MANAGEMENT OF ENDOCRINE DISEASE

Long-term outcomes of the treatment of central precocious puberty

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Abstract

GnRH analogues (GnRHa) are the treatment of choice for central precocious puberty (CPP), with the main objective to recover the height potential compromised by the premature fusion of growth cartilages. The aim of this review was to analyze long-term effects of GnRHa on height, body weight, reproductive function, and bone mineral density (BMD) in patients with CPP, as well as the potential predictors of outcome. Because randomized controlled trials on the effectiveness and long-term outcomes of treatment are not available, only qualified conclusions about the efficacy of interventions can be drawn. GnRHa treatment appears to improve adult height in girls with CPP, especially if diagnosed before the age of 6, whereas a real benefit in terms of adult height is still controversial in patients with the onset of puberty between 6 and 8 years of age. No height benefit was shown in patients treated after 8 years. Gonadal function is promptly restored in girls after cessation of treatment, and reproductive potential appears normal in young adulthood. Data are conflicting on the long-term risk of polycystic ovarian syndrome in both treated and untreated women. Fat mass is increased at the start of treatment but normalizes thereafter, and GnRHa itself does not seem to have any long-term effect on BMI. Similarly, analogue treatment does not appear to have a negative impact on BMD. Owing to the paucity of data available, no conclusions can be drawn on the repercussions of CPP and/or its treatment on the timing of menopause and on the health of the offspring.

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Introduction

Puberty results from the reactivation of the hypothalamic–pituitary–gonadal (HPG) axis following the quiescent period occurring during childhood. It is characterized by an increase in the amplitude and frequency of the hypothalamic gonadotropin-releasing hormone (GnRH) pulses, which in turn promote follicle-stimulating hormone and luteinizing hormone secretion by the pituitary, leading to the activation of gonadal function (1).

Precocious puberty is clinically defined by the appearance of secondary sexual characteristics, i.e., Tanner stage II of breast development before the age of 8 in girls and the increase in testicular volume ≥ 4 ml before 9 years in boys (2, 3). Central precocious puberty (CPP) due to early activation of pulsatile GnRH secretion is the most

common form (2). It occurs in $\sim 1:5000$ – $10\,000$ children, with a female-to-male ratio ranging from 3:1 to 23:1 (3). Females typically present with idiopathic forms, whereas in boys CPP is mostly due to organic lesions such as hypothalamic–pituitary congenital malformations, tumors, infections, infiltrative/inflammatory disorders, and iatrogenic or traumatic injuries (3). Genetic factors (mutations of *KISS1*, *KISS1R*, and *MKRN3* genes (4)), secular trend, ethnicity, nutritional status, and environmental changes have all been involved in the pathogenesis of CPP (2, 3, 5), although their exact mechanisms of action remain to be elucidated.

Short stature caused by rapid advancement of skeletal maturation driven by premature exposure to sex steroids is

the main unfavorable event associated with precocious puberty. Historical data on untreated patients with CPP show mean final heights ranging from 151 to 156 cm in boys and from 150 to 154 cm in girls, being the height loss inversely correlated with the age at the onset of puberty (2, 6).

Treatment is aimed at selectively and effectively suppressing gonadal steroid secretion through medical treatment or removing the underlying cause whenever possible to allow normal sexual maturation and statural growth (2, 3, 6). The avoidance of potential psychosocial problems derived from experiencing precocious puberty and undesirable behaviors like early sexual intercourse and substance abuse reported in some cohorts of patients may also be acknowledged as objectives of the treatment (2, 3, 7). The decision to treat depends on the age at onset of puberty, pace of pubertal development, estimated adult height, and psychological impact of the premature sexual development (2, 3). Treatment is undisputed in rapidly progressive forms, defined on the basis of clinical, radiological, and biochemical criteria (8), for the significant risk of short adult height, while it is not required in patients with nonprogressive or slowly progressive forms who were shown to achieve an adult height within the normal range without treatment (2, 3).

