Precocious puberty: a question to be answered
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Precocious puberty (PP) is allied with accelerated growth, advanced bone age, development of secondary sex characteristics, and early closure of epiphysis. This article aimed to review PP in both sexes. A search for a review of published articles was carried out using PubMed, medical subject heading databases, and Scopus engine. Keywords used to accomplish these concerned associations were puberty, PP, adolescence, adrenarche, menarche, pubarche, and thelarche. Etiologically, PP is divided into gonadotropin-releasing hormone (GnRH)-dependent and GnRH-independent causes. GnRH-dependent PP [central precocious puberty (CPP)] is based on hypothalamic–pituitary–gonadal axis activation associated with progressive pubertal development, accelerated growth rate, and advanced skeletal age. CPP is one of the common forms of PP resembling the normal route of puberty at an age less than 8 and 9 years for girls and boys, respectively. Peripheral precocious puberty is related to sex steroid exposure independent of hypothalamic–pituitary–gonadal axis activation. Therapy is indicated in children with CPP with accelerated bone age, height progress, or psychosocial stress to halt puberty succession to a socially satisfactory age, allowing the child to achieve optimal height potential. GnRH analog is the treatment of preference, with best height result if initiated before 6 years of age.

Keywords:
adolescence, adrenarche, menarche, precocious puberty, pubarche, puberty, thelarche

Introduction
Puberty is a complex physical and psychological process that culminates in reproductive capacity. The initiation of puberty depends on a decrease in factors that inhibit the release of gonadotropin-releasing hormone (GnRH) combined with increased stimulatory factors [1,2]. Increased excitatory and decreased inhibitory inputs, and glial secretory factors such as TGF-α and prostaglandin allow the activation of the gonadotropic axis at the pubertal onset [3,4]. Synthesis of GnRH starts early in fetal life, being active during the first 6 months of life in boys and during the first 2 years of life in girls. This neonatal period is called 'mini-puberty' and then the gonadotropic axis becomes inactive. Nevertheless, the timing of puberty is highly heritable, with reactivation of hypothalamic GnRH secretion being determined by genetic, ethnic, nutritional, and environmental influences [5–7].

Precocious puberty
Precocious puberty (PP) is defined as the development of pubertal changes at an age younger than the accepted lower limits for the onset of development of secondary sexual characteristics (the first step toward attaining reproductive capacity) – that is, younger than 8 years for girls and younger than 9 years for boys [8]. PP is responsible for early progression of secondary sexual characteristics, rapid bone maturation, reduced ultimate height, inappropriate body appearance, and psychological behavioral abnormalities [9]. Therefore, PP is a spectrum disorder that may either manifest with development of all secondary sexual features (progressive PP) or present as isolated premature thelarche, adrenarche, or menarche [10].

PP has a predictable register-based population prevalence of about 0.2% in girls and below 0.05% in boys [11]. Its diagnosis is confirmed by the presence of increased gonadotropin and/or sex steroid levels, hastened somatic development, and bone age (BA) advancement with follow-up of the early signs of sexual development. Kisspeptin produced by the arcuate nucleus and the anteroventral periventricular area of the hypothalamus is critical to puberty initiation. Neurokinin B and dynorphin from the same neurons stimulate and inhibit the release of kisspeptin, respectively, and these kisspeptin, neurokinin, and dynorphin neurons were recognized to be central to puberty initiation [12,13]. Optimal management is an important cause for long-term biological, psychosocial, and health insinuation. Early onset of puberty and untreated PP were demonstrated to be linked to compromised adult height, increased incidence of metabolic syndrome, dyslipidemia, dysglycemia, cardiovascular events, hyperandrogenism, increased risk for breast cancer, increased psychological disturbance, and sexual activity [14].

Classification

(1) Gonadotropin-dependent, progressive (central/true PP).
(2) Gonadotropin-independent (PPP/pseudo-PP).

