Review article

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# 2022 Clinical practice guidelines for central precocious puberty of Korean children and adolescents

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The Committee of Central Precocious Puberty of Korean Pediatrics and Adolescents of the Korean Society of Pediatric Endocrinology has newly developed evidence-based 2022 clinical practice guidelines for central precocious puberty in Korean children and adolescents. These guidelines provide the grade of recommendations, which includes both the strength of recommendations and the level of evidence. In the absence of sufficient evidence, recommendations are based on expert opinion. These guidelines have been revised and supplement the previous guidelines "Clinical Guidelines for Precocious Puberty 2011," and are drawn from a comprehensive review of the latest domestic and international research and the grade of recommendation appropriate to the domestic situation. This review summarizes the newly revised guidelines into 8 key questions and 27 recommendations and consists of 4 sections: screening, diagnosis, treatment, and long-term outcome of central precocious puberty.

Keywords: Precocious puberty, Central precocious puberty, Practice guideline, Child, Adolescent, Korea

## Highlights

- Central precocious puberty accounts for the largest number of outpatient pediatric endocrine diseases, and is also a disease of high social interest. The newly revised "Clinical Practice Guidelines for Central Precocious Puberty 2022" has been revised and supplements the previous edition. The revisions present the level of evidence based on the latest domestic and international research and the grade of recommendation appropriate to the domestic situation.

## Introduction

Precocious puberty (PP) is defined as the onset of secondary sexual characteristics earlier than 2 to 2.5 standard deviations (SDs) of the mean. In general, PP is the onset of puberty in girls younger than 8 years old and boys younger than 9 years old, according to the criteria laid down by Marshall et al. in 1969.[1)] In epidemiological studies in Korea, a higher prevalence and incidence of central PP (CPP) have been reported. A study that analyzed 2004–2010 data reported a prevalence of 57.6 per 100,000 (females 55.9; males 1.7) and an incidence rate of 15.9 per 100,000 (females 15.3; males 0.6).[2)] However, in a study that analyzed 2008–2014

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data, the prevalence (193.2 per 100,000) and incidence (122.8 per 100,000) of CPP increased steeply each year.[3] The Korean Society of Pediatric Endocrinology (KSPE) developed "Clinical Guidelines for Precocious Puberty 2011" to standardize domestic CPP treatment and improve medical quality.[4] Now, 10 years after the publication of the first edition, the need to update the clinical practice guideline (CPG) to reflect the latest clinical research has emerged, and the Committee of CPP of Korean Children and Adolescents of KSPE was formed. The newly revised "Clinical Practice Guidelines for Central Precocious Puberty 2022" has been revised and supplements the previous edition. The revisions present the level of evidence based on the latest domestic and international research and the grade of recommendation appropriate to the domestic situation. This newly revised CPG uses 8 key questions (KQs) to summarize 4 sections: screening, diagnosis, treatment, and long-term outcome of CPP.

## Development of CPGs

The final decision of recommendation was made through the deliberation process of the committee and the review process of external experts. The level of evidence was modified according to the classification of the research design, and based on the SIGN level of evidence system (Table 1). In principle, all recommendations are based on evidence to determine the grade of recommendation. The grades of recommendation are defined as 4 grades through the blind voting methods of the committee by evaluating the degree of benefit and harm of the intervention based on evidence. The grade of the recommendation does not indicate the strength but denotes the generality of the recommendation. In the recommendation level, "Strong" means that most patients who are provided with sufficient information choose the intervention because the desirable effects are greater than the undesirable effects. "Conditional" means that it is uncertain whether the favorable effects of the intervention outweigh the undesirable effects, so that a fully informed patient can choose another intervention. Table 2 shows the 4-grade notations and meanings of the grade of recommendation.

**Table 1. Levels of evidence**

| Notation | Classifications based on research design |
|---|---|
| Randomized controlled study | Systematic review, meta-analysis, randomized controlled study |
| Nonrandomized controlled study | Cohort study, cross-sectional study, case-control study |
| Other | Others (case series, etc.) |
| Expert opinion | Expert opinions |

### Section 1: Screening for CPP

**KQ 1. When should pubertal progression and CPP be carefully monitored?**

**Recommendation 1-1. Consider careful observation for CPP in children with obesity (Randomized controlled study. Do, Conditional)**

