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Long-term health consequences of central precocious/early puberty (CPP) and treatment with Gn-RH analogue: a short update

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Abstract. *Background:* The relationship between precocious or early puberty and its treatment has received significant research attention, yielding diverse outcomes. This short review aims to comprehensively analyze and summarize research articles to elucidate the potential link between precocious or early pubertal onset (CPP) and crucial health factors. *Methods:* We conducted a systematic review of studies published from January 2000 to March 2023, sourced from databases of Medline, PubMed, Google Scholar and Web of Science. We assessed the relationship between CPP and final adult height (FHt), bone health, reproductive function, body mass index, metabolic and cardiovascular abnormalities, and increased cancer risk. *Results:* Upon reviewing and analyzing selected studies, the following key findings emerged: (a) treating CPP in girls before age 6-7 and in boys before age 9 improves FHt; (b) bone mineral density (BMD) decreases during GnRHa treatment but normalizes afterward, with no lasting effects on peak bone mass during puberty; (c) GnRH treatment does not negatively affect menstrual cycles; however, untreated CPP increases the risk of premature or early-onset menopause; (d) the incidence of PCOS/hyperandrogenemia may be slightly elevated in women with a history of CPP, but overall reproductive function remains largely unaffected; (e) earlier thelarche and menarche may enhance susceptibility to breast carcinogenesis; (f) CPP contributes to an increased risk of obesity and type 2 diabetes in both genders; (g) early menarche may slightly increase the risk of coronary heart disease and ischemic strokes and (h) early pubertal timing increases the risk of depression and anxiety disorders. *Conclusion:* Monitoring and early diagnosis of these conditions are of paramount importance for successful management. (www.actabiomedica.it)

Key words: Central precocious puberty (CPP), final adult height, bone health, reproductive function, breast cancer, metabolic abnormalities, cardiovascular risk

Introduction

Central precocious puberty (CPP) represents an abnormal acceleration of pubertal development, characterized by the premature emergence of secondary sexual characteristics, advanced skeletal maturation, and accelerated physical growth in affected children. CPP not only impacts the final adult height of affected individuals but can also give rise to psychological and behavioral issues, including fear and anxiety (1).

Currently, the gold standard for the treatment of CPP worldwide is the use of gonadotropin-releasing hormone analogs (GnRHa). These agents effectively suppress the hypothalamic-pituitary-gonadal (HPG) axis by desensitizing pituitary gonadotrophs, resulting in regression or stabilization of pubertal symptoms.

Moreover, treatment with GnRHa extends the growth period by reducing growth velocity to prepubertal levels and mitigating bone age advancement (2,3). Clinical and diagnostic evaluation of treatment efficacy involves Tanner staging, linear growth assessment, radiological assessment of bone age maturation, and biochemical analysis through luteinizing hormone (LH) and 17-β estradiol measurements (4,5).

Despite the well-established efficacy of GnRHa therapy, several questions surrounding its long-term consequences and potential side effects persist. Notably, concerns arise regarding its association with conditions such as obesity, metabolic syndrome, bone health, reproductive function, cardiovascular effects, and the risk of breast cancer.

Objectives and methods

In this study, we conducted a systematic review of pertinent literature, encompassing articles available in databases such as Medline, PubMed, Google Scholar, and Web of Science from 2000 to March 2023. Our aim was to explore the relationship between precocious/early puberty and the occurrence of various health-related outcomes, including bone disorders, metabolic abnormalities, reproductive function, and the risk of cancer. A total of 148 research papers, comprising meta-analyses, review articles, randomized controlled trials, and both prospective and retrospective studies, were meticulously reviewed and analyzed (Figure 1).

Results

Precocious/early onset of puberty (EP) in relation to final adult height (Fht)

A review of 24 studies showed that final adult height (FHt) gain in subjects on GnRH treatment varied between 2 and 8 cm. Although treatment of CPP before 6-7 years of age resulted in better gain in the FHt, Yang et al. (6) showed that GnRHa treatment can help to increase FHt even in patients diagnosed with EP after the age of 8 years (6-11).