Central precocious puberty

Central precocious puberty (CPP) is characterized by same biochemical and physical features as normally timed puberty but occurring at an earlier age [15]. CPP is due to early maturation of the hypothalamic–pituitary–gonadal (HPG) axis, with a frequency of 1/5000–1/10 000; the female-to-male ratio varies between 3/1 and 23/1 [16]. Although the majority of CPP cases are idiopathic, organic lesions and environmental factors, as well as endocrine disrupters, might have estrogen activity, or may cause increased endogenous estrogen secretion [17]. Moreover, childhood obesity could be associated with early menarche in girls due to increased caloric intake, consumption of fast foods, and decreased physical activity. Endocrine disturbances and low birth weight are among factors that were held responsible for increased frequency of thelarche variants in PP distribution [18,19]. In their work, Durmaz *et al.* [20] showed that the estrogenic effects of bisphenol A, which is an industrial chemical particularly used to harden plastics, may be an etiologic factor.

The etiology of CPP cannot be established in many cases in which the condition might be acknowledged as an idiopathic one. One of the common pathologies is hypothalamic hamartoma, which is a congenital, non-neoplastic, and tumor-like lesion occurring earlier, even below 4 years of age, compared with idiopathic and additional organic etiologies in both sexes. The tissue in hypothalamic hamartomas includes functional GnRH neurons secreting GnRH episodically with TGF-α receptors expressing astroglial cell [21].

Other causes that should be thought-out are the gene mutations that cause PP. The genetic component of CPP was demonstrated by the evidence that the deficiency of the MKRN3 gene, located on the long arm of chromosome 15, causes familial CPP in humans [22]. Moreover, the kisspeptin/G-protein couple receptor-54 (GPR54) system was shown to play a key role in the activation of the gonadotropic axis at puberty. Therefore, the genetic variations of KISS1 gene can be contributing factors for the development of CPP [23]. Using meta-analysis, Luo *et al.* [24] suggested that estrogen receptor (ESR1) polymorphisms (PvuII and XbaI) and ESR2 polymorphisms (RsaI and AluI) are associated with PP susceptibility. Recently, Mazaheri *et al.* [25] reported polymorphism in KISS gene among patients with idiopathic central precocious puberty.

Lee *et al.* [26] investigated the association between serum 25-hydroxyvitamin D (25OHD) and PP in girls. The authors pointed to a significant difference in the mean serum 25OHD concentration between the PP group and the control group (17.1 vs. 21.2 ng/ml). Seventy percent of the girls with CPP demonstrated vitamin D deficiency (serum 25OHD < 20 ng/ml), concluding that vitamin D levels might be associated with PP.

Peripheral precocious puberty

In girls, one of the common etiologies of peripheral precocious puberty (PPP) is ovarian follicular cysts causing vaginal bleeding in younger girls.

Causes

(1) *McCune–Albright syndrome*: McCune–Albright syndrome is a rare syndrome characterized by excess function of the peripheral endocrine organs and activating mutations of the stimulatory G-protein α subunit. The main findings of this disease include hyperpigmented café au lait spots, fibrous dysplasia, and increased endocrine functions and excess secretion of growth hormone [27,28]. Clinical signs may fail to be noticed in these patients because of PP and craniofacial fibrous dysplasia, which occur because of the mutation that activates the gene encoding Gs protein α subunit. The other endocrine organ hyperfunction (hyperthyroidism, Cushing syndrome, acromegaly, and hypophosphatemic rickets) should also be investigated [29,30].

(2) *Testotoxicosis*: It is a form of gonadotropin-independent PP in which boys experience an early onset and progression of puberty with accelerated growth, early development of secondary sexual characteristics, and reduced adult height [31]. Testotoxicosis is caused by an activating mutation of the luteinizing hormone (LH) receptor, leading to increased levels of sex steroids in the context of low LH [32]. LH receptor-activating mutations (familial testotoxicosis) are autosomal dominant rare diseases in male children, characterized by symmetrical testicular enlargement. Jeha *et al.* [33] revealed a D564G mutation in the third cytoplasmic loop of the LH/choriogonadotropin receptor in cases of familial testotoxicosis.

