways that precocious puberty clinically presents in girls is vital for the decision on therapeutic management, as the optimal treatment is often not evident during the initial evaluation.

### Evaluation of the Pubertal Stage

One of the first steps in diagnosis is the estimation of pubertal stage. The Tanner stages have been the reference for many years, as they are very well codified (table 1). In routine clinical practice, this relatively precise staging is complemented by examination of the sesamoid bone of the hand. This marker of bone maturation appears toward 11 years and signals the start of puberty.

The Tanner stages have been the reference for generations of pediatric endocrinologists. In an American study of a very large cohort of girls examined between the ages of 3 and 11 years [5], most of the girls appeared to enter puberty at a younger age (9.9 years for B2 and 10.5 years for P2). This drop in the age of puberty onset was
most evident in black girls. The authors attributed their findings to the impact of environmental factors (chemical pollution). The findings that most of the girls entering puberty at the youngest ages (between 6 and 8 years) do not present with short adult height [6] and that the duration of puberty (tempo) is inversely linked to the age of onset (timing) should be considered as relevant to clinical practice, especially to any decision about therapeutic management. The prediction of adult height based on bone age, according to the method of Bayley-Pineau [7], is one of the most reliable parameters in this regard [8].

These works as a whole have done much to elucidate the development of secondary sexual characteristics and the normal course of puberty in girls [9, 10].

The activation of the gonadotropic axis is marked by a peak in LH above 5 μIU/ml and an LH/FSH ratio above 1 during LHRH testing [11]. Conversely to the assertions of other groups, we do not accept the basal values of LH (whatever the standard used) as a marker of pubertal onset.

The measurement of plasma estradiol by radioimmunology is not a reliable method to evaluate the onset of puberty because of its low specificity and high fluctuations. Only the analysis of the biological activity of estrogens using ultrasensitive methods is able to provide useful information on pubertal onset.

Last, pelvic ultrasonography with measurement of the uterus should be systematically performed: onset of puberty shows an increase in ovarian volume (>1.5 cm³) and uterine size, with length exceeding 3.5 cm. The finding of an increased diameter of the uterine fundus and a uterine vacuity line reflects significant estrogenization.

Clinical, biological, anthropometric and radiographic evaluations are all helpful in distinguishing normal puberty from precocious puberty, which may have important clinical, psychological and therapeutic implications [12, 13].

**Puberty Onset**

A substantial number of clinical, biological and experimental studies has demonstrated that the onset of puberty is a central process [14]: the activation of the GnRH pulse generator [15], which is modulated by peripheral signals (intrauterine and postnatal growth, fat mass, insulin sensitivity, gonadal steroid levels) and environmental signals (light, stress and environmental pollution) (fig. 1). The essential role of the GnRH pulse generator in puberty onset (which is part of the global process of maturation) was confirmed by the recent identification of key genes whose natural or experimental loss of function abolished GnRH production [16].

These genes were essentially IAP, TTF1, Nell-2, GPR-54 and FGF-Rc, all of which regulate the processing or secretion of GnRH either directly or through its glutamatergic regulation. Moreover, at the level of the astroglia, TGF-α and the neuroregulins are able to stimulate GnRH production via the Erb β-4 receptor. Although
a hyperproduction caused by TGFα has been associated with CPP, it is also possible that the hyperexpression of one of the genes regulating glutamate production or GnRH itself is a cause of CPP. In fact, the high frequency of the familial form of CPP supports the major role of a genetic factor in gonadotropic activation [17, 18].

**Clinical Expression of Precocious Puberty**

Precocious puberty is eight times more frequent in girls than in boys [19]. Premature breast development, pubic hair and growth acceleration should prompt several questions (table 2), the answers to which will provide clues as to the best adapted treatment strategy [20, 21].

1. Did puberty clinically begin before 8 years?
2. What has been the progression of the clinical symptoms?
3. Are there biological or radiographic signs of exaggerated maturation?
4. How is predicted adult height affected?
5. What are the psychological consequences?
6. Is the hormonal secretion gonadotropin-dependent or gonadotropin-independent?
7. In the case of central gonadotropin activation is it due to a tumor or is it idiopathic?