GnRH analogues (GnRHa) are the medical treatment of choice for progressive CPP (2, 3). They derive from a chemical substitution at position 6 and 10 of the native GnRH molecule, which increases its resistance to the enzymatic degradation and affinity to the GnRH-pituitary receptor leading to desensitization of the receptor, ultimately resulting in the inhibition of gonadotropin secretion and return of sex steroids to prepubertal levels (9). Several active principles and formulations are available. Depot formulations are generally preferred because of better patient compliance. Drug choice depends on physician experience, patient needs, and government regulations of drug prescription (6, 7). GnRHa is generally safe and well tolerated. Local events such as bruising, pain, injection reactions, and sterile abscesses are the most common side effects, followed by minor menopausal symptoms – that is, hot flushes, headaches, and nausea (7) – while anaphylaxis is extremely rare (10).

In the last decades, the widespread use of GnRHa has increasingly demonstrated its favorable effects on statural growth, although the net height gain (HG) associated with the treatment and predictors of long-term outcomes remains debated (2, 6, 7, 8), as no randomized controlled trials (RCTs) have been performed and growth

estimation suffers from important methodological limitations, which will be discussed later. Moreover, concerns have been raised on the potential negative effects of treatment on weight and metabolic profile, bone mineral density (BMD), and reproductive function in adulthood (2, 3, 6). The aim of our review was to analyze long-term effects of GnRHa on height, body weight, reproductive function, and BMD in patients with CPP, as well as potential predictors of outcome.

A literature search was performed using the PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>) and entering the string 'precocious puberty AND (treatment OR GnRH analogues) AND (height OR body mass index OR bone OR fertility OR reproduction OR polycystic ovary syndrome)' with no date limits. Only original studies performed in humans, written in English, reporting data at the beginning and after the completion of treatment were considered for BMI and metabolic parameters, reproductive function, and BMD. Studies focusing on height were considered only if baseline values and adult heights were reported and data expressed as mean (absolute values or SDS) $\pm$ S.D. or S.E.M. for study comparison and calculation of treatment efficacy (i.e. HG). Additional articles were identified through a hand search of reference lists in the papers retrieved (Fig. 1).

Figure 1

Methodological flow chart summarizing the main steps followed for the identification of articles of interest. CPP, central precocious puberty; GnRHa, gonadotropin-releasing hormone agonists; PCOS, polycystic ovary syndrome; PP, precocious puberty.

Outcomes of GnRHa therapy for CPP

Adult height

GnRHa have been extensively used since the 1980s in children with rapidly progressing CPP with the primary aim to restore genetic growth potential otherwise compromised by sex-hormone-driven premature closure of bone growth plates. The great majority of studies indicate some beneficial effect of treatment on statural growth, with limitations related to the absence of RCTs and the fact that the effects of GnRHa therapy have been traditionally analyzed by comparing the achieved adult height with predicted adult height at initiation of treatment or with adult heights of historical, untreated cohorts.

Bone age (BA) assessment is essential in the management of patients with CPP as it allows the identification of rapidly progressing forms of CPP with compromised predicted adult height requiring treatment. It is also important for monitoring treatment efficacy, as deceleration of BA maturation is a desired effect of treatment. Moreover, BA evaluation is valuable in defining the appropriate time for treatment discontinuation, because the best results in terms of adult height are achieved when treatment is discontinued at around 12–12.5 years in girls and 13.5 years in boys (11), although the optimal age for treatment interruption is not clearly defined by international guidelines. It should be pointed out, however, that BA assessment is affected by a great intra-observer variance, and Bayley and Pinneau tables, the reference standards for height prediction, have been validated for height prediction in normal children (11). In patients with CPP, height prediction based on both ‘average’ and ‘advanced’ tables is insufficiently reliable, especially when skeletal maturation is markedly advanced, and it is associated with a systematic overestimation of adult height (3.7–5.9 cm in girls, and even greater in boys in historical series) (2, 3).