Childhood obesity can cause hyperandrogenemia and insulin resistance, which can accelerate puberty.[5] The association between obesity and CPP is well-established in girls.[6] Although controversial in boys, a recent large-scale cohort study conducted in Denmark reported that obesity in boys is associated with early puberty.[7] However, in children with obesity, only bone age (BA) can be advanced without other physical changes of puberty, so it is necessary to differentiate it from CPP.[8]

**Recommendation 1-2. Consider careful observation for CPP in children born SGA or with IUGR (Randomized controlled study. Do, Conditional)**

In the case of children who are small for gestational age (SGA) or have intrauterine growth retardation (IUGR), there has been controversy over whether the onset of puberty is earlier than in peers or within the normal range.[9,10] In children born SGA, BA may be delayed at the onset of puberty, but caution is needed as BA can advance rapidly as puberty progresses.[11] More research is needed on the onset and progression of puberty in preterm or full-term infants with SGA or IUGR.[12]

**Recommendation 1-3. Consider careful observation for CPP, if there is a family history of early puberty (Nonrandomized controlled study. Do, Conditional)**

Several genes such as kisspeptin (*KISS1*), kisspeptin receptor (*KISS1R*), makorin ring finger protein 3, (*MKRN3*), and delta-like homolog 1 (*DLK1*) have been reported to be associated with CPP.[13] Some studies have reported a close relationship between the age of onset of puberty in parents and their children.[14] Therefore, history taking for parental puberty timing and progression should be conducted.

### Section 2: Diagnosis of CPP

**KQ 2. What tests are performed to diagnose CPP and how are**

**Table 2. Grades of recommendation**

| Grades of recommendation | Significance |
|---|---|
| Do, Strong | It is recommended for most patients. |
| Do, Conditional | It is recommended to selectively use it considering the benefit/harm/cost/preference of the patient. |
| Do not, Conditional | It is recommended to use it as a limitation, considering the benefit/harm/cost/preference of the patient. (It can be used on a limited basis, but caution is required.) |
| Do not, Strong | It is not recommended for most patients. |

**they interpreted?**

**Recommendation 2-1. BA measurement is recommended for the diagnosis of CPP (Nonrandomized controlled study. Do, Strong)**

When secondary sexual characteristics appear early and BA is beyond the chronological age (CA), BA measurement is helpful in diagnosing CPP and predicting adult height (PAH).[15,16] However, significant advanced BA (difference of more than 2 SDs from the CA) does not confirm CPP. Therefore, BA should be used as an auxiliary tool to help diagnose CPP.

**Recommendation 2-2. GnRH stimulation test is recommended for the diagnosis of CPP (Nonrandomized controlled study. Do, Strong)**

Gonadotropin-releasing hormone (GnRH) stimulation tests are performed to differentiate CPP from normal pubertal variants such as precocious thelarche or precocious adrenarche and to confirm activation of the hypothalamic-pituitary-gonadal axis. In Korea, CPP is defined as an increase of 2 to 3 times the baseline value after a luteinizing hormone release hormone (LHRH) stimulation test and a peak luteinizing hormone (LH) >5 IU/L. A short-acting GnRH agonist (triptorelin 0.1 mg) can be used instead of LHRH.[17] The diagnostic criterion is the same as peak LH > 5 IU/L, but it should be noted that the time to reach the peak LH is around 3 hours. In children with obesity, LH suppression may be seen in the GnRH stimulation test, so caution is needed in the interpretation.[18]

To diagnose CPP, clinical features such as sexual maturity rate (SMR) Tanner stage II or higher, accelerated growth velocity (GV), and advanced BA should be considered along with the GnRH stimulation test.

**Recommendation 2-3. Unstimulated LH measurement can be considered an auxiliary method for the diagnosis of CPP (Nonrandomized controlled study. Do, Conditional)**

Random unstimulated LH levels measured by ultrasensitive assays such as immunochemiluminometric assay (ICMA) or electrochemiluminescence immunoassay (ECLIA) are helpful in diagnosing CPP. Recent studies suggested unstimulated LH < 0.3 IU/L (ICMA method) as the pre-pubertal state[19] and unstimulated LH >0.83 IU/L (ICMA method) as the pubertal state.[20] In a domestic study of 803 subjects, unstimulated LH level > 1.1 IU/L (69.1% sensitivity, 50.5%, radioimmunoassay method) was the cutoff point related to pubertal response.[21] In addition, methods for diagnosing CPP using morning unstimulated LH levels have been reported, morning unstimulated LH > 0.11 IU/L (sensitivity 66.7%, specificity of 78.7%, chemiluminescence immunoassay method)[22] and LH > 0.22 IU/L (positive predictive value of 0.9, ECLIA method)[23] have been suggested as meaningful cutoff values. Since suppression of LH levels may occur in children with obesity, care should be taken in interpreting unstimulated LH levels.[18]