**Fig. 1.** Onset of puberty.
Central Precocious Puberty

**Typical Form**

The simultaneous development of breasts >B3 and pubic hair >P3 in a girl younger than 8 years suggests CPP when growth rate is also accelerated (>2 SD of the mean for chronological age). When the medical history is taken, the family should be questioned about past head X-rays, brain trauma, and neonatal infection of the central nervous system (meningitis, encephalitis) [22]. In addition, the impact on the child's psychological health or well-being should be assessed [23].

The clinical examination will reveal a modification in the orientation of the vulva, development of the labia majora, and vaginal secretion. The weight curve should be systematically analyzed. The child should be examined for scoliosis or body asymmetry, as this is a constitutive element of a syndrome associated with CPP. Once this initial clinical step is concluded, it is important to confirm the diagnosis of a central cause and to determine the etiology. The hormonal work-up is limited to LHRH testing and a predominant LH response signals central gonadotropin activation [24].
In CPP, X-ray of the left wrist and elbow always reveals advanced bone maturation and bone age is often greater than chronological age. This sign is fundamental. In certain forms of explosive precocious puberty, however, clinical expression may precede the accelerated bone maturation, which only occurs some months later.

Pelvic ultrasonography is indispensable. Uterine length greater than 35 mm indicates puberty onset. Multifollicular ovaries reflect central stimulation. Girls differ from boys in that CPP in the former is more frequently idiopathic (75% of the cases) (table 3), although brain MRI should still be systematic [25]. A central nervous system tumor (hypothalamic hamartoma, optic chiasm glioma, etc.) is found in 10–15% of the cases. Moreover, central structures can be affected secondary to infection (meningitis, meningoencephalitis), radiation, or brain trauma.

**Other Clinical Forms**
In addition to the typical presentation of CPP, which usually occurs between 5 and 8 years, several other forms have been identified and can be distinguished by their etiology, progression, and therapeutic indications (table 3).

**Extremely Precocious Puberty**
Extremely precocious puberty occurs between 1 and 4 years: the clinical progression is rapid and more anarchic, and menstruation occurs. The search for a cerebral tumor should be particularly painstaking.
Slowly Progressing Puberty
Slowly progressing puberty was defined by Rappaport [26] as moderate breast enlargement, E2 concentration less than 25 pg/ml, an advance in bone maturation of less than 2 years, and a ratio of LH peak over FSH peak less than 1. Moreover, the circulating concentration of IGF-1 is prepubertal. If the clinical picture remains stable after 6 months of observation, treatment to stop puberty is not indicated [27].

Spontaneously Regressive Puberty
Cases of spontaneously regressive puberty have long been a subject of discussion: these are authentic cases of CPP in which the signs of estrogenic secretion spontaneously and completely regress in the 12 months following the consultation for precocious puberty [28]. In our experience, no clinical, biological or radiologic element predicts this particular course. This rare form requires no treatment but points to the need for systematic follow-up over 6–12 months for all cases of sexual precociousness.

Central Precocious Puberty in Adopted Children
Central precocious puberty in adopted children is seen almost exclusively in girls between 4 and 8 years, whatever the country of origin, and its occurrence is variable after arrival in the country of adoption. This form is characterized more by the rapidity of the acceleration in growth velocity and maturation than by the clinical signs, and it evokes the relationship of denutrition/inadequate caloric intake → renutrition → rapid rise in IGF-1 → precocious onset of puberty [29]. According to Bourguignon's group [30], these children have been contaminated by pesticides: the plasma concentration in DDT is unusually elevated. They hypothesize that the cessation of environmental contamination after adoption removes the inhibition of the GnRH pulse generator and favors the premature entry into puberty.