The comparison of adult heights of treated CPP patients with those of historical cases is of limited value because data are derived from a small number of patients, usually the most severe, and do not take into account the influence of the secular trend on human growth over the decades. Moreover, studies are heterogeneous for patients – that is, chronological and BA at diagnosis and initiation of treatment and idiopathic vs organic forms of CPP – and treatment characteristics (2, 3).

Predictors of treatment outcomes also remain debated. Treatment efficacy appears to depend mainly on the age of CPP onset and treatment initiation with best

outcomes reported in girls with onset of CPP before the age of 6 years and treated soon thereafter. BA advancement at the time of initiation of therapy, duration of therapy, mid-parental height, and height at the end of therapy have also been considered predictors of height outcome but with no definite conclusions reached on their appropriateness. The optimal age for treatment discontinuation is also questionable as several auxologic and treatment characteristics involved in post-treatment HG should be taken into account together with the psychological impact of the resumption of pubertal development on the patient and family (7, 8).

To clarify the impact of GnRHa treatment on statural growth and identify the most reliable predictors of height outcome in treated patients with CPP, 20 articles fitting the above-mentioned inclusion criteria were analyzed (Supplementary Table 1, see section on [supplementary data](#) given at the end of this article). For each of them, the following parameters, reported by authors or calculated from raw data, were recorded: number of enrolled patients; treatment type; target height (TH); chronological age, BA, and height at the beginning and end of treatment; HG (computed from the difference between adult and predicted height at diagnosis, according to average and/or advanced BA, as per authors’ choice); and the difference between adult and predicted height at the end of treatment. Treatment efficacy was estimated from the comparison of adult height with predicted height at the beginning and end of treatment and/or adult height of historical, untreated patients, as well as the pace of bone maturation progression.

Data analysis demonstrated the efficacy of the various GnRHa formulations in halting BA progression, indicated by the statistically significant difference between BA and chronologic age at the end vs the beginning of treatment (Supplementary Table 1). The great majority of patients was female (female (F):male (M)=947:90) and treated with triptorelin or leuprolide depot formulations administered monthly. Overall, the mean chronologic age at the start of treatment was 7.5 ± 1.2 years in females and 6.7 ± 1.5 years in males, with a mean BA of 10.3 ± 1.4 years in females and 10.6 ± 2.5 years in males. The mean chronological age at the end of treatment was 11.1 ± 0.9 years in females and 12.2 ± 1.8 years in boys, with a mean BA of 12.4 ± 0.7 and 13.6 ± 1.0 years respectively.

Mean adult height was significantly higher in treated patients than in untreated ones reported in an historical series adjusted for age at diagnosis (12, 13) (mean difference in adult height of 8.3 cm in girls and 13.7 cm in boys) (12) and in age- and sex-matched untreated study

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controls (mean difference in adult height ranging from 3.3 to 8.9 cm) (12, 14, 15, 16).

The great majority of patients reached an adult height consistent with the TH (13, 14, 15, 17, 18, 19, 20, 21, 22, 23, 24, 25), a minority of them did not reach the TH (19, 26), and a very small portion of patients remained shorter than the predicted height before treatment (13, 27). Discordant results were obtained when comparing the efficacy of treatment in females and males. According to a study by Bajpai *et al.* (21), in patients treated with monthly triptorelin depot, mean HG was similar in females and males (mean HG: 6.4 ± 2.4 cm vs 7.6 ± 1.0 cm respectively). In contrast, Galluzzi *et al.* (13) reported a higher HG in boys (7.3 ± 3.8 cm; $n=11$) than in girls (3.3 ± 3.0 cm; $n=22$), with an achieved adult height SDS higher in the former than in the latter (0.13 ± 0.91 vs -0.62 ± 0.88 ; $P<0.001$). In general, HG was highly variable among studies depending on sample characteristics including the progression of pubertal development. Pubertal development was specified as rapidly progressing in some studies (17, 22, 24, 27, 28, 29), whereas in others pubertal progression was not detailed.