**Recommendation 2-4. Pelvic ultrasonography can be considered an auxiliary tool for the diagnosis of CPP (Randomized controlled study. Do, Conditional)**

As the increase in uterine length and ovarian volume in pelvic ultrasound reflects the stimulation of estrogen and gonadotropin, it can be used as an auxiliary diagnostic tool in patients suspected of CPP. In previous studies, a uterine length of 3.5–4 cm or more and an ovarian volume of 2 $cm^3$ or more have been considered appropriate for puberty. However, the results are inconsistent, and pelvic ultrasonography is highly influenced by the examiner.[24,25] A recent meta-analysis including 1,977 girls reported that when the length of the uterus is 3.2 cm or more, it could be used as a supplementary tool to distinguish between CPP and precocious thelarche with a sensitivity of 81.8% and a specificity of 82.0%.[26]

**Recommendation 2-5. Breast ultrasonography is not recommended for the diagnosis of CPP (Expert opinion. Do not, Strong)**

Breast ultrasonography is not recommended because it has no advantages over other testing methods. In addition, there are few related studies, and clinical results are not suitable as a CPP screening method.

**KQ 3. When should a brain MRI be performed to identify organic causes in patients with CPP?**

**Recommendation 3-1. Brain MRI is recommended for girls younger than 6 years of age who have been diagnosed with CPP, and for girls older than 6 years who have neurologic signs and symptoms suggesting a CNS abnormality (Randomized controlled study. Do, Strong)**

**Recommendation 3-2. Brain MRI is selectively considered for girls with an onset of puberty between the age of 6 and 8 years who have no neurological signs or symptoms suspicious of CNS abnormality (Nonrandomized controlled study. Do, Conditional)**

**Recommendation 3-3 Brain MRI is recommended for boys diagnosed with CPP (Nonrandomized controlled study. Do, Conditional)**

In girls, the prevalence of central nervous system (CNS) abnormalities decreases with age.[27] In a meta-analysis of 1,853 girls diagnosed with CPP, the incidence of brain magnetic resonance imaging (MRI) abnormalities was 7% overall, however, it was 25% in the group of girls that were younger than 6 years old and 3% in the 6 to 8 years old group. The most common brain MRI abnormality was hypothalamic hamartomas, and brain tumors were 1.6% of all age groups.[27] In a domestic study that analyzed brain MRIs of 317 girls diagnosed with CPP, 91.8% were normal and 8.2% discovered benign findings of the CNS (Rathke cleft cyst, pineal cyst, suspected pituitary hyperplasia, etc.), but there were no pathological CNS lesions.[28] Clinical factors that can predict abnormal findings on brain MRI in patients diagnosed with CPP have not yet been identified, but puberty onset before the

age of 6 was reported as the most likely predictor.[27]

In boys, the incidence of brain MRI abnormalities has been reported higher than that of girls, but recent studies have shown that the incidence of idiopathic CPP is increasing in boys, especially in boys recently diagnosed with CPP. In a study of 100 boys diagnosed with CPP, brain MRI abnormalities were found in 26%, most of which were diagnosed under the age of 7 years. When the diagnosis period was 2003–2005, the frequency of idiopathic CPP was 33.3%, but it showed a tendency to increase to 81.6% in 2012–2014.[29] In a domestic study that analyzed 138 boys diagnosed with CPP (average age at diagnosis, 9.51±0.56 years), brain MRI abnormalities were found in 7%, and no lesions requiring treatment were observed.[30] Recently, several studies have reported that the incidence of idiopathic CPP in boys has increased, but it should be considered that the average age at the time of diagnosis is 8 years or older in some studies. Further studies such as a meta-analysis or systematic review will be needed to predict the organic causes of CPP in boys.

