

Central Precocious Puberty in Girls: Diagnosis, Management and Outcome

Somchit Jaruratanasirikul, M.D.

Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

ABSTRACT

Puberty is a normal physiological process of during which children develop secondary sex characteristics, experience growth acceleration, and achieve bone maturation and reproductive competence. The onset of puberty is initiated by the activation of the hypothalamic–pituitary–gonadal (HPG) axis. Precocious puberty is defined as the appearance of secondary sex characteristic at an age younger than 8 years in girls and 9 years in boys, or the beginning of menstruation before 9 years in girls. The most common etiology of central precocious puberty (CPP) is idiopathic (>90.0% in girls and 25.0–60.0% in boys), in which at present the etiologies of idiopathic CPP in some patients can be identified to be from a mutation of *KISS1* or *MKRN3* genes. The standard treatment for CPP is a gonadotropin–releasing hormone analog (GnRHa). The aims of treatment are to halt and regress the pubertal status of the patient to the prepubertal state that is appropriate for their age, prevent early onset of menses and attenuate the loss of height potential consequence upon advanced skeletal maturation. A study of long–term follow–ups of former CPP women at the age of mid–20s to 50 years found that most of the participants had regular menstrual cycles. The marital status and the pregnancy rate were the same as in controlled group and were not different between the GnRHa–treated and untreated CPP women.

Keywords: gonadotropin; gonadotropin–releasing hormone; precocious puberty; puberty

INTRODUCTION

Puberty is a normal physiological process during which children develop secondary sex characteristics, experience growth acceleration, and achieve bone maturation and reproductive competence. The onset of puberty is initiated by the activation of the hypothalamic–pituitary–gonadal (HPG) axis as a result of a complex neuroendo-

crine regulation in a process which has not yet been completely elucidated.^{1–3} In girls, the tempo of pubertal development begins with thelarche, followed by growth spurt, pubarche and menarche, whereas in boys pubertal development begins with testicular enlargement, followed by pubarche and a peak growth spurt.

Corresponding author: Prof. Somchit Jaruratanasirikul, M.D.
Department of Pediatrics, Faculty of Medicine, Prince of Songkla University,
Hat Yai, Songkhla 90110, Thailand
E-mail: somchit.j@psu.ac.th
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Precocious puberty is defined as the appearance of secondary sex characteristic at an age younger than 8 years in girls and 9 years in boys, or the beginning of menstruation before 9 years in girls.⁴⁻⁶ The exact incidence of precocious puberty is not known because of the overlapping of pathological precocious puberty and normal pubertal variants particularly in girls 7-8 years old. The clinical presentations in each category are different which leads to the necessity of specific laboratory investigations for definite diagnosis. This review focuses on only central precocious puberty in girls.

NORMAL PHYSIOLOGICAL CONTROL OF THE ONSET OF PUBERTY

Puberty is initiated with a sustained increase in pulsatile release of gonadotropin-releasing hormone (GnRH) from GnRH neurons located in the preoptic area and infundibular nucleus of the hypothalamus.¹⁻³ There are many neurotransmitters which regulate the GnRH neuron secretory pattern, with excitatory or inhibitory effects on GnRH secretion. During childhood, the GnRH neurons are in a quiescent state regulated by an inhibitory network of neurotransmitters, mainly γ -aminobutyric acid (GABA) and *makorin ring finger protein 3 (MKRN3)*. At the onset of puberty, the excitatory system network is augmented, mainly by glutamate and kisspeptin, while the inhibitory system deteriorates in its activities. The physiological control of the onset of puberty by various factors is shown in Figure 1