Several factors were postulated to influence the effects of GnRH treatment on statural growth. According to the majority of studies, earlier age at start of puberty (i.e. 5 years (15, 22)) and of treatment (i.e. 6 years (18, 20, 21, 23, 24, 25)) are associated with a taller adult stature. In a study by Klein *et al.* (24) performed in 98 patients (F:M=80:18) treated with histrelin or deslorelin, the average adult height and HG (14.5 ± 9.9 cm vs 6.8 ± 6.9 cm; $P<0.001$) were greater in girls with puberty onset <6 years of age than those with onset of puberty between 6 and 8 years of age. Few studies (12, 26) showed no correlation between HG and age at puberty onset or initiation of treatment, suggesting that girls with late onset CPP benefit from treatment similarly to girls with earlier pubertal onset (12). A longer treatment duration appears to be a positive outcome predictor in the majority (19, 20, 21, 24, 30), although not all (15, 23), of the studies, together with a short interval between pubertal onset and the start of treatment (24, 30), a great growth spurt after the end of treatment (12), low pre-treatment estradiol levels (30), and advanced BA at the start of treatment (14, 18, 19, 20, 21, 25). The impact of advanced BA at the start of treatment on adult height was not documented in the study by Brito *et al.* (30), whereas Carel *et al.* (12) found a negative association between the BA/statural age ratio at the onset of treatment and adult height suggesting that treatment is not capable of restoring a full adult height potential if started after an irreversible advancement of BA. This was

also confirmed in a study by Kauli *et al.* (26) showing that therapy is more beneficial if started before BA exceeds 12 years.

Elevated height (or height SDS) before (16, 17, 19, 20, 24, 30) and at the withdrawal of treatment (12, 16, 17, 19, 20, 25, 30), as well as high TH (or TH-SDS) (17, 20, 21, 23, 30), has also been positively associated with adult height, supporting the primary influence of genetic factors in the determination of adult height even in patients treated with GnRHa (20).

Finally, BA at the end of treatment appears to be crucial on adult height, as it determines post-treatment growth potential (7). Indeed, the tallest heights were achieved by patients who stopped treatment at a BA of 12–12.5 years (20) or even <11.5 years (27), whereas continuing treatment after a BA ≥ 13 years negatively impacted on statural growth (20).

The efficacy of the various GnRHa in terms of HG appeared similar (24, 27, 31), except for a study (32) showing a higher adult height SDS in patients treated with leuprolide depot compared to triptorelin depot.

BMI and correlates of metabolic syndrome

Several studies reported an association between overweight and early/precocious puberty (5, 33) suggesting the involvement of various environmental, genetic, and biochemical factors (5, 7, 17, 34, 35) to explain this association. However, what remains to be clarified is whether it is the high BMI that results in precocious pubertal development or is it the latter that promotes the weight gain (33, 35).

Preliminary studies reported weight gain during treatment with GnRHa in patients with CPP, raising concerns for potential permanent obesity in adulthood (33, 35, 36). According to two independent studies (33, 37) analyzing normal-weight and overweight children separately, BMI-SDS during treatment increased in normal-weight children, whereas it remained stable in overweight subjects. The majority of long-term studies showed an increased prevalence of overweight and obesity in patients with CPP at diagnosis (22, 38), but no significant mean or individual BMI-SDS changes were shown at the end of treatment, irrespective of sex, age at puberty onset and at the start and discontinuation of treatment (15, 17, 22, 23, 24, 25, 30, 32, 39), and type of GnRHa (31). Recently, a study by Colmenares *et al.* (39) evaluated the effects of GnRHa in treated ($n=29$) and untreated ($n=8$) CPP patients and in treated ($n=14$) and untreated ($n=20$) rapidly progressing early puberty (EP), during a 3-year follow-up period. Treatment duration was ≥ 2 years.