A study compared data on post-GnRHa treatment course and FHt in 115 girls [22 diagnosed before chronological age of 6 yr; 38 between ages 6 and 8 yr; and 55 early fast puberty (EFP), between ages 8 and 9 yr] treated with GnRHa from Tanner stage

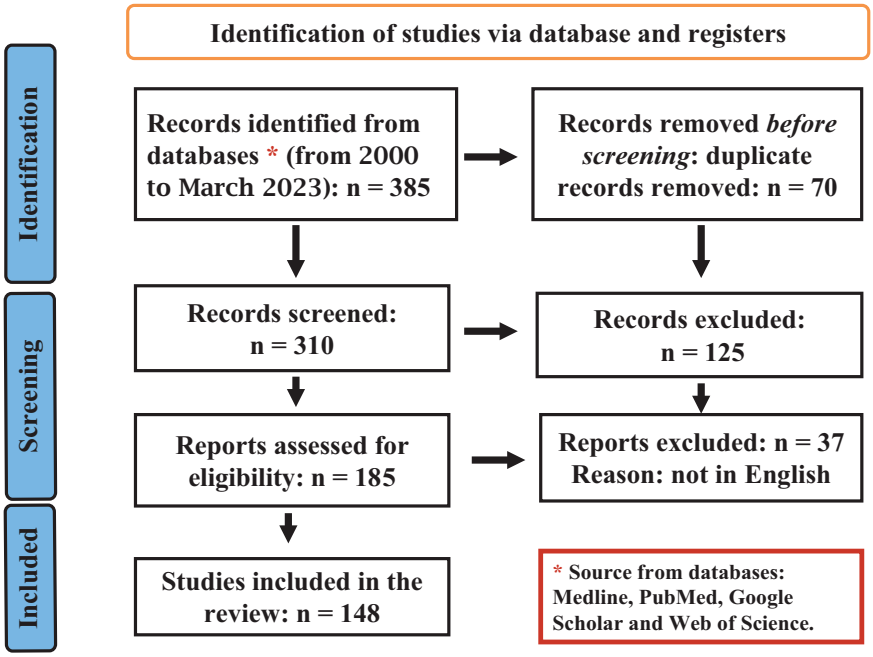

Figure 1. PRISMA chart for the review.

2-3 to chronological age 11-12 yr and bone age 12-12.5 yr. Height gain from cessation of therapy to FHt was greater, and time to epiphyseal fusion was longer in the younger CPP than in the older CPP (P: < 0.05), in those with early fast puberty (P: < 0.001) groups and those with smaller ovarian volume (OV) compared to those with larger OV at diagnosis (11,12).

On the other hand, 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. Two studies by Lazar et al. (11) and Bouvattier et al. (13) analyzed the data of 63 girls and 30 girls respectively who were treated with GnRHa and compared them to untreated girls. They showed that the height gain was similar between the treated and untreated groups.

Pasquino et al reported a large variability of individual responses suggested that one should choose more parameters than increment in height, especially in girls with pubertal onset over 8 yr of age (14). Cheuiche et al. (15) recommended that treatment should be considered in girls before the age of 6 and boys before the age of 9 with progressive CPP, while in girls between 6 and 8 years the treatment decision is individualized.

Early onset of puberty in relation to adult bone health

Peak bone mass (PBM), shares similarities with pubertal timing (physiological variability, genetic influence and environmental aspects). Factors influencing pubertal timing significantly affect bone acquisition. Analysis of the 20 research articles revealed the following:

a. Epidemiological studies show that women with early menarche are at higher risk of premature and early menopause.
b. The Gothenburg Osteoporosis study demonstrates a negative association between age at peak height velocity (PHV) and bone mineral density (BMD) in young men (16). Age at PHV predicts fractures, independently of risk factors, such as: birth weight, childhood body mass index (BMI) and adult height. The National Health and Nutrition Examination Survey (NHANES) data reveals that late menarche ≥16 years is associated with lower lumbar spine (LS) BMD, even after adjusting for confounding factors (16,17).

   An age at menarche ≥16 years was associated with lower lumbar spine BMD compared to those with a menarche age ≤12 years, while another study found that late puberty was associated with increased risk for adult fracture (18,19). A longitudinal study in girls with CPP showed an increased BMD, but this advantage waned when corrected for their advanced bone age. In another study GnRHa treatment seemed to have no detrimental effect on BMD (20).
c. Longitudinal studies on British participants suggested that male subjects gained BMD faster than females and confirmed that late pubertal age is associated with persistently lower BMD in both genders (21). Studies analyzing GnRHa treatment in children with CPP revealed variable results. Some suggested a reversible reduction in BMD during treatment that improved when using calcium and vitamin D supplementations (22-25). Others find spontaneous restoration of bone mass 2-3 years after cessation of therapy and one study showed structural bone changes with treatment (20, 26-32).

Patients with CPP have increased expression of carboxy-terminal telopeptide of type 1 collagen (ICTP), a bone resorption marker, and procollagen type 1 C-terminal propeptide (PICP), a bone formation marker, before GnRHa treatment that decreases during a 6-month treatment period and stabilizes after treatment. Bone age-adjusted bone turnover markers normalized 2 years after treatment cessation (33,34).