(3) *Human chorionic gonadotropin (hCG)-secreting tumor*: It is another cause of PPP in boys, which is located in organs other than gonads, such as the liver, pineal region, brain, or mediastinum, resulting in testicular enlargement and elevated serum testosterone levels. Although the production of tumor-associated hCG by a germinoma is a rare event, it may lead to PP due to its structural and functional similarity to LH [34].

(4) *Virilizing diseases*: Diseases that arise from the adrenal gland, especially congenital adrenal hyperplasia (CAH), are the most common PPP etiological factors during childhood. Although it causes isosexual PPP in boys, it results in heterosexual PPP in girls. CAH is a monogenic autosomal recessive disease caused by mutations or deletions in CYP21A2, the gene encoding steroid 21-hydroxylase [35,36]. Recently, Alqahtani *et al.* [36] identified a novel nonsense mutation mainly clustered in exons 3 and 8 in the CYP11B1 gene that causes classic steroid 11β-hydroxylase-deficient CAH. Wang *et al.* [37] identified seven novel CYP11B1 mutations, including p.R454H, p.Q472P, p.Q155X, p.K173X, IVS2-1G > A, R454A fs 573X, and g.2704_g.3154del, and six previously described mutations (p.P94L, p.G267S, p.G379V, p.R448H, p.R454C, and p.R141X).

(5) *Chronic primary hypothyroidism*: Early secondary sexual development in the setting of profound primary hypothyroidism is a form of PPP also known as Van Wyk–Grumbach syndrome. In addition to the classic

features of hypothyroidism, such as delayed linear growth and skeletal maturation, affected girls have breast development, galactorrhea, and/or vaginal bleeding, and boys have testicular enlargement without virilization [6]. Acceleration in somatic development is not seen and increased prolactin level and galactorrhea may accompany the pubertal signs. Cabrera *et al.* [38] reported a 24% incidence of PPP among 33 children with profound hypothyroidism, and those with PPP were older and trended toward a higher thyroid-stimulating hormone.

Premature thelarche

Premature thelarche is an isolated breast enlargement that typically starts in infants below 2 years of age whereas somatic development is not accelerated and the BA is not advanced. Breast development may be cyclical in relation to blood estrogen levels that regress with time. Such regression is not observed in children older than 2 years and have significant glandular structure. Primary hypothyroidism should be ruled out in these cases. It was observed that premature thelarche that starts after 2 years of age may progress to CPP [36].

The physiologic baseline event in premature thelarche is the increased circulating Follicle stimulating hormone (FSH), and inhibin B secreted from the granulosa cells is thought to be responsible for this increase [39]. FSH response is the forefront both in night pulses and peak response to GnRH stimulation test GnRH stimulus. LH response with FSH may increase to higher levels in premature thelarche cases starting before 2 years of age, and it may interfere with CPP, a phenomenon termed 'mini-puberty' [40]. However, the ovaries and uterus are within prepubertal sizes. Some premature thelarche cases are due to exposure to estrogenic environmental pollution [41–44]. In this context, Sahin *et al.* [45] demonstrated that the mean serum Anti-Müllerian hormone levels of the CPP group were significantly lower than those in the premature thelarche group (13.57 vs. 58.42 pmol/l), suggesting that Anti-Müllerian hormone may be a marker for distinguishing between CPP and premature thelarche (PT).

