Review Article

A narrative review: treatment outcomes of central precocious puberty (CPP)

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Central precocious puberty (CPP) is defined as the onset of breast development (thelarche) before age 8 years in girls and testicular development (gonadarche) before age 9 years in boys due to early activation of the hypothalamic-pituitary-gonadal (HPG) axis. In most cases, the exact etiology of CPP is not known. In girls, CPP is commonly idiopathic. In contrast, CPP in boys is likely pathologic. Gonadotropin-releasing hormone agonists (GnRHa) are the gold standard treatment of CPP, with the main objective to halt the pubertal progression and delay skeletal maturation preserving final adult height. In this narrative review, our focus is to review the treatment outcomes of GnRHa on adult height, reproductive function, BMI, cardiovascular and bone health in patients with CPP after brief description of CPP, etiology, and diagnosis.

Methods: Literature was searched from PubMed using appropriate search terms. A total of 61 articles published in English were included in this review.

Key Content and Findings: We identified a total of 388 articles between 1990 and 2021. Of those, sixty-one articles were selected for inclusion based on their relevance to the aim of this article.

Conclusions: While the safety and efficacy of GnRHa are well known, there continues to be conflicting data on long-term outcomes in treated patients. In general, long-term outcomes appear to be favorable with minimal adverse outcomes regarding menstrual and reproductive function, polycystic ovarian syndrome, metabolic concerns, and bone health.

Keywords: Central precocious puberty (CPP); GnRH agonists; menarche; adult height

Received: 03 November 2021; Accepted: 10 March 2022; Published online: 21 March 2022.
doi: 10.21037/pm-21-105
View this article at: https://dx.doi.org/10.21037/pm-21-105

Introduction

Puberty is a period of development of secondary sex characteristics and maturation of the reproductive system. Timing of puberty is determined by genetic and environmental factors. Precocious puberty is when a child starts to show signs of puberty earlier than what is considered the normal timing of initiation. Worldwide, the declining age of onset of puberty in children has been noticed since the early 20th century. In Northern Europe, the average age of menarche was recorded as late as 17 years in the early 19th century (1). By the mid-20th century, the age for menarche dropped to 12–12.5 years (1,2).

Precocious puberty remains one of the most common indications for referral to pediatric endocrinology. Fortunately, not all these referrals are true precocious puberty. Epidemiologic studies regarding the incidence of precocious puberty are limited. One study from Denmark

reported that the prevalence of some form of precocious pubertal development was 0.2% in girls and less than 0.05% in boys (3). However, when inclusion criteria were limited to central precocious puberty (CPP) also called gonadotropin-dependent puberty, the incidence of CPP was 5.66 cases per million person-years at risk, with an annual incidence ranging between 0.02 and 1.07 new cases per 100,000 (4). Overall, CPP is more common in girls with a female to male ratio of 10:1 (5). A retrospective analysis of 104 US children (87% girls) who were examined by a single pediatric endocrinologist for CPP showed that 9% (all girls) of them had true precocious puberty (6).

In this article, we review the treatment outcomes of GnRH agonists (GnRHa) on adult height, reproductive function, BMI, cardiovascular, and bone health in patients with CPP after briefly discussing the definition, etiology, and diagnosis of CPP. We present this article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-105/rc).

Methods

We searched PubMed for articles published in English between 1990 and 2021. Articles ranged from studies, meta-analyses, retrospective studies, and reviews. Search terms included but were not limited to a combination of the following words: "central precocious puberty", "GnRHa", "adult height", "treatment central precocious puberty", "menarche". There were no affiliations or conflicts of interest with the authors of the articles used.

A total of 388 articles were identified as relevant to our review. Of those, sixty-one articles were selected based on their relevance to the aim of this review.

Definition

Precocious puberty is described as the onset of breast development (thelarche) before age 8 years in girls and testicular development (gonadarche) before age 9 years in boys due to early activation of the hypothalamic-pituitary-gonadal (HPG) axis. The age limits for girls and boys were derived from the epidemiologic studies in the 1940s and 1970s (7). While the latest studies have shown that the onset of puberty in girls continues to downtrend, the average menarchal age did not change over the last 50 years (7,8). Similarly, the mean age at the onset of puberty in boys also has declined but only by a few months (9,10). Many factors have been attributed to the earlier onset of puberty including increased incidence of childhood obesity, pre-and postnatal exposure to endocrine disrupters, and stress (2,11).

Etiology

To date, what exactly triggers activation of the HPG axis remains poorly understood. Genome wide association studies have identified numerous genes that affect pubertal timing.