The kisspeptin system network

Since the discovery of kisspeptin in 2003, many studies have shown that kisspeptin is a potent activator regulating GnRH release from the GnRH neurons of the hypothalamus, and it is postulated to function as a gatekeeper controlling the timing of pubertal onset. Kisspeptin is encoded by the *kisspeptin* gene (*KISS1*). GnRH neurons express the kisspeptin 1 receptor (*KISS1R*)

and are highly sensitive to kisspeptin. Gain-of-function mutations in *KISS1* have been identified in girls with idiopathic central precocious puberty (iCPP), confirming the importance of the kisspeptin system (*KISS1* and *KISS1R*) on the timing of pubertal onset.⁷ Moreover, circulating plasma kisspeptin levels have been shown to be higher in girls with iCPP than in the normal prepubertal girls.⁸ A recent study found that kisspeptin neurons coexpress two specific neuromodulators, neurokinin B (NKB) and dynorphin (Dyn). NKB and Dyn have been identified in kisspeptin neurons and have been named as Kisspeptin, Neurokinin B and Dynorphin neurons (KNDy: Kiss/NKB/Dyn) neurons.⁹ Research studies on the role of NKB and Dyn on *KISS1* and the kisspeptin system are now ongoing in an effort to expand our knowledge of the various factors controlling the HPG axis.

Makorin ring finger protein 3

The first identified gene with an inhibitory effect on GnRH secretion in human beings was *Makorin ring finger protein 3 (MKRN3)* located on human chromosome 15q11-13. A recent study showed that serum MKRN3 concentrations were low before the onset of puberty in normal girls and low MKRN3 levels were observed in girls with iCPP.¹⁰ At present, a loss-of-function mutation of *MKRN3* is the most common known genetic cause of iCPP, particularly familial CPP.¹¹

Neuropeptides and metabolic factors controlling GnRH secretion

Various studies have found that overweight or obese girls enter puberty at an earlier age and undernourished girls enter puberty at a later age than girls with average weight, indicating that body weight and nutritional status play a role in the action of the HPG axis and the age at onset of puberty.¹²⁻¹⁵ A recent study showed that leptin involved in the pubertal development through a permissive metabolic signal helping to activate the kisspeptin network.¹⁶