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At diagnosis, a higher BMI (z-score of 1.1 ± 0.8 vs 0.6 ± 0.7) and a higher prevalence of obesity/overweight (72.9% vs 35.3%) was observed in subjects with CPP when compared to those with EP. BMI z-score and obesity/overweight rates did not change significantly in girls with CPP or EP during 3 years of follow-up, regardless of treatment. Weight z-scores were higher at 3 years in treated than in untreated girls with CPP, while it was higher in untreated than in GnRHa-treated patients with EP at baseline, 1, 2, and 3 years. Both CPP- and EP-treated patients showed a reduction, although not statistically significant, in BMI z-scores and in obesity/overweight rate following treatment discontinuation, supporting the potential, although time limited, detrimental effect of GnRHa on weight. Indexes of glucose and lipid metabolism were in the normal range at diagnosis and remained unchanged during the follow-up period, independent of treatment.

Recently in a case-control study of a historical cohort, Lazar *et al.* (35) assessed the prevalence of obesity, the metabolic outcome (hyperlipidemia, diabetes, and hypertension), and the malignancy rate of former CPP GnRHa-treated and -untreated women between the third and fifth decades of life. The control group comprised women randomly matched for age, year of birth, and community clinic. Weight status of both GnRHa-treated and -untreated former CPP women resembled that of the general population from late adolescence to early-mid adulthood despite their above-average BMI at the onset of puberty. Permanent obesity was detected in women who were already obese in early childhood only. Moreover, weight gain of the treated CPP girls was not aggravated by GnRHa therapy. The incidence of obesity-related complications, such as metabolic dysfunctions and cancer comorbidities, were not increased in former CPP women, reassuring the health status of adult former CPP women.

Results from studies meeting inclusion criteria are summarized in [Supplementary Table 2](#), see section on [supplementary data](#) given at the end of this article.

Reproductive function and risk of polycystic ovarian syndrome

The occurrence of menarche, or in some cases resumption of menses, after the discontinuation of either daily or long-acting GnRHa treatment was investigated by follow-up studies of girls in their late teens and women up to 56 years of age ([Supplementary Table 3](#), see section on [supplementary data](#) given at the end of this article). The majority of the studies reported a 100% occurrence of menarche, with a few exceptions mostly related to

CPP secondary to organic lesions such as hypothalamic hamartoma (40).

Spontaneous menses occurred 0–62 months after the end of treatment (mean 1.1 ± 0.4 years); the mean duration of treatment varied widely among the studies, from 1 to 14 years. It was suggested that the longer time interval to menarche might be related to a longer duration of treatment and/or younger age at the start of therapy (40), but this hypothesis was not confirmed by other authors (41). Age at the discontinuation of treatment, BA, Tanner breast stage, or uterine development at the end of treatment, and the frequency of injections required to suppress the HPG axis function were all proposed as potential predictors of time interval to menarche, without consistency across studies. Interestingly, girls who had experienced menarche prior to GnRHa therapy showed a significantly shorter interval between the last injection and resumption of menses than those who had not experienced menarche before GnRHa treatment (~ 25 months vs 63 months) (19).

In the last decade, a subcutaneous hydrogel implant releasing histrelin continuously for at least 1 year has become available in the USA. Few reports of follow-up after histrelin implant treatment were published. Gillis *et al.* (31), evaluating a group of CPP patients treated with the monthly GnRHa and one with the histrelin implant showed that the mean time between the removal of the implant or last injection and menarche was shorter in the histrelin implant group. Fisher *et al.* (41) reported the resumption of puberty in 26 of the 30 girls treated with the histrelin implant, with occurrence of menarche 2–36 months after explantation in treatment-naïve and -non-naïve CPP girls, with an older age at explantation correlating with earlier menarche. In a recent study by Silverman *et al.* (43), menarche occurred in two patients, 9 and 2 months after the final explant respectively.