Kisspeptin, encoded by the *KISS1* gene, is a family of neuropeptides in the hypothalamus and is one of the key players in the initiation of puberty (12,13). Increased production of kisspeptin instigates and regulates gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus. Neurokinin B and dynorphin A are other essential neuropeptides for pubertal onset and progression (12,14,15) and co-expression with kisspeptin is referred to as "KNDy neurons" (16).

While inactivating mutations of kisspeptin receptor (*KISS1R*) cause isolated hypogonadotropic hypogonadism (IHH) (17), *KISS1R*-activating mutations have been described in CPP) (18). New genes are being investigated for their involvement in pubertal development. Three specific genes, *MKRN3*, *DLK1*, and *KCNK9* have been linked to dysfunction in the kisspeptin system that disinhibits the activation of the HPG axis in both familial and *de novo* forms of CPP (13).

The etiology of CPP in girls is mostly idiopathic, comprising about 90% of cases (19). In contrast, boys with CPP are more likely to have an underlying pathology (20). International adoption and several genetic syndromes are also associated with CPP (19,21). Another broad category of etiology of CPP is an injury to the central nervous system. This can be caused by pathologies such as congenital anomalies, tumors, ischemic insults, trauma, infection, and edema (13). While rare, the most common tumors associated with CPP involve the hypothalamus or the pituitary gland. Cranial radiotherapy is also a risk factor for CPP. Though tumors make up a small percentage of the overall CPP cases, the prevalence of CPP is almost 30% in these populations (22). *Table 1* summarizes the causes of precocious puberty.

Diagnosis

While the discussion of CPP diagnosis is beyond the scope of this review, it is worth acknowledging the challenges that present with diagnosis, especially when luteinizing

Table 1 Causes of precocious puberty

Central precocious puberty (GnRH-dependent, true puberty)	Peripheral precocious puberty (GnRH-independent, peripheral precocious puberty)	Variants of precocious puberty
Idiopathic	Females: ovarian cyst; granulosa cell tumor	Premature thelarche
CNS abnormalities: congenital (hypothalamic hamartoma, septo-optic dysplasia, hydrocephalus, arachnoid cyst, suprasellar cyst); acquired (tumors, abscess, infections, trauma, irradiation, granulomatous diseases)	Males: Sertoli-Leydig cell tumors; HCG secreting tumors; familial male-limited precocious puberty	Premature adrenarche
Syndromes: Sturge-Weber syndrome; neurofibromatosis type 1; tuberous sclerosis; Pallister-Hall	Both males and females: adrenocortical tumors; McCune Albright syndrome (rare in males); primary hypothyroidism; exogenous steroids and endocrine disruptors; glucocorticoid resistance	Premature menarche
Genetics: activating mutations of *KISS1* gene and its receptor; inactivating mutations of *MKRN3* and *DLK1* genes		
Environmental: chronic exposure to sex steroids; international adoption		

CNS, central nervous system; HCG, human chorionic gonadotropin.

hormone (LH), the most reliable biochemical parameter, is prepubertal in the setting of clinically progressive puberty. GnRH stimulation test was developed to differentiate central from peripheral precocious puberty (23). It is also a helpful tool to monitor the adequate suppression of the HPG axis in patients who are treated with GnRHa for CPP.

Treatment

GnRHa were developed shortly after the discovery of the amino acid sequence of GnRH and have been used in clinical medicine since then (24). GnRHa are the mainstay of treatment for CPP. They occupy the GnRH receptors causing desensitization of pituitary gonadotrophs followed by suppression of gonadotropin secretion, and eventually reducing the gonadal steroid hormone levels to prepubertal levels (25).

The goals of treatment are to preserve the adult height potential and prevent/alleviate psychosocial sequelae and stress (26,27). Therefore, girls younger than 7 years and boys younger than 9 years with progressive CPP or findings of advanced puberty require GnRHa treatment; such evidence includes Tanner stage III breast or genital development with evidence of accelerated growth at their first visit (26,28). Many girls with breast bud development between 7 and 8 years do not have rapid pubertal progression and therefore do not need treatment with GnRHa (29). Before deciding treatment with GnRHa in these age groups, it is important to document whether it is a rapid progression of puberty, and the final height is then compromised.

Treatment with GnRHa is generally considered safe, well-tolerated, and effective. The most common reported adverse effects of GnRHa are allergic or local reactions including sterile abscess, hot flushes, withdrawal bleeding, convulsions, and slipped capital femoral epiphysis. While prolonged QT interval and pituitary apoplexy are rare complications of GnRHa treatment, they have been reported only in adult males treated with GnRHa for prostate cancer (28). Pseudotumor cerebri is another rare complication of GnRHa treatment and reported in two cases with CPP; first in a 6-year-old girl who developed pseudotumor cerebri after the 4th dose of triptorelin acetate (30), and second case, in another 6.5-year-old girl treated with leuprolide acetate (31).