## Section 3: Treatment of CPP

**KQ 4. What are the indications and considerations for treatment in patients with CPP?**

**Recommendation 4-1. An observation period of 3 to 6 months is recommended to evaluate the tempo of pubertal progression in patients with suspected CPP (Randomized controlled study. Do, Strong)**

Most patients with suspected CPP do not require treatment due to early or transient pubertal development; therefore, periodic observation is required to determine treatment.[31] Before treating CPP, the following should be discussed with parents and the patient to decide whether to treat or observe.[32]; (1) The decision on GnRH agonist treatment in patients with CPP depends on the age, rapid pubertal progression, SMR, accelerated GV, advanced BA, and loss of PAH. In general, slow progressive-precocious puberty (SP-PP) is not considered to change the stage of SMR during an observation period of 6 months or more.[33] In SP-PP, the BA progression and GV are not too fast, and the age of menarche may not be too early.

(2) In patients with CPP who are above average in height and do not have severely advanced BA, final adult height (FAH) is likely to be within the normal range and GnRH agonist treatment may not improve FAH significantly.

(3) The results of studies on height gain according to CPP treatment are diverse,[34] some studies have shown that girls treated for CPP after the age of 8 years do not show significant increases in FAH, and some may show decreases.[35-37]

**Recommendation 4-2. Treatment is recommended for rapid progressive-precocious puberty (Randomized controlled study. Do, Strong)**

Rapid progressive-precocious puberty is associated with highly accelerated pubertal development, premature menarche, and loss of FAH if untreated.[38,39] In a recent meta-analysis, treatment with a GnRH agonist in patients aged 6.3 to 9 years showed an increase in FAH of 3.2 cm. Among these patients, those with an average increase of 5.1 cm started treatment before the age of 8 years old, but those with an average increase of 2.5 cm started after the age of 8 years old.[40] There are few long-term data on FAH in boys because the prevalence is lower than in girls, but the average increase in FAH after GnRH agonist treatment was 6.2±8.7 cm, and the effect was better when the age at the start of treatment was younger.[41]

In contrast, treatment is not generally recommended for early puberty or SP-PP because the FAH without treatment is similar to the median parental height.[42] In addition, if BA has progressed significantly at the time of diagnosis, the height gain after treatment may be insignificant.

**Recommendation 4-3. Treatment is considered for girls with CPP that are at high risk for psychosocial stress due to early menarche (Nonrandomized controlled study. Do, Conditional)**

Early breast development and menarche can cause discomfort and psychological stress in girls, which can lead to problems such as depression, anxiety, and behavioral disorders.[43] However, it is difficult to identify the correlation between psychiatric problems and CPP clearly, and in long-term follow-up studies of patients with CPP, there was no significant difference in the level of psychosocial well-being in adulthood compared to the general population.[44] There are concerns about psychosocial stress due to CPP, but behavioral problems may be less common than expected.[45]

**KQ 5. What is the treatment for CPP?**

**Recommendation 5-1. GnRH agonist is recommended as a standard treatment of CPP (Nonrandomized controlled study. Do, Strong)**

**Recommendation 5-2. Leuprolide or triptorelin is recommended according to the usage and dosage approved in Korea (Randomized controlled study. Do, Strong)**

**Recommendation 5-3. Since there is no difference in the effects of GnRH agonists with different administration intervals,**

**Table 3. Gonadotropin-releasing hormone agonist formulations approved for use in central precocious puberty treatment in Korea**

| Ingredient | Dosing interval | Brand name |
|---|---|---|
| Triptorelin acetate | 4 Weeks | Decapeptyl depot injection 3.75 mg<br>Diphereline PR injection 3.75 mg |
| Triptorelin pamoate | 3 Months | Diphereline PR injection 11.25 mg |
| | 6 Months | Diphereline SR injection 22.5 mg |
| Leuprolide acetate | 4 Weeks | Lorelin depot injection<br>Leuplin injection 3.75 mg<br>Leuplin DPS injection 3.75 mg<br>Luphere depot injection 3.75 mg |
| | 3 Months | Leuplin DPS injection 11.25 mg |

**it is recommended to select a drug according to the situation (Randomized controlled study. Do, Strong)**

Currently, there are various GnRH agonist formulations with different doses and durations of action. The GnRH agonists approved for use in the treatment of CPP in Korea are summarized in Table 3. In the case of leuprolide, the dosage determined by body weight used in the past is not recommended due to a lack of evidence.[38] In recent domestic studies comparing the effects of 4-week and 3-month formulations of leuprolide or triptorelin, there was no difference in the effect between the formulations.[46,47]

**Recommendation 5-4. GnRH antagonists or aromatase inhibitors are not recommended due to insufficient evidence of their effectiveness (Nonrandomized controlled study. Do not, Strong)**

Neither GnRH antagonists nor aromatase inhibitors are approved for the treatment of CPP. In girls with CPP, it has been reported that LH inhibition is faster when anastrozole (aromatase inhibitor) is added or when a GnRH antagonist is combined with a GnRH agonist at the beginning of treatment, but mid- to long-term clinical results have not been reported.[48] Therefore, evidence for the use of GnRH antagonists or aromatase inhibitors in patients with CPP is insufficient.