In summary, some studies indicate associations between GnRHa treatment and decreased BMD while others emphasize good potential for recovery post-treatment cessation. Bone mineral density decreases during GnRHa treatment but recovers to normal afterward, and peak bone mass formation through bone mineral accretion during puberty is not affected.

Early/precocious puberty: Effects on menarche, menstrual status, and onset of menopause

The impact of GnRHa treatment on the timing of menarche, menstrual cycles, and onset of menopause in girls with early/precocious puberty is of clinical interest. Ten studies were reviewed and analyzed.

Three long-term studies demonstrated that pubertal reactions in CPP patients were restored within 1 year, with most recovering within 6 months after treatment discontinuation. After GnRHa treatment cessation, the onset of menarche required an average interval of 0.9-1.5 years, with menarche starting around 12.6-13.6 years old chronologically (27, 35-37).

In a Korean study (38), menarche began approximately 14 months post-GnRHa treatment, corresponding to 11.9 years in chronological age and 12.8 years in bone age (similar to normal girls' average age at menarche). The age at CPP diagnosis (< 6, 6-8, or 8-9) did not significantly impact the prepuberty period or onset of menarche post-treatment.

In another study, among CPP patients, GnRHa-treated individuals exhibited an average age at menarche of 12 years, showing a delay compared to the untreated group's age of 9.6 years (39).

A study reported regular menstrual cycles in the majority (82/87) of GnRHa-treated patients, with few (5/87) experiencing oligomenorrhea due to excessive exercise, which improved after exercise control (27). Other investigators found that in adulthood, 80% of CPP patients who received GnRHa treatment maintained regular menstrual cycles (39).

A long-term follow-up study reported that patients treated with GnRHa treated subjects presented regular menstrual cycles and no breast or uterine disorders, after an average of 12.5 years post-treatment (37).

A pooled study of postmenopausal women, from different countries, indicated that early menarche (≤11 years) is a risk factor for both premature or early menopause (<40 and 40–44 years, respectively) (40).

In addition, random-effect meta-analysis of six studies observed a pooled risk ratio (RR) estimate of 4.71 (95% CI 2.81–7.90) for the combined association of early menarche and nulliparity with premature menopause (41).

In summary, GnRHa treatment does not seem to negatively affect the history of menstrual cycles. Nevertheless, untreated early puberty increases the risk of premature or early-onset menopause, which can potentially be mitigated by GnRHa therapy.

The impact of GNRH analog treatment on reproductive function of girls with precocious/early puberty

When discussing GnRHa treatment for CPP, one of the common concerns raised by parents pertains to its potential long-term effects on fertility.

The development of signs and symptoms of polycystic ovarian syndrome (PCOS) in former CPP women is controversial. In a review article analysis of 14 studies focusing on reproductive function, PCOS morphology detected by ultrasound (US) was reported in 0–37% of treated CPP girls (median 2%) with different lengths of post-treatment follow-up (up to 20 years) (42). A similar percentage (2%) was reported by Heger et al. (43).

In contrast, another study involving 46 young women (average age 18.1 years) treated with GnRHa during childhood revealed that 32% had PCO, with 28% exhibiting clinical hyperandrogenism, and 48% showing biochemical hyperandrogenism (44).

Lazar et al. (45) reported that the clinical signs of hyperandrogenism (acne/hirsutism with oligomenorrhea) were more frequent in CPP women than in controls with normal puberty, matched for age and year of birth but not for BMI. The relative risk for the development of clinical hyperandrogenism with irregular menses was twofold higher in the untreated than the treated group. The reproductive outcome in early and mid-adulthood was normal in the majority of the patients studied. A high prevalence of fertility problems was present in the untreated CPP group only, suggesting that GnRHa therapy may have a protective effect on the reproductive outcome.

Another study indicated a significant correlation between GnRHa treatment and PCOS (P: 0.03). Specifically, 36% of girls previously treated with GnRHa for CPP developed PCOS, compared to 14.5% of untreated girls with CPP (46). However, contrasting findings were reported in other studies. No statistically significant difference in the prevalence of

PCOS was in 2751 women treated with GnRHa versus non treated subjects. The overall prevalence of PCOS was 19.6%. (47) Similarly, the overall prevalence of either clinical or laboratory hyper-androgenism was 29.4% and 33.3% for the treatment and non-treatment groups, respectively (48). Another report showed a significant incidence of PCOS in former CPP patients, with a lower prevalence of PCOS in GnRHa-treated girls than in nontreated girls [17.2% (n = 33) vs. 30.8% (n = 14)]. Elevated DHEAS and androstenedione concentrations occurred in 56% of those receiving GnRHa versus 23.6% among those who did not (49).