Currently, intranasal, subcutaneous, and intramuscular forms of GnRHa are available (*Table 2*). The depot forms of GnRHa are preferred due to fewer injections and better compliance (27).

Treatment outcomes

Final adult height

Final adult height is one of the most often measured standards to determine the efficacy of CPP treatment with GnRHa. It is also one of the few measures that consistently shows statistically significant improvement with timely

Table 2 GnRH analogs (GnRHa)

Medication	Frequency	Route of administration
Leuprolide acetate	Lupron Depot-PED®: monthly, 3-monthly	Intramuscular (monthly and 3-monthly)
	Fensolvi®: 6-monthly	Subcutaneous (6-monthly)
Triptorelin pamoate (Triptodur®)	6-monthly	Intramuscular
Histrelin implant (Supprelin LA)	Every 1–2 years	Subcutaneous implant
Nafarelin acetate (Synarel®)	Twice daily	Intranasal spray

treatment. However, the degree of height gain varies among studies. The greatest height gain has been observed in girls when GnRHa treatment is initiated at 6 years or younger (27,28). However, final adult height outcome varies in those who are treated between 6 and 8 years (32), and no increase in adult height is seen in girls who are treated after age 8 years (33). Lazar *et al.* analyzed the data of 63 girls treated with GnRHa and 63 girls without treatment. All patients had Tanner stage III pubertal development and were followed up for 2–4 years. The height gain was similar between the treated and untreated groups (34). In a small and long-term randomized control study, GnRHa did not have a significant effect on final adult height in girls with advanced puberty (35).

A comprehensive review summarizing 29 studies from 1994 to 2015 found that the increase in adult height over the predicted height varied from 2 to 10 cm (32). In this review, variation in height outcomes among studies was attributed to a lack of well-designed, randomized control studies and a unified method for height prediction. Although the data on the long-term outcomes of GnRHa treatment on growth in boys with CPP are scarce, overall positive final adult height outcomes have been observed (36,37).

Menarche, menstrual cycles, and reproductivity

One of the parental concerns about GnRHa treatment for CPP is whether their child's reproductive function will be affected adversely. Menarche usually occurs on average 16 months (2–61 months) after cessation of treatment with regular ovulatory menstrual cycles (38-40). When the rate of spontaneous pregnancies was compared, there were no differences between women with treated CPP versus controls (39,41). Moreover, there was no difference between the groups in the incidence of pregnancy complications or outcomes (42). In a cross-sectional cohort study, a larger group of women with CPP, both treated and untreated, were compared with women without CPP; overall, the number of completed pregnancies was comparable in women with and without CPP (43). There was a slightly higher rate of need for assisted fertilization techniques in women with untreated CPP compared to both women with treated CPP and women without CPP (43).

Polycystic ovarian syndrome (PCOS)

There have been concerns that PCOS may occur more often in those with CPP than in those with normal puberty (44). It has been speculated that there is a similar and possibly overlapping mechanism between PCOS and CPP; the augmentation of GnRH pulsatility which causes increased secretion of LH is seen in both conditions (45,46). However, the prevalence of PCOS in treated or untreated CPP varies and there is no clear evidence that CPP increases the risk for PCOS (27).

Another concern is whether GnRHa treatment predisposes to PCOS development. Chiavaroli *et al.* reported a significantly higher prevalence of PCOS and hyperandrogenism in the treated CPP group than the untreated group (47). However, other studies found no differences in developing PCOS between treated and untreated CPP (48,49); also, GnRHa treatment for CPP was not associated with increased risk of PCOS later in life (50). Jensen *et al.* did not observe PCOS during or after treatment (51). Furthermore, Lazar *et al.* reported a twofold higher increased risk for hyperandrogenism with irregular menstruation in the untreated group than the treated group (43). They concluded that GnRHa treatment may reduce the risk of PCOS and subsequent fertility problems (43).

Reproductive outcomes of GnRHa in males treated for CPP

Few data are available on the reproductive outcomes of males treated for CPP and limited to a small number of

studies. Bertelloni *et al.* reported pubertal LH response to GnRH testing within 1.5 years after the discontinuation of GnRH analogue therapy in 9 males (52). They all had normal pubertal development, testicular volume, gonadotropins, and testosterone (52). Another small study in 11 males showed similar results; normal gonadotropins and testosterone levels in one year and increased testicular volume after 2 years of stopping therapy (53). Although there are no data available on fertility and paternity rates, sperm analysis in 6 males in a study appeared normal (52).