A great variability in the occurrence of regular ovarian cycles was so far reported in CPP-treated patients (44–96%; [Supplementary Table 3](#)), probably related to the heterogeneity of the study sample, type and duration of treatment, and follow-up. The highest prevalence of regular cycles (96%) was observed in 87 treated idiopathic-CPP girls during a 7-year follow-up period after the discontinuation of treatment (15). Jay *et al.* (43) described menstrual cycle lengths as becoming increasingly regular, from 41% in the first year post-menarche to 65% at 3 or more years post-menarche (44).

Fertility was reported to be normal in treated CPP girls, in contrast to the untreated ones. [Supplementary Table 3](#) summarizes over 100 pregnancies reported in the

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literature, with 97 uneventful pregnancies resulting in healthy children, five elective abortions, and 11 early miscarriages. In a recent study by Lazar *et al.* (45) assessing the reproductive outcome of former CPP women between the third and fifth decades of life, the frequency of pregnancy complications, such as early spontaneous abortion or pre-eclampsia, was comparable in the CPP women and controls. In the same study, spontaneous pregnancy was equally achieved by the treated CPP women and their control groups, while the percentage of women requiring ovulation induction and/or IVF was significantly higher in the untreated CPP group (33%) than in either the control (12.6%) or the CPP-treated groups (11.1%) (45). These findings suggest, according to the authors, a protective role for gonadotropin suppressive treatment on the reproductive outcome of CPP women.

PCO morphology detected by ultrasound (US) was reported in 0–37% of treated CPP girls (median 2%) (21, 36, 46, 47, 48, 49, 50, 51), with different lengths of post-treatment follow-up (up to 20 years), as summarized in [Supplementary Table 4](#), see section on [supplementary data](#) given at the end of this article. Feuillan *et al.* (40) described the ovarian volume larger than normal at 4–5 years post-treatment, whereas another study including adult CPP-treated women showed the ovarian volume within normal range (52). Ovarian volume >10 ml was observed in 20% of CPP-treated patients (49, 50), a percentage similar to that found in age-matched, healthy controls (48). CPP patients with regular vs irregular menses showed no differences in the ovarian volume (22).

The development of signs and symptoms of polycystic ovarian syndrome (PCOS) in former CPP women is controversial. Data from the literature are limited, and the criteria used for PCOS diagnosis are not uniform among studies. While Heger *et al.* (22) observed a low incidence of PCOS (2%) based on Franks criteria, one study is supportive of the relationship between CPP and PCOS (48). In this cohort, which did not include a control group of untreated CPP girls, the prevalence of PCOS was 32% using the 2003 Rotterdam criteria and 30% using the Androgen Excess Society (AES) criteria. Moreover, the prevalence of hirsutism and biochemical hyperandrogenism was 23 and 48%, respectively, while irregular menses were present in 15% and PCO morphology in 37% of women. High prevalence of PCO morphology by US is also detected in normal young women (up to 33%) (53). Using the 1990 NIH criteria, Magiakou *et al.* (36) found that PCOS prevalence in CPP-treated young women was not different from that in the untreated ones (17.2 and 30.8% respectively),

suggesting that GnRHa treatment does not predispose to PCOS development or menstrual irregularities.

Recently, in a large group of treated and untreated former CPP women aged 25–56 years, Lazar *et al.* (45) evaluated clinical signs potentially related to androgen excess, without performing hormonal assessment or imaging procedures. With these limitations, 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. Moreover, among the treated women a small number had received cyproterone acetate with outcomes similar to those of GnRHa-treated women, suggesting that pubertal suppression itself may reduce the risk of PCOS rather than the kind of medical treatment. Study findings also suggest an association between CPP and ovarian dysfunction later in life, probably related to the underlying neuroendocrine dysfunction, manifesting as CPP and persisting into adult life. The reproductive outcome in early and mid adulthood was normal in the great majority of the patients studied. A high prevalence of fertility problems was present in the untreated CPP group only, suggesting that gonadotropin-suppressive therapy may have a protective effect on the reproductive outcome.