Four reports did not establish a clear link between CPP, whether treated or untreated, and the development of PCOS (46,50,51). A longitudinal study of 20 CPP patients who reached adulthood revealed that 7 patients achieved a total of 12 pregnancies, with normal childbirth experiences (52).

The PREFER (PREcocious puberty, FERtility) study prospectively analyzed fertility, via a series of questionnaires, in women treated during childhood with triptorelin (depot formulation) for CPP. Most pregnancies (84.4%, 95% CI [67.2–94.7%]) occurred within 1 year of trying to conceive, in line with the waiting time to pregnancy (WTP) for women without previous CPP (53).

Demographic data analysis of 214 CPP women (135 GnRHa-treated and 61 untreated) compared to controls with normal puberty showed that both treated CPP and control groups achieved spontaneous pregnancy at similar rates (90.4% vs. 90.2%). (53) However, untreated CPP subjects were associated with higher fertility problems and assisted fertilization rates (45).

In summary, while the incidence of PCOS/hyperandrogenemia may be slightly elevated in women with a history of CPP, their overall reproductive function remains largely unaffected.

The association between precocious/early puberty and the risk for breast cancer

A comprehensive analysis of 117 epidemiological studies, involving 118,964 women with invasive breast cancer and 306,091 controls, demonstrated that younger age at menarche correlated with an increased breast cancer risk and each year younger at menarche was associated with a 5% increase in relative breast cancer risk (54). Several other studies have confirmed these observations (55- 60).

Sister-matched case-control research involving 1,406 women diagnosed with breast cancer before the age of 50 years and 1,648 control subjects reaffirmed the relationship between older age at menarche and reduced young-onset of breast cancer risk (61). A study involving 1,811 pairs of female twins with breast cancer demonstrated that the twin with earlier puberty was more likely to receive an earlier diagnosis of breast cancer (62). A case-control study of 237 breast cancer cases and 237 age-matched controls found that early menarche (OR = 1.60, 95% CI: 1.08–2.38) significantly heightened breast cancer risk (63).

A prospective US cohort study on women aged 35–74 years without breast cancer history but with a diagnosed sister revealed that early pubertal development ages at thelarche and menarche was positively associated with breast cancer risk. A 30% higher risk of breast cancer compared to those without these risk factors (64,65).

In a Japanese study, age at menarche was somewhat more closely associated with the risk of progesterone receptor-negative than positive breast cancer (66). On the contrary, other cohort and meta-analysis studies did not find a relation between early puberty and the risk of breast cancer (66-70).

In summary, the collective evidence supports the notion that earlier ages at thelarche, and menarche may heighten susceptibility to breast carcinogenesis and may add another potential advantage to hormonal suppressive therapy.

The relationship between precocious/early puberty and obesity associated to metabolic abnormalities

The impact of early-onset puberty on the development of obesity, overweight and metabolic abnormalities has been the subject of extensive research with variable outcomes. (71,72).

The Gothenburg osteoporosis and obesity determinants study followed 579 subjects with early pubertal onset. The Authors demonstrate that early pubertal onset in males predicts a central fat mass distribution, while a predominantly subcutaneous obese phenotype is strongly predicted by a high prepubertal BMI (73).

The long-term community-based Bogalusa Heart Study revealed that girls with an history of early menarche presented a significant higher BMI, skinfold thickness, fasting insulin and insulin resistance (HOMA-IR) in childhood and adulthood (74).

A twin cohort analysis documented a strong heritability in the age at the onset of the pubertal growth spurt and adult height. These traits were found to be associated with childhood BMI and early adulthood stature due to shared genetic factors (75). A Finnish cohort study supported a strong genetic correlation between early puberty and higher childhood BMI, especially in girls (76).

A meta-analysis of 34 studies demonstrated that early menarche correlated with increased adult BMI, while late menarche correlated with decreased BMI (77). Another meta-analysis, including 28 studies, found that earlier age at menarche was associated with a higher risk of type 2 diabetes mellitus (T2DM) even after adjusting the results with adiposity (78).

A Swedish study of 30,697 men demonstrated that earlier pubertal onset was linked to a higher risk of early diabetes and early need for insulin therapy even after BMI adjustments, while late puberty correlated with reduced diabetes risk (79).

An analysis of the Nurses' Health Study cohorts showed that early menarche was associated with an increased risk of T2DM. Adiposity partly mediated this association (80).