**KQ 6. What are the precautions for GnRH agonist treatment in patients with CPP?**

**Recommendation 6-1. Consider maintaining GnRH agonist treatment if there are minor adverse effects that may occur temporarily during administration (Others. Do, Conditional)**

Systemic symptoms such as a headache or hot flashes may occur after the administration of a GnRH agonist, but these are usually transient and do not affect treatment.[49] Allergic or local adverse effects occur infrequently.[38] In a domestic study, four of 621 patients (0.6%) with CPP who received a GnRH agonist developed local adverse effects such as aseptic abscesses.[50] If local reactions persist, changing to another formulation is recommended. After the initiation of GnRH agonist treatment, transient withdrawal bleeding may occur. But if it persists for more than 2 months, other causes should be considered.[51]

**Recommendation 6-2. Immediate evaluation and treatment are recommended when SCFE, pseudotumor cerebri, or anaphylaxis occurs during GnRH agonist treatment (Others. Do, Strong)**

Risk factors for slipped capital femoral epiphysis (SCFE) are obesity, male sex, growth spurt, and prior radiation therapy. Since SCFE has been reported during or after treatment with a GnRH agonist, evaluation and treatment are required when complaining of pain.[50,52,53] There are few case reports of pseudotumor cerebri after the administration of a GnRH agonist, which were improved after the discontinuation of the GnRH agonist and treatment with acetazolamide and V-P shunt.[54,55] Anaphylactic reaction after the administration of a GnRH agonist is rare but requires immediate treatment, and it has also been reported in domestic studies.[50,56]

**Recommendation 6-3. GH combination treatment is considered optional when the growth rate is severely reduced during treatment or the prognosis for FAH is poor (Nonrandomized controlled study. Do, Conditional)**

In a meta-analysis including 1,268 patients, an untreated group, a group treated with the GnRH agonist alone, and a growth hormone (GH) combination treatment group were compared.[57] The GH combination treatment group was 1 cm taller than the GnRH agonist monotherapy group and 3.3 cm taller than the untreated group. In a domestic study of 166 patients with CPP, the average age at the start of treatment was 7.89 years, and additional height gain was reported in a GH combination therapy group compared to a GnRH agonist monotherapy group.[58] However, GH combined therapy can cause stress related to long-term self-injections for patients and a burden of cost for parents. Furthermore, differences in effects and adverse effects according to GH treatment may occur depending on the patient's situation and should be selectively considered when the prognosis for FAH is poor. It is recommended that pediatric endocrinologists, patients, and families fully discuss the benefits, risks, and costs of GH combination therapy to determine treatment.[48]

**KQ 7. What are the appropriate periodic evaluation and treatment lengths for GnRH agonists in patients with CPP?**

**Recommendation 7-1. It is recommended to evaluate the effects of GnRH agonist treatment every 3 to 6 months (Nonrandomized controlled study. Do, Strong)**

**Recommendation 7-2. If treatment failure is suspected, re-evaluation should be considered sooner (Nonrandomized controlled study. Do, Conditional)**

The effect of a GnRH agonist can be seen after 2 to 6 months of treatment, and when it is effective, the progression of secondary sexual characteristics stops and the GV decreases to pre-pubertal levels.[59,60] On physical examination, it is important that the SMR of the breast/testis does not progress, but pubic hair may not change or may be progressed by normal adrenal cortex maturation.[49] Measurement of basal or stimulated LH, estradiol/testosterone, and BA are also considered. It is helpful to measure BA every 6 months to one year.[61] According to some studies, treatment failure can be considered if basal LH > 0.6 IU/L, or estradiol > 30 pg/mL (girls)/testosterone > 30 ng/dL (boys), and stimulated LH > 4 IU/L.[20,62] However, several studies have shown that measurements of basal or stimulated LH or estradiol/testosterone alone are not helpful in determining treatment effectiveness, and an increase in results compared to pre-pubertal levels does not necessarily indicate treatment failure.[63] Therefore, it is necessary to evaluate treatment effects on the overall condition of the patient, including laboratory tests and physical examinations. Treatment failure is determined by a combination of SMR and BA progression, lack of slowing down GV, and unsuppressed hormonal testing, in which a case

re-evaluation of treatment effect is required.