Familial Central Precocious Puberty
Routine clinical experience has shown that the age of menarche has remained remarkably consistent across generations and that in certain families puberty onset has always been more or less precocious. A recent study from the group of Philips [17] reported a high proportion (27.5%) of the familial form of CPP. Analysis indicated autosomal-dominant transmission with weak penetrance. These data suggest the need to pay particular attention to the girls in these families, especially since in this study the girls with familial CPP were evaluated later than the girls with sporadic forms. This clinical form of CPP is a remarkable illustration of the implication of genetic factors in puberty onset.

Advanced Puberty
Advanced puberty is the situation most often encountered in clinical practice [31, 32].
**Simple Advanced Puberty**

Simple advanced puberty refers to pubertal advance that remains within 2 SD of the norm, generally appearing between 8 and 10 years of age. This type is often the reason for short adult height, because the acceleration of bone maturation is more rapid than statural growth. It is particularly seen in girls of Mediterranean background and a girl showing this simple advance of puberty often has a mother who experienced the same advance (genetic character).

Some authors [33, 34] have tried to delay puberty in order to increase the growth period and thus improve the final adult height. In fact, LHRH analogues did not improve the predicted final height.

**Simple Advanced Puberty and Growth Retardation**

In many cases, a simple advance of puberty occurs in girls showing growth delay ≤-2 SD, especially those who presented intrauterine growth retardation. The prognosis for final height is affected, with adult height of 145–150 cm. In these cases, treatment to stop puberty can be considered, such as the association of an LHRH analogue and growth hormone [35].

**Advanced Puberty after Premature Pubarche**

At a chronological age of 8–10 years, some girls have presented with premature pubarche and gonadal onset of puberty at a bone age of 10–11 years. Some of these girls, especially the obese, are at risk of developing polycystic ovarian disease in adolescence [36]. They require close clinical, biological and radiologic follow-up throughout the adolescent period.

**‘Incomplete’ Puberty**

Incomplete puberty refers to the premature and often isolated development of a secondary sexual characteristic: the breast (premature thelarche) or pubic hair (premature pubarche). Occasionally isolated metrorrhagia is seen. These situations are very frequently observed in daily practice and are difficult to diagnose. Incomplete puberty is usually considered to be a variant of normal puberty, but it may be caused by an underlying pathology that should be sought or it may be the only current sign of a CPP that will develop in the future.

**Premature Thelarche** (fig. 2)

Premature thelarche refers to isolated breast development in girls between 2 and 7 years, which differs from the genital crisis of the newborn whose breast development (associated with strong estrogenization and even milk production) may last for the first 18 months of life. This premature breast development is bilateral in half the cases, unilateral, or, less frequently, asymmetric. Volume varies: 60% at B2, 30% at B3, and 10% at B4. The breast is often tender and palpation is sometimes painful. There is no discharge.
In persistent or marked forms of thelarche, the hormonal work-up should be limited to the LHRH test to confirm a predominant FSH response [37]. Bone maturation is rarely accelerated. The progression is characterized by fluctuations over time: spontaneous remission, persistence, and aggravation of breast volume, which should evoke the possibility of puberty onset [38–40]. In this case, pelvic ultrasound can provide useful information.

When estrogen secretion if patent (simultaneous increase in uterine volume), contamination by products with estrogen-like activity should be considered and sought (soy-rich foods, environmental pesticides, etc.). In its usual form, premature thelarche requires no treatment.

**Premature Adrenarche/Pubarche** (fig. 3)  
Premature pubarche refers to the appearance of pubic hair before 8 years. It is usually isolated although axillary hair is occasionally observed. The clinical examination
Clinical Expression of Precocious Puberty

is centered exclusively on the detection of other signs of hyperandrogenism, such as acne, abnormal perspiration, and clitoral hypertrophy. Growth velocity and bone maturation are usually only slightly accelerated.

Depending on the clinical picture, an androgen work-up (testosterone, 17OHP, DHEAS and possibly a synacthen test should be done.