Premature adrenarche/pubarche

Adrenarche is the increase in pubertal adrenal androgens that may be seen in both sexes in normal children between 6 and 8 years of age. Pubarche – that is, genital and axillary hair – does not accompany this situation. Adrenarche occurs because of increased secretion of androgens from the zona reticularis of the adrenal cortex, with increased serum Dehydroepiandrosterone (DHEA) and its metabolite sulfate due to increased 17,20-lyase and 17α-hydroxylase activities. Increased serum DHEA-S greater than 40 μg/dl is the biochemical indicator of the adrenarche [46]. In premature adrenarche (PA), clinical signs of androgen action appear in girls and boys below 8 and 9 years of age, respectively, with the circulating DHEA-S concentrations above the usually low prepuber-

tal level. The most pronounced sign of PA is the appearance of pubic/axillary hair, but other signs of androgen effect (adult type body odor, acne/comedones, greasy hair, and accelerated stature growth) are important to be recognized. PA children are often overweight and taller than their peers, and the higher prevalence of PA in girls than in boys is probably explained by higher female adiposity and peripheral DHEA-S conversion to active androgens. PA has been linked with unfavorable metabolic features, including hyperinsulinism, dyslipidemia, and later-appearing ovarian hyperandrogenism [47].

CAH or adrenal tumors, in which androgen production is increased, are the pathologies that should be ruled out initially in premature pubarche. Some partial enzyme deficiencies such as 21-Hydroxylase and 3β-OHD deficiency may manifest first with premature pubarche. Both somatic growth and advanced BA are accelerated in these cases. Therefore, DHEA-S measurement should be performed in addition to testosterone and 17-Hydroxyprogesterone (17OHP). Although DHEA-S is increased in isolated premature pubarche, testosterone and 17OHP levels are in normal range. Sometimes, an Adrenocorticotropic hormone (ACTH) stimulation test is important in borderline cases for diagnosis. The onset of puberty in cases of PA is generally expected in normal time but there is a risk for early menarche in some cases with onset of pubarche between 7 and 8 years of age [48,49].

Diagnosis of precocious puberty

The diagnosis of PP should be based on hormonal data combined with clinical signs and follow-up. When faced with PP, there are a few questions to be answered.

(1) Normal or abnormal variant?
(2) If abnormal sign, central or peripheral?
(3) If peripheral, adrenal or gonadal?
(4) If central, idiopathic or intracranial pathology?

History taking

History taking includes complete family history (age of onset of puberty in parents and siblings) patient's age at onset of puberty, and progression of pubertal manifestations. History should be sought for information about the onset of the signs, progression rate and growth rhythm in the last 6–12 months, presence of secondary sex characteristics (acne, oily skin, erection, night ejaculation, and vaginal bleeding), and the presence of pubertal signs. Evidence suggesting a possible cerebral dysfunction, such as recurrent vomiting, headache, increased head circumference, visual impairment, or seizures, should be assessed.

Clinical examination

(1) Pubertal staging carried out according to the Tanner–Marshall method on physical examination. Anthropometric evaluations should be distinct by measurement of weight, height, and body proportions. CPP, in contrast to PPP, classically mimics the normal path of pubertal development of thelarche, followed by

adrenarche and menarche, and is associated with height acceleration and advanced BA.

(2) Recording of height velocity and BA determined with radiograph of the left hand and wrist. If BA is advanced more than 2 SD of chronological age (CA), it is unlikely the child has a normal variant of pubertal development [50]. If it is possible, BA/CA must be calculated. If this ratio is greater than 1.2, it is in favor of progressive CPP [51].

(3) Examination of testicular volume in male patients, as boys with CPP typically have symmetric enlarged bilateral testis in pubertal range (> 4 ml or > 2.5 cm in length) in contrast to boys with PPP who have disproportionately small testis [52]. If the testis volume is below 4 ml in the presence of secondary sex characteristics in a boy, this PP is probably caused by adrenal pathologies. Asymmetric testicular enlargement is found in McCune–Albright syndrome and Leydig cell tumor cases, whereas bilateral testicular enlargement is common in testotoxicosis, hCG-secreting tumors, and CPP cases [8].

Biochemical evaluation

It confirms the diagnosis of CPP (GnRH-dependent) and distinguishes incomplete nonprogressive forms of PP, such as premature thelarche and PA.