Limited data are available on the reproductive outcome of male patients treated for CPP ([Supplementary Table 3](#)). Three small studies showed normal gonadal function in former CPP male adolescents aged 15–18 years (19, 54, 55). Feuillan *et al.* (54) described a progressive increase in testicular volume, similar to controls after 2 years post-therapy, with normal gonadotropins and testosterone levels 1 year after the discontinuation of treatment. Bertelloni *et al.* (55) confirmed normal testicular function in adolescent boys after GnRHa therapy with full pubertal development and, normal testicular volume, gonadotropins, testosterone, and inhibin B levels into normal adult range. Even though paternity rates have not been reported, sperm analysis, performed in six patients, appeared normal for age (55). Following histrelin implant removal, a spontaneous increase in testicular volume was observed within 1 year of histrelin explantation in five boys with CPP (42).

Bone mineral density

Few studies assessed BMD in CPP during GnRHa treatment, showing minor or no changes in BMD parameters

(56, 57, 58). Boot *et al.* (56) found normal BMD for chronological age but decreased BMD for BA after 2 years of treatment with GnRHa.

Pasquino *et al.* (15) reported that both mean BMD lumbar spine and spine volumetric BMD at the discontinuation of treatment were significantly lower in treated CPP girls than in untreated controls. However, at the complete resumption of gonadal activity, both increased to levels similar to those detected in controls. In a more recent study, Magiakou *et al.* (36) showed BMD values adjusted for height were not different between GnRHa-treated and -untreated girls, evaluated at least 2 years after cessation of treatment. Alessandri *et al.* (59) evaluated bone mass, body composition, and bone remodeling in two groups of girls with idiopathic CPP, namely, one group assessed at diagnosis and a second group 3 years after GnRH agonist treatment. BMD and body composition were not affected by CPP, and GnRHa treatment did not seem to have a detrimental effect on the acquisition of bone mass. Heger *et al.* (22) described normal BMD for age in women after GnRHa treatment, with a 17% prevalence of osteopenia. In a small group of CPP-treated female adolescents, Bertelloni *et al.* (27) showed patients' BMD was not different from that of their mothers. In male patients, evaluated at adult height, BMD was similar to that found in a group of healthy young Italian men with normal pubertal development (55). The highest prevalence of osteopenia (45%) was observed by Tung *et al.* (60) in a small group of Taiwanese women, but a plausible explanation for the finding was not provided by the authors.

Conclusions

GnRHa therapy is efficacious in restoring the growth potential in the majority of children with CPP under the age of 6 years, although the estimate of HG is variable and difficult to assess because of sample heterogeneity, methodological limitations associated with height prediction, and the absence of randomized trials. Age at puberty onset, BA advancement, age at initiation, and duration of treatment are the most important outcome predictors, although their impact on adult height remains to be established. Above-average BMI is present at diagnosis at a high rate among children with CPP, but long-term GnRHa treatment does not appear to cause or aggravate obesity. Long-term data do not support adverse consequences of GnRHa therapy on BMD. Gonadal function is preserved after treatment cessation with normal reproductive potential. An association between CPP and ovarian dysfunction independent of GnRHa treatment was

suggested, with a potential protective role of GnRHa therapy on the reproductive outcome. Data on the long-term risk of PCOS in CPP-treated and -untreated patients are conflicting although the majority of studies are not supportive of an association between GnRHa use and PCOS. Further studies to assess whether CPP has long-term implications on the general health status and the risk for premature ovarian failure and premature menopause in late reproductive years and to evaluate the impact of GnRHa therapy on the fertility, fecundity, and health of offspring are warranted.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-15-0590>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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