In most situations, the maturation of the adrenal function that precedes puberty is accelerated or early, although the reason remains unknown. The ‘physiological’ character of adrenarche cannot mask the authentic forms of secondary congenital adrenal hyperplasia, during the course of which the precocious puberty reveals a deficiency in 21-hydroxylase (21OH). The finding of a homozygous mutation of the 21OH gene (or a double heterozygous mutation) requires specific treatment, but the efficacy of treatment for heterozygous forms has not been determined.

Last, precocious puberty in the context of intrauterine growth retardation and insulin resistance should be followed closely for several years, according to some [36]:

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Fig. 3. Decision tree for premature pubarche.
it is thought that precocious puberty might provide the conditions for CPP, PCOS in adolescence [41] and adult metabolic syndrome, which has become a serious management problem in public health.

Isolated Metrorrhagia

Several clinical manifestations of transitory ovarian activity have been observed in isolated metrorrhagia: menstruation that is isolated or associated with breast development, with inconsistent response to the LHRH test and the frequent presence of functional ovarian cysts. Menstruation may recur cyclically. These rises in estrogenization increase the risk of accelerated bone maturation, and treatment to stop puberty is thus often discussed but rarely undertaken.

Peripheral Precocious Puberty: Precocious Pseudopuberty

Peripheral precocious or precocious pseudopuberty is not characterized by the premature activation of the gonadotropic axis: it is caused by an abnormally high production of estrogens and, more rarely, androgens because of a ‘tumor’ on the ovary or adrenal glands. It is iso- or heterosexual depending on the whether the excess steroid hormone strengthens or transforms the child’s phenotype.

The considerable progress in determining the molecular mechanisms of hormone transduction signals has greatly contributed to our understanding of the physiopathology and clinical expression of peripheral precocious puberty caused by ovarian autonomy. This progress may one day culminate in a specific treatment for this rare but incapacitating disorder. Heterosexual precocious pseudopuberty secondary to a virilizing adrenal or ovarian tumor is much rarer.

Increasing attention should be given to precocious pseudopuberty secondary to environmental contamination by chemical products such as pesticides, herbicides, and fungicides. Endocrine disruptors with the capacity to mimic estrogens are able to generate estrogen secretion, resulting in simple thelarche to veritable menstruations.

Peripheral Precocious Puberty Caused by Ovarian Autonomy

McCune-Albright Syndrome

McCune-Albright syndrome (MAS) is a sporadic disorder characterized by the classic triad of precocious puberty, fibrous bone dysplasia, and café-au-lait spots. Diverse endocrine abnormalities can also be associated: somatotrophic pituitary adenomas, hypothyroid goiter, and adrenal hyperplasia.

Precocious Puberty. MAS affects girls almost exclusively and is characterized by its extreme precociousness and the gravity of the immediate clinical picture: isolated menstruation as early as the first months or first years of life. The full clinical picture will develop later, with breast enlargement and pubic hair. The often voluminous ovarian cysts discovered by ultrasound are cyclic and are difficult to treat: cystectomy or ovariectomy
is often necessary when all other treatments fail. The acceleration of growth velocity is considerable (+2, +3 SD) and constant, on the order of 9–10 cm per year. Bone maturation is also accelerated and will thus compromise the prognosis for final adult height.

The biological work-up will show very high plasma estradiol associated with dramatically low plasma gonadotropins and no response to GnRH stimulation. This indicates LH/FSH-independent precocious puberty and situates this type of precocious puberty within the context of the ovarian-autonomous syndromes.

*Café-au-Lait Spots.* The café-au-lait spots of MAS are hyperpigmented, typically light brown or brown, with irregular borders (‘coast of Maine’) that distinguish them from the smooth-bordered spots observed in neurofibromatosis. The spots are usually unilaterally distributed, on the same side as the bone lesions. The size and number are variable but may increase with the patient’s age. When associated with precocious puberty, they are an essential diagnostic element.