A meta-analysis of 28 observational studies (N = 1,228,306) reported that without adjustment for adult adiposity, impaired glucose tolerance and T2DM risk was higher for early versus later menarche (78).

Moreover, in a UK Biobank study, it was reported that in women and men earlier puberty timing was associated with higher risks for angina, hypertension and T2DM (81).

A study performed in Brazil, involving 8,075 women, demonstrated that early menarche was linked to a higher risk of diabetes, even after controlling for socio-demographic factors and maternal diabetes (82).

A small study on girls with CPP reported worse lipid profiles and lower insulin sensitivity at diagnosis with further worsening of the metabolic profile during GnRHa treatment. Another report also showed increased insulin resistance during GnRHa treatment (83,84). However, a case-control study of the incidence of obesity and obesity-related metabolic outcomes 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 (45, 85).

Collectively, early puberty appears to contribute to an increased risk of obesity and T2DM in both men and women, often mediated by factors such as childhood BMI and genetic predisposition. Monitoring and early diagnosing of these conditions are important for successful management.

Early puberty in relation to coronary heart disease (CHD) and stroke

Early menarche is generally associated with an increased risk of coronary heart disease (CHD) and stroke. Six research articles were reviewed (86- 89). Early menarche increased the risk of ischemic stroke regardless of age at menopause and reproductive span in contrast to the associations between these factors and myocardial infarction (90).

In a population-based retrospective cohort study from the National Health Insurance Service database of Korea, including a total of 1,224,547 postmenopausal women, a U-shaped association between age at menarche and the risk of ischemic stroke (IS) was found, with a 16% higher risk in early menarche group (≤ 12 years). Women who had undergone early menarche and had a short reproductive span had the highest risk of IS, perhaps due to the combined effect of improper timing of estrogen production and insufficient estrogen exposure (91.92).

In summary, early menarche may increase the risk of coronary heart disease and ischemic strokes.

Psychological aspects of early puberty and treatment

Children with CPP may experience significant behavioral, social, and emotional problems. They may also face different social pressures of fitting in their body's development before peers.

Recent studies have found an increase of social anxiety, depressive and externalizing symptoms, and risk of psychopathology, in association with physical

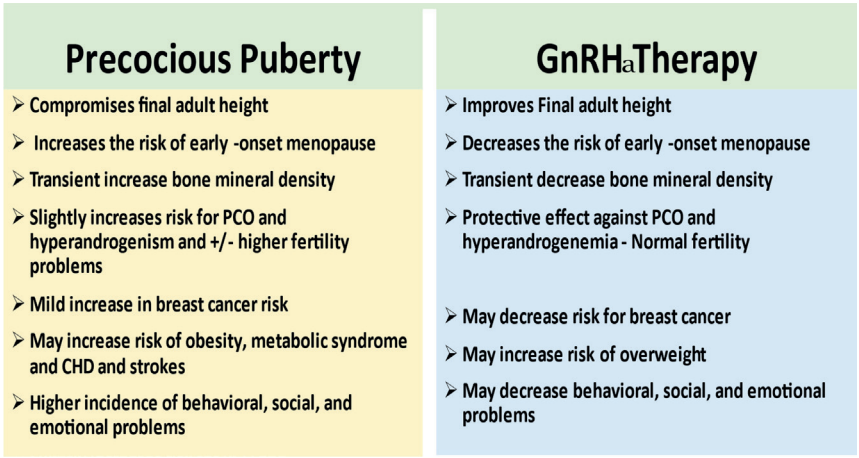

Figure 2. Consequences of precocious puberty in relation to GnRHa treatment.

changes secondary to early pubertal maturation, mainly in females (93-99). Therefore, these signs and symptoms should be taken in deep consideration as an additional indication for GnRHa treatment (100- 102).

In summary, findings across all studies revealed that early pubertal timing served as a transdiagnostic risk factor for depression and anxiety disorders, requiring GnRHa treatment in selected cases.

Conclusions

The therapeutic approach for the treatment of children with CPP using various GnRHa preparations has rapidly evolved. While the efficacy and safety of these formulations in suppressing puberty and slowing down the pubertal growth spurt appear to be acceptable, several unresolved questions persist regarding the clinical management of affected children. These areas of concern include the long-term effects of precocious/early puberty and the effects of GnRHa. Despite their relatively low risk, there is a need for vigilant and long-term monitoring of these patients. Therefore, any effort directed to establish the optimal strategy for monitoring treatment is imperative (Figure 2).

Conflict of Interest Statement: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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