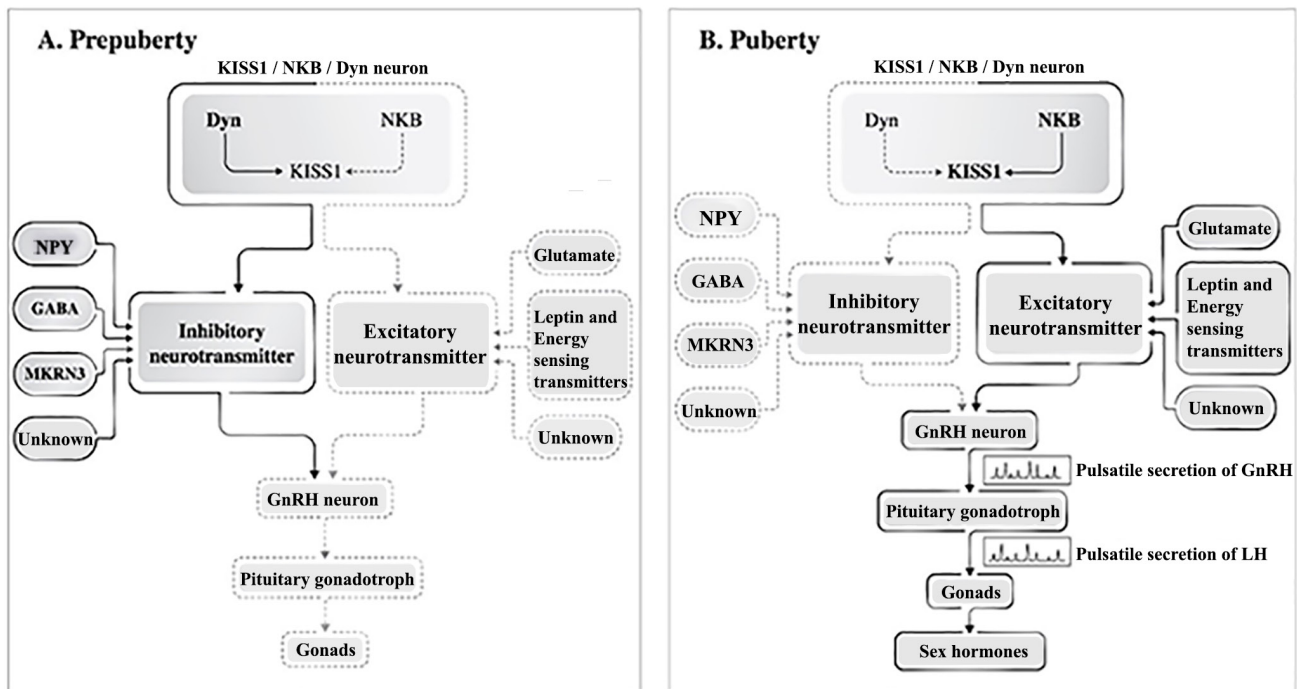


Figure 1 Factors controlling hypothalamic–pituitary–gonadal axis
A.Prepuberty B.Puberty

GnRH = gonadotropin-releasing hormone; MKRN3 = Makorin ring finger protein 3; GABA = gamma-aminobutyric acid; NPY = neuropeptide Y; Dyn = dynorphin; NKB = neurokinin B; KISS1 = kisspeptin1; LH = luteinizing hormone

Various studies on the involvement of other neuropeptides regulating the pubertal onset such as neuropeptide Y, ghrelin, melanocortin, neuroestradiol, etc, are ongoing.¹⁻³

ETIOLOGIES

The most common cause of CPP is idiopathic (iCPP), in >90.0% of affected girls and 25.0–60.0% of affected boys. Brain pathological abnormalities such as cerebral palsy or hydrocephalus or post-cranial irradiation have been identified as associated with an increased risk of CPP.^{4-6,17,18} In recent years, iCPP has been found to be caused by a gain-of-function mutation of *KISS1* or a loss-of-function mutation of *MKRN3*.^{11,17} The various known etiologies of CPP are summarized in **Table 1**.

Table 1 Etiologies and disorders giving increased risk of central precocious puberty^{17,18}

Idiopathic (>90.0% in girls, 25.0-60.0% in boys)
- Gain-of-function <i>KISS1</i>
- Loss-of-function <i>MKRN3</i>
- Idiopathic or unidentified genes or neurotransmitters
Hypothalamic hamartoma
Central nervous system abnormalities
- Congenital hydrocephalus
- Cerebral palsy
- Post cranial irradiation
Central nervous system tumor
- Germinoma

Note: *KISS1* = kisspeptin 1; *MKRN3* = Makorin ring finger protein 3

DIAGNOSIS AND LABORATORY TESTS

The main clinical presentations in girls with CPP is early breast development (60.0–70.0%), followed by earlier menstruation (20.0–30.0%), and in boys the main presentation is penile enlargement with the presence of pubic hair (100%).^{4–6,17,18} The average age at the time of diagnosis is 6–8 years with the ranges of 1–9 years. Patients with hypothalamic hamartoma usually present at a younger age of 1–4 years while those with iCPP usually present at the average age of 6–8 years. All CPP patients have advanced bone age of 2–4 years. Most patients with CPP, except those with underlying brain abnormalities, have weight and height at or above the 97th percentile of the general population of the same age and sex. Growth acceleration and advanced bone age are the typical clinical signs indicating CPP.^{19–28}

Hormonal evaluation regarding the activation of the HPG axis is necessary for the diagnosis of CPP. The standard laboratory test used to verify HPG activity is the basal luteinizing hormone (LH) level or the LH response to a standard 0.1 µg GnRH stimulation test. With the chemiluminescent assay, a basal peak LH level of >0.3 IU/L or a peak LH after a GnRH test of >5.0 IU/L indicates pubertal development in both boys and girls.^{19–28} A recent study in 2020 by Wankanit et al. suggested a cut-off basal LH level of 0.2 IU/L for CPP diagnosis with a sensitivity and specificity of 90.0–95.0%.²⁹

Brain pathology has been identified in 5.0–15.0% of CPP girls and 50.0–100% of CPP boys. The most common brain pathology is a hypothalamic hamartoma. Using the cut-off age of 6 years, various studies found no brain lesions in CPP girls >6 years old at the time of initial evaluation.^{19–28,30} Therefore, an MRI brain scan is recommended in all boys and girls <6 years with CPP.