*Fibrous Bone Dysplasia.* Fibrous bone dysplasia is the third element in the classic triad. This bone abnormality may remain silent for many years, only to be revealed by a spontaneous fracture or on the occasion of a slight injury. X-rays reveal pseudocysts of the bone cortex that rapidly invade the entire skeleton.

*Other Endocrine Pathologies.* Other endocrine pathologies are seen to varying degrees: hyperthyroidism, acromegaly, gigantism, hypercorticism, hyperprolactinemia, and hyperparathyroidism. These types of endocrine hyper-functioning are also caused by autonomous hormonal hyperproduction.

The hyperproduction of growth hormone is much greater than that which is seen in CPP: generally, it is due to a pituitary tumor, hyperplasia or adenoma, and both medical and surgical treatment are difficult. Hyperprolactinemia is frequently noted: it is usually due to the same mechanism as involved in GH hypersecretion. It does not modify the course of precocious puberty. Hypercorticism is also observed in some cases. It is autonomous and ACTH levels are always low. In certain cases, hyperfunctioning of the thyroid gland is seen with goiter and low TSH. Hyperparathyroidism associated with high levels of calcium and alkaline phosphatase has been reported in patients presenting bone lesions and spontaneous fracture.

*Molecular Bases of McCune-Albright Syndrome.* The specific location of the skin lesions and the sporadic character of MAS (no documented cases of hereditary transmission) suggest that this disorder is due to a somatic mutation that occurs early in development. The result is a mosaic distribution of abnormal cells. The appearance and the severity of the bone, skin and endocrine abnormalities thus depends on the number of cells carrying the mutation.

Moreover, the diverse endocrine hyperfunctioning syndromes observed in the course of MAS have in common the presence and activation of cells that respond to extracellular signaling by activation of the adenyl cyclase system. The growth and activity of gonads, thyroid, adrenal cortex, certain pituitary cells, melanocytes and osteoblasts are stimulated by an increase of intracellular AMPc under the dependence of adenyl cyclase membrane.
The hypothesis of local hyperproduction of AMPc was confirmed several years ago: MAS is caused by a genetic abnormality that causes a constitutive activation of adenyl cyclase. The evidence of activating Gαs mutations in various tissues of MAS patients [42] further supports this mechanism.

Granulosa Cell Tumors
Although rare (10% of the ovarian tumors in children), granulosa tumors are expressed in early childhood by strong estrogen secretion that results in marked breast development, accelerated growth velocity, and by menstruation. These ovarian tumors are discovered in a wide variety of circumstances:

- Endocrine disturbances:
  - The hormonal activity of the tumor explains why 80–90% of the girls under 8 years present isosexual precocious pseudopuberty. This pubertal advance induced by the estrogen secretion of the tumor cells is independent of the low levels of GnRH and prepubertal gonadotropins. On clinical examination, breast development is frequently noted but this is variable, metrorrhagia, accelerated growth velocity and sometimes advanced bone age are also noted. The preoperative plasma estrogen concentration is almost always elevated. Virilization with precocious pubarche, acne, hirsutism and rarely clitoromegaly is related to aromatase deficiency inside the tumor.
  - Endocrine symptoms may also be present in cases of ovarian granulose cells in the post pubertal period. Symptoms are more difficult to detect, such menometrorragia and hyperandrogenism.
  - Precocity of diagnosis and an early recognition of endocrine signs from ovarian granulosa cell tumors significantly improves its prognosis with a lower risk of peritoneal extension [43].

In most patients, the levels of inhibin and AMH are elevated and return to normal postsurgery. The level of inhibin is correlated with tumor extension and eventual relapse. If the estradiol level is initially high, this too can be useful for follow-up. However, its interest is limited because (1) 30% of granulosa tumors are nonsecreting, (2) its level depends on the surrounding theca cells and is thus variable, and (3) physiological puberty can interfere with measurement.