Obesity and metabolic outcomes

Early-onset of puberty has been observed more commonly in girls with increased BMI (29,54). The median age of menarche was 5.4 months earlier in girls with obesity than normal-weight girls of the same age (54). The Observations from the Bogalusa Heart Study, a long-term community-based study of cardiovascular risk factors since childhood, have shown that females with early menarche displayed significantly higher body mass index (BMI) and triceps skinfold thickness, higher fasting insulin and homeostasis model assessment index of insulin resistance (HOMA-IR) in childhood and adulthood, and higher fasting glucose in adulthood (55). Thus, treatment with GnRHa in patients with CPP raised concerns about whether GnRHa may affect BMI and cause permanent obesity as well as obesity-related comorbidities in adulthood. Most studies reported higher BMI in patients with CPP at diagnosis but no significant changes during and after treatment (39,40,43,48). Magiakou *et al.* did not find changes in BMI during GnRHa treatment; also, there was a slight increase in total fat mass, though it is unclear whether that effect persists into adulthood (56).

There are limited studies on obesity-related metabolic outcomes (i.e., hypertension, diabetes, and hyperlipidemia) of GnRHa therapy for CPP. One small study examined lipid profiles and insulin sensitivity at the time of diagnosis of CPP and during GnRHa treatment in 23 girls (57). The study found that girls with CPP had worse lipid profiles and lower insulin sensitivity with a negative correlation to the age of diagnosis; also, GnRHa seemed to further worsen the metabolic profile during treatment (57). Another report also showed increased insulin resistance during GnRHa treatment (46). In addition, in a recent case-control study, the incidence of obesity, obesity-related metabolic outcomes, and malignancy rates in former CPP GnRHa-treated and -untreated women did not differ from the age-matched control group, reassuring the health status of adult former CPP women (43).

Bone health

Bone mass density (BMD) increases significantly during puberty with approximately 40% of peak bone mass being acquired between Tanner stages II and V (58). It is widely known that a surge of gonadal steroids, specifically estrogen, during puberty accelerates skeletal maturation with continued bone mass accrual and consolidation (58). Children with CPP often have elevated BMD for their age at the time of diagnosis (28). The use of GnRHa in children with CPP suppresses pituitary hormones to prepubertal levels resulting in deceleration of skeletal maturation preserving peak adult height. The suppression of ovarian activity with GnRHa is associated with decreased BMD (44). However, there are several studies that report no long-term adverse outcomes affecting BMD after GnRHa treatment (33,39,44,49,58-60).

Calcium supplementation during bone accrual appears to be important to reach peak bone mass and reduce the risk for postmenopausal osteoporosis (60). Antoniazzi *et al.* demonstrated decreased BMD loss with the use of calcium supplementation during GnRHa treatment as compared to those patients who did not take calcium supplementation during treatment (60). The findings of this report, along with suggestions reported by other authors, point to the significance of adequate nutritional intake for bone formation in patients with CPP (60,61). In brief, while studies have demonstrated decreased BMD during GnRHa treatment, bone mass is sufficiently preserved after discontinuation of treatment in CPP patients.

Conclusions

GnRHa remains the preferred treatment in patients with CPP. This treatment is generally considered safe, well-tolerated, and has demonstrated great effectiveness in restoring growth in children with CPP. Greater preservation of growth potential is demonstrated when treatment is initiated in younger children. Although more research is needed, the data to date are reassuring that GnRHa treatment in CPP patients does not increase the risk for menstrual or reproductive problems, PCOS, obesity, and bone health. There are limited data suggesting GnRHa treatment may aggravate or increase the risk for metabolic derangements but this risk is not different from

age-matched control groups in adulthood.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Pediatric Medicine* for the series "Clinical Pearls in Pediatric Endocrinology and Metabolism". The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-21-105/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-21-105/coif). The series "Clinical Pearls in Pediatric Endocrinology and Metabolism" was commissioned by the editorial office without any funding or sponsorship. BEL serves as an unpaid editorial board member of *Pediatric Medicine* from October 2022 to September 2024. BEL and PVM served as the unpaid Guest Editors of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/pm-21-105
Cite this article as: Ergun-Longmire B, Vining-Maravolo P, Graham B, Greydanus DE. A narrative review: treatment outcomes of central precocious puberty (CPP). Pediatr Med 2023;6:15.