**Recommendation 7-3. It is recommended to determine when to discontinue GnRH agonist treatment by considering several factors including CA, BA, recovery of puberty, and FAH (Nonrandomized controlled study. Do, Conditional)**

Based on BA, GnRH agonist treatment until 12 to 12.5 years in girls and 13 to 14 years in boys is the most helpful for FAH.[41,64-66] In general, the longer the treatment period, the higher FAH, but in girls who are treated with GnRH agonist after a CA of 13 years, no further increase in FAH is observed and even a negative correlation may be shown.[38,67,68] In girls with CPP, menarche is predicted after an average of 12 to 18 months after the completion of treatment and may begin after a few months or be delayed as long as 2 years.[58,69] It is recommended that the discontinuation of GnRH agonist treatment be decided after providing information about the FAH and pubertal progression to the guardians and patients, as well as an achievement of appropriate BA or CA.

**Recommendation 7-4. Consider evaluating pubertal recovery and growth after the GnRH agonist treatment (Expert opinion. Do, Conditional)**

After GnRH agonist treatment, regular follow-up is recommended until the FAH is reached and the recovery of gonadal function is confirmed (for girls, until menarche).

### Section 4: Long-term outcome of CPP

**KQ 8. Is the treatment with a GnRH agonist associated with an increased risk of other diseases in the long term?**

**Recommendation 8-1. GnRH agonist treatment does not affect reproductive function nor increase the risk of PCOS in patients with CPP (Randomized controlled study. Do not, Strong)**

Evidence that GnRH agonist treatment is associated with reduced fertility or increased infertility is lacking. The reproductive function returns to normal with menarche and regular ovulatory menstruation after GnRH agonist treatment in most girls, except in some cases with structural abnormalities of the pituitary gland.[70] In studies that compare the group with CPP who received GnRH agonist treatment, the group with CPP who did not receive treatment, and a control group, all 3 groups gave birth without problems, and there was no difference in the rate of spontaneous pregnancy between groups.[71,72] Although there are limited data on reproductive function in males treated with a GnRH agonist for CPP, testosterone, gonadotropins, and semen analysis have been reported to be in the normal range.[73] The evidence that polycystic ovary syndrome (PCOS) occurs more frequently in patients with CPP compared to normal controls is not clear, and in a recent meta-analysis, the incidence of PCOS was no different between GnRH-treated and untreated groups.[74,75] Therefore, long-term evaluation and monitoring for reproductive function or PCOS in patients with CPP are not recommended.

**Recommendation 8-2. GnRH agonist treatment does not affect metabolic disease, bone health, or mental health in patients with CPP (Randomized controlled study. Do not, Strong)**

It has been reported that body fat increases at the beginning of treatment with a GnRH agonist, but there is no difference in body mass index (BMI) after treatment.[76] In long-term studies, the body weights of patients with CPP were similar to that of the general population regardless of treatment, and high BMI at diagnosis was associated with overweight or obesity in adulthood. Therefore, GnRH agonist treatment does not appear to have any long-term effects on obesity in adulthood.[71,75] In previous studies, it was reported that patients with CPP had higher bone mineral density (BMD) than peers at the time of diagnosis and that BMD decreased during GnRH agonist treatment.[77,78] However, BMD in late adolescence after treatment was within the normal range, and it does not appear to affect BMD in the long term.[78,79]

Some studies have reported that prolonged exposure to estrogen in girls with early puberty may be associated with an increased risk of breast cancer, obesity, type 2 diabetes, cardiovascular disease, and other malignancies.[80] However, these studies have limitations in that they did not adjust confounding factors such as obesity and exposure to other endocrine disruptors, so further research is needed on the effects of GnRH agonist treatment on these diseases. Taken together, long-term evaluation and monitoring for metabolic disease, bone health, or mental health in patients with CPP is not recommended.

## Conclusion

CPP is one of the most common pediatric endocrine diseases, and it is of high social interest due to its increasing prevalence and incidence every year. The second edition of 2022 CPGs for the CPP of Korean children and adolescents has been revised and supplements the previous edition based on the latest domestic and international research. These guidelines will help pediatricians standardize the diagnosis and management of CPP in Korean children and adolescents.

## Notes

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