MANAGEMENT

Without treatment, precocious puberty can result in physical growth acceleration, advanced bone age,

premature closure of the epiphyseal plate, and shorter adult height than their genetic potential.^{19–28} The aims of treatment are to halt and to regress the pubertal status of the patients to the prepubertal state that is appropriate for their age, prevent early onset of menstruation and attenuate the consequent loss of height potential upon advanced skeletal maturation. The standard treatment for CPP is gonadotropin-releasing hormone analog (GnRHa), a synthetic decapeptide that binds to the GnRH receptors in the pituitary with more stability and longer half-life than natural GnRH.^{4–6} The mechanism of high-dose GnRHa treatment is suppression of the episodic release of GnRH from the hypothalamus and downregulation of the pituitary GnRH receptors resulting in suppression of the HPG axis. GnRHa treatment is recommended in CPP patients who have advanced bone age at the time of initial evaluation <12.5 years in girls or <14 years in boys for the purpose of height preservation. GnRHa is not recommended for treatment of CPP in patients with markedly advanced bone age of >12.5 years in girls or >14 years in boys at the time of diagnosis since there are no beneficial outcomes in of HPG axis suppression or height preservation beyond these ages.^{4–6,31} In treated patients, GnRHa should be discontinued when the patient is at the appropriate age to resume normal pubertal development or when their calculated predicted final adult height is at about their target height or their bone age >12.5 years in girls or >14 years in boys. The benefit of height preservation by GnRHa of CPP girls has been widely demonstrated ranging from 2–11 cm (Table 2). The experience of treatment in CPP patients at our hospital, Songklanagarind Hospital, a major tertiary care and teaching hospital in southern Thailand, found that GnRHa-treated girls reached their final height at their genetic potential whereas untreated girls were 4–10 cm lower in height than their genetic potential.

Table 2 Comparison of the results of gonadotropin-releasing hormone analog (GnRHa) treatment in previous studies^{19–28}

Study (year of study)	N	Chronological age at start of treatment (yr)	Bone age at start of treatment (yr)	Duration of treatment (yr)	Target height (cm)	Predicted final height (cm)	Final adult height (cm)
Carel ¹⁹ (1999)	58	7.5	10.1	3.7	160.1	156.4	161.1
Cassio ²⁰ (1999)	23	8.5	10.6	2.0	157.0	157.8	158.1
Klein ²¹ (2001)	80	5.4	10.0	5.7	164.0	149.0	160.0
Tanaka ²² (2005)	63	7.7	10.2	3.8	154.9	154.5	154.5
Pasquino ²³ (2008)	44	8.1	11.1	4.7	157.1	155.2	160.9
Brito ²⁴ (2008)	45	7.3	10.6	3.2	157.5	160.6	155.3
Magiakou ²⁵ (2010)	33	7.9	10.0	2.7	158.0	158.2	158.5
Jaruratanasirikul ²⁶ (2011)	32	6.8	10.7	2.9	152.7	147.2	152.4
Poomthavorn ²⁷ (2011)	47	8.5	11.1	3.4	155.8	155.3	158.6
Lee ²⁸ (2011)	30	7.3	10.2	3.7	163.8	157.4	162.5

A 2016 International Consensus recommendation on the use of GnRHa in children was that GnRHa should be discontinued at a chronological age of 10–10.5 years, at which time the bone age is 12–13 years, since there is no benefit of further height gain after that.³¹ Furthermore, long-duration HPG axis suppression in adolescence, the period of peak bone mass accretion, would risk osteopenia and decreased bone mass. The average age at menarche in GnRHa-treated girls is 11–13 years, the same age as menarche in normal girls, whereas the average age at menarche in untreated CPP girls is 10–11 years, significantly earlier than in the normal girls. The average time interval from the cessation of GnRHa treatment to the resumption of menstruation is 0.9–2.0 years.^{19–28} Moreover, girls who began menstruation before treatment have a shorter time interval to resumption of menstruation than those who had never menstruated before treatment (0.7 and 1.6 years, respectively).²⁶