(1) Estimation of gonadotropins (LH, FSH) and other sex steroids: the patient must be evaluated using the GnRH stimulation test. Although FSH response is dominant in premature thelarche, LH is the dominant gonadotropin in CPP patients. LH and FSH are suppressed or at prepubertal levels in PPP cases. In premature thelarche cases below 2 years of age, LH may increase in addition to FSH, but FSH response is dominant [50,53]. In general, a basal LH of 0.3–0.6 IU/l can be considered positive for HPG axis activation [54,55]. An early sampling 30–60 min after GnRH/gonadotropin-releasing hormone analog (GnRHa) administration is considered sensitive and specific for diagnosis, and a stimulated LH of 4–5 IU/l can be considered positive for HPG axis activation [56–58]. FSH estimation is not helpful because of the considerable overlap of prepubertal values with puberty, and because of its elevation in premature thelarche. However, a peak LH/peak FSH greater than 1 is helpful in differentiating true CPP from premature thelarche that has a predominant FSH response [52]. In female children, Çatlı et al. [51] pointed that a peak LH/FSH ratio greater than 0.24 could be used in the diagnosis of CPP.

(2) Plasma level of kisspeptin is associated with the initiation of pubertal development, and it serves as an important parameter in the diagnosis of idiopathic central precocious puberty and the evaluation of therapeutic effects [59]. Abacı et al. [42] pointed that increased serum levels of leptin, kisspeptin, and neurokinin B in patients with premature thelarche and CPP suggest that they take part during the initiation of pubertal process; however, these markers are not able to differentiate patients with CPP from premature thelarche.

(3) Basal plasma testosterone levels in boys increase both in CPP and PPP, but it is much higher in PPP patients. In contrast, the importance of estrogen level is limited in girls with CPP, because in many affected girls it has low ranges [60].

(4) Other endocrinology evaluations include thyroid tests, 21-hydroxylase, 17OHP level, and hCG.

(5) Serum alkaline phosphatase levels are significantly higher in 5–8-year-old girls with PP than in age-matched girls with normal puberty and were higher in girls with PP than bone-age-matched girls with normal puberty [61].

Imaging

(1) Pelvic ultrasonography should be performed in girls, as bilaterally enlarged ovaries are determined in CPP patients and the uterine volume is pubertal in all CPP cases. The ovaries may be asymmetrically enlarged in girls with gonadal PPP, and the ovaries are more than 2 ml and the uterine length is greater than 4 cm [62]. A uterine length greater than 3.5 cm, and a uterine volume greater than 1.8 ml are believed to be the two most specific indicators for true CPP, and are useful to differentiate CPP from premature thelarche or adrenarche [63]. Ovarian cysts can be found in both CPP and PPP, but cysts greater than 9 mm are also suggestive of CPP [64].

(2) Cranial and pituitary MRI could rule out organic CPP. However, imaging needs to be repeated periodically in cases younger than 4 years that were reported to be normal [65]. It may be a good practice to perform an MRI of the brain in all children under 6 years of age with CPP, irrespective of their sex, but should be avoided in children older than 6 years [66].

Specific tests

(1) A GnRH stimulation test is required to diagnose CPP; however, this test is expensive and time consuming. An elevated level of basal LH and basal LH/FSH ratio is a significant predicting factor of positive responses during the GnRH stimulation test [67]. Suh et al. [68] pointed that no single parameter can predict a positive response on the GnRH stimulation test with both high sensitivity and specificity.

(2) The leuprolide stimulation test with stimulated LH/FSH ratio and LH gave the most useful parameters for the diagnosis of CPP. Cutoff points for CPP are as follows: for baseline – LH greater than 0.1 mUI/l, FSH greater than 2.3 mUI/l, LH/FSH ratio greater than 0.23, and estradiol greater than 12 pg/ml; for stimulated – LH greater than 5.5 mUI/l, LH/FSH ratio greater than 0.24, and estradiol greater than 79.67 pg/ml. The best diagnostic parameter for progressive puberty is stimulated LH/FSH ratio (sensitivity, 100%; specificity, 94%), followed by stimulated LH (sensitivity, 93%; specificity, 100%) [69].