- During emergency surgery (10% of the cases) for acute abdominal pain and vomiting that is mistakenly diagnosed as acute appendicitis. These symptoms are due to torsion of the ovary or more rarely tumor rupture.
- An abdominal-pelvic mass that may be quite voluminous. This mass is frequently asymptomatic and it is discovered by the parents. It may also cause compression of the urinary tract (lumbar pain, colic nephritic, urinary infection) or the intestine (constipation, incomplete occlusion syndrome).
- As a fortuitous discovery during surgical intervention for other reasons.
- By discovery of an ovarian cyst during prenatal diagnosis, which is an exceptional situation.
Surgery is the treatment of choice for a granulosa cell tumor. A careful preoperative evaluation is necessary to preserve fertility and future hormonal functioning. Staging includes peritoneal cytology and exploration of the abdominal cavity. Limited tumors can be treated by salpingo-oophorectomy, as the rate of relapse is minimal. For bilateral tumor, a conservative treatment of the contralateral ovary should be discussed. In stages with extraovarian extension, chemotherapy is recommended. Follow up includes careful clinical, hormonal and ultrasonographic evaluation.

Due to its excellent prognosis and the often complete recovery after initial surgery, juvenile OGCT has usually been considered as benign condition. Survival of the patients with stage Ia tumors is around 90%, the overall survival in the whole group approximating 85%. However, the minority of tumors that have spread within the abdomen or recurred after initial therapy have a much poorer prognosis and OGCT should be considered a ovarian cancer of good prognosis rather than a benign condition. It is still not possible to identify those patients who will relapse in the future, and the mechanism of this relapse remains to be elucidated. Nevertheless, molecular biology [44] has identified 2 markers of prognosis:

– Mutations of the Gs alpha protein – a protein included in the transduction of the FSH signal – have been found in hot spot position 201 in 30% of patients’ DNAs [45]. The oncologic stages were significantly different according to the gsp oncogene status. Patients with a hyperactivated Gαs exhibited a significantly more advanced tumor (p < 0.05). Gsp oncogene is indeed implicated in cell proliferation level and cell invasion capacity.

– Another prognostic factor of OGCT could be the level of the differentiation of the tumoral cell. One of the earliest differentiating genes of granulosa cell in the fetus is FOXL2. FOXL2, a forkhead transcription factor, is a regulatory element of the organogenesis of the mammalian ovary. The patients with no or reduced expression of FOXL2 in thei tumor exhibit significantly more advanced oncologic staging. All patients requiring complementary treatment (chemotherapy or complementary surgery) showed reduced FOXL2 expression in the tumor. The extinction of this gene implicated in granulosa cell differentiation is compatible with an uncontrolled proliferation of these cells [46].

Feminizing tumors of the adrenal gland are relatively rare causes of precocious pseudopuberty.

Precocious Pseudopuberty and Environmental Pollution
The lower age for onset of puberty is thought to be due to environmental contamination by pesticides [5]. Moreover, European pediatric endocrinology groups unanimously agree that the frequency of premature thelarche has clearly been rising over the past several years.
Several reports have detailed veritable epidemics of precocious pseudopuberty. In Italy, 21% of the girls in preschool classes presented with premature thelarche in association with poultry intake. More recently, the high frequency of premature thelarche before 7 years (34%) in Puerto Rico was associated with phthalates levels three times higher than that seen in controls [47].

Many experimental data indicate the impact of chemical contamination (pesticides) during gestation on the timing and tempo of puberty, and these data have been extensively reviewed [48]. The growing recognition of the potential impact of endocrine disruption on the timing of puberty should prompt in-depth investigation of the environmental conditions of a child’s development [49] when conventional etiologies prove negative.

Conclusions

Daily clinical practice reveals a wide diversity in the clinical expression of precocious puberty in girls. Pubertal development seems to occur along a continuum from normal to advanced to precocious, which reinforces the importance of an etiological approach to these increasingly frequent situations, through clinical, biological and radiologic examinations. A better understanding of the clinical presentation should improve the therapeutic indication, especially concerning the use of LHRH analogues, which should be limited to CPP before the age of 8 years as this particular situation is liable to compromise final adult height, according to the clinical, biological and radiologic data [50].

References