FOLLOW-UP IN THE ADULTHOOD

Long-term follow-up studies of former CPP women at the ages of mid-20s to 50 years have found that most of the participants (75.0–85.0%) had regular menstrual cycles with the average interval between cycles of 28–32 days and days of menstrual bleeding of 3–5 days.^{32–35} The marital status and the pregnancy rates were the same as in the controlled groups and were not different between the GnRHa-treated and untreated women. A study on former CPP women, at the ages of 16–30 years, at Songklanagarind Hospital found that 85.0% of the participants had regular menstruation and no participants had breast or uterine diseases.³⁵ Of the married women, 43.0% were fertile with 1–2 healthy children indicating normal reproductive function in both GnRHa-treated and untreated women. The lower fertility rate in our study was likely due to the low number of participants, most of whom at the time being single and still studying in high

school, college or university, and those who were married using contraceptive pills. To confirm normal reproductive function and fertility of our former CPP participants, further follow-ups in the next 10–20 years when they have reached mid-adulthood will be required.

There is no confirmed evidence that former CPP women, either GnRHa-treated or untreated, are more likely to develop polycystic ovary syndrome (PCOS) than the age-matched women. High prevalences of PCOS of 17.2% in former GnRHa-treated CPP women and 30.8% in untreated CPP women at ages of 20–40 have been reported.³³ The prevalence of PCOS is estimated to be between 6.0–8.0% in reproductive-age women worldwide.^{36,37} In our study on CPP girls, PCOS was found in only 3.0% of both the GnRHa-treated and the untreated women. This low prevalence for PCOS, the same in both treated and untreated women, suggests that CPP is not a risk factor of PCOS, at least at the age of early adulthood, which was a finding also in the study of Jensen et al that CPP girls were not at risk to develop PCOS either before, during or after GnRHa treatment.³⁸

Some previous studies reported significant increases in BMI and higher prevalence rates of obesity of 20.0–40.0% in CPP girls at the end of GnRHa treatment^{23,33,34} while other studies reported no increase in BMI after GnRHa treatment.^{25,27} Some studies of long-term follow-up of former CPP women at the ages of 20–36 years reported higher BMIs and increased prevalences of obesity in untreated women than in GnRHa-treated women.^{25,27,33} In our experience, both the GnRHa-treated and untreated women had similar weight gains from 51–52 kg at the time of reaching final height at 11–13 years to 57–58 kg at the age of 16–30 years, although the percentage of obesity as defined by BMI >25 kg/m² was significantly higher in the untreated women than in the GnRHa-treated women.³⁵ This finding would seem to indicate that the higher weight gain and prevalence of obesity in the former CPP women was not

related to the GnRHa treatment. The higher percentage of participants with BMI >25 kg/m² in the untreated CPP women at the time of reaching final height and after 12 years of follow-up could be explained by the shorter average final height compared to the GnRHa-treated women. These findings support the belief that GnRHa treatment in CPP girls can preserve the height potential, preventing shorter final height than the target height resulting in the proper proportion of weight and height, thus lower BMI, and decreased prevalence of obesity.

CONCLUSIONS

Most cases of central precocious puberty (CPP) in girls are idiopathic, with the common known etiologies being mutations of the *KISS1* or *MRKN3* genes. Gonadotropin-releasing hormone analog (GnRHa) is the treatment of choice for CPP as it can regress the pubertal status, thus allowing final adult height to reach the genetic potential. Long-term follow-up studies of former CPP women at the ages of mid-20s to 50 years have found regular menstrual cycles and normal reproduction function in most of the study women as shown by the same pregnancy rates as in the controlled groups. To date, there has been no clear evidence that polycystic ovary syndrome (PCOS) is more likely to occur in former CPP women, whether GnRHa-treated or untreated. The prevalence of obesity as defined by BMI >25 kg/m² is higher in untreated than GnRHa-treated former CPP women, which can be explained by the shorter average final height in the untreated women.

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