Treatment

Treatment options depend on the presence of psychological/behavioral disorders, anxiety about height, and probability of early menarche. Although psychological influences of PP have not been investigated sufficiently, there are some case reports on sexual abuse and early pregnancy. The indications for psychological assessment and intervention should be considered on individual basis.

The main objectives of treatment of PP are as follows:

(1) Delay the process of puberty progression to an age matching with peers.
(2) Allow normal social, psychological, and intellectual development of the child.
(3) Relieve associated anxiety of the parents.
(4) Allow the child to achieve the optimal height potential.

The gold standard treatment for CPP is GnRHa therapy if initiated in children diagnosed before 6 years of age, variable if initiated between 6 and 8 years of age, and with little benefit if initiated after 8 years of age [16,54]. Their effects depend on desensitization and downregulation of GnRH receptors. They are safe and have minimal side effects. Good predictors of height outcomes include young CA, young BA, greater height standard deviation score for CA at initiation of therapy, and a higher adult height using Bayley–Pinneau tables [70]. GnRHa should be continued until 11 years of age when pubertal progression commensurate with peers [67]. GnRHa discontinuation was shown to be linked with initiation of the menses within 1–2 years in girls [71]. Bone mineral density generally dips with the start of GnRHa but normalizes after discontinued therapy, without impact on long-term outcomes [14]. The most commonly used GnRHa is leuprolide acetate in subcutaneous form, being less painful, at 3.75 mg/4 weeks or leuprolide acetate depot (11.25–30 mg) administered intramuscularly every 3 months with an acceptable safety profile, providing maintenance of LH suppression in the majority of children with CPP [72,73]. It is followed by triptorelin depot preparation buserelin and histrelin. The first injection of GnRHa is linked with a transient surge in LH and FSH with a transient increase in estradiol levels that may result in vaginal spotting/bleeding in some girls following the first injection [74]. Li *et al.* [75] suggested that GnRHa therapy may have a positive effect on final adult height in girls with early puberty and adding Growth hormone to the treatment could suggest more advantage. Coinjection of depot medroxyprogesterone acetate (MPA) only with the first dose of GnRHa is a realistic option to prevent estradiol surge and associated vaginal bleed [76].

MPA or cyproterone acetate could be used for managing PP in children who cannot afford GnRHa and is a good option in children older than 6 years, whereas the use of GnRHa is associated with minimal gains in height outcomes. Advantages of MPA include low cost, easy administration, and efficacy. It has several mechanisms of actions: inhibits central gonadotropin release by acting on hypothalamic pulse generator, and directly inhibits gonadal steroidogenesis by inhibiting 3β-hydroxysteroid dehydrogenase-2 enzyme [77]. Its glucocorticoid mimetic action is responsible for the adrenocorticotropic hormone suppression, hypertension, and development of cushingoid habitus. MPA use is linked with bone mineral loss, mostly if used for a long period [55]. Cyproterone acetate has advantages and disadvantages similar to MPA, except for its ACTH-suppressing and cortisol-suppressing effect, leading to symptoms of iatrogenic adrenal insufficiency. MPA is classically initiated in the form of depot deep intramuscular injections, at a low dose of 50 mg/month that can be increased up to 400 mg/month [55,78].

Another treatment option is the use of a histrelin subcutaneous implant of GnRH agonist developed to decrease the monthly hospital visits. Rosati *et al.* [79] and Silverman *et al.* [80] pointed that the use of a histrelin subcutaneous implant for controlling CPP is safe and effective. Additional options are antiestrogens (tamoxifen) or aromatase inhibitors (anastrozole). Moreover, pamidronate constitutes an option in the treatment of fibrous dysplasia in McCune–Albright syndrome [81,82].

Conclusion

PP is a not an uncommon problem seen in clinical practice and its diagnosis and management still remain a challenge. There is a need for establishment of cutoffs for diagnosis, treatment, and follow-up of these children.

Acknowledgements

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