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Review

# Long-term effects and significant adverse drug reactions (ADRs) associated with the use of gonadotropin-releasing hormone analogs (GnRHa) for central precocious puberty: a brief review of literature

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**Summary.** Central precocious puberty (CPP) is defined as an early pubertal development that occurs before the age of 9 years in boys and 8 years in girls. It results from premature activation of the hypothalamic-pituitary-gonadal axis. Gonadotropin-releasing hormone agonists (GnRHa) have been the gold standard therapy for CPP for more than 30 years. These compounds have a high affinity for the pituitary LHRH receptor and are resistant to enzymatic degradation. Through continuous stimulation, GnRHa inhibit the pulsatile secretion of gonadotropin, resulting in hormonal suppression, cessation of pubertal development, and normalization of growth and skeletal maturation rates. The goal of therapy is to halt pubertal progression and delay epiphyseal maturation that leads to improvement of final adult height. There are no widely accepted guidelines for how long to continue treatment with a GnRHa for CPP, and individual practice varies widely. Furthermore, conflicting results have been published on the long-term effects of GnRHa therapy in patients with CPP. Therefore, we reviewed the current literature focusing our attention on the long-term effects and the significant adverse drug reactions (ADRs) observed during treatment with GnRHa in patients with CPP. Our review may provide the necessary data to enable clinicians to administer GnRHa in the safest and most appropriate way. Further studies are necessary to identify the mechanisms of development of potential adverse drug reactions related to GnRHa therapy in CPP. (www.actabiomedica.it)

**Key words:** precocious puberty, gonadotropin-releasing hormone analogs, long-term effects, significant adverse drug reactions (ADRs), Hartwig and Siegel severity scale

## Introduction

Precocious puberty (PP) is one of the most common reasons for referral to pediatric endocrinologists. PP is defined as the development of secondary sexual characteristics before the age of 8 years in females and 9 years in males (1-3). The overall incidence of sexual precocity is estimated to be 1:5,000 to 1:10,000, with the female-to-male ratio being approximately 10:1 (1).

Central precocious puberty (CPP) results from premature activation of the hypothalamic-pituitary-gonadal (HPG) axis) unlike peripheral precocious puberty, where the HPG axis is not involved.

Although the precise mechanisms triggering the onset of puberty are unclear, the earliest known biochemical change during puberty is increased production of kisspeptin produced by arcuate nucleus and anteroventral periventricular area of the hypothalamus.

This step is critical to puberty initiation. Neurokinin B and dynorphin from the same neurons stimulate and inhibit the release of kisspeptin respectively, and hence these kisspeptin, neurokinin and dynorphin neurons have now been recognized to be central to puberty initiation (1-4).

In females, CPP more frequently is idiopathic while in boys is more likely to be due to a pathological source (1-3). Risk factors for CPP include a history of international adoption, as well as congenital or acquired CNS insults. Several genetic syndromes are associated with CPP (4).

Apart from recognized genetic syndromes, from 5.2% to 27.5 % of cases have been reported to be familial and segregation analysis has suggested an autosomal dominant transmission with incomplete sex-dependent penetrance (4,5). Currently, mutations in the kisspeptin system, MKRN3, and DLK1 have been identified in sporadic and familial cases of CPP. In familial CPP, *MKRN3* defects were found in about 30% of families while in patients with apparently sporadic CPP, *MKRN3* defects were detected in about 8% of cases. In theses cases, genetic counselling should be considered in affected patients and their families (6).

The earliest clinical manifestation of central puberty in girls is usually breast development (thelarche), followed by pubic hair (pubarche). The pubertal growth spurt typically occurs during Tanner stage II-III, with the first menstrual period usually occurring at Tanner stage IV. In boys, the initial clinical sign of central puberty is testicular enlargement and the pubertal growth spurt happens later than in girls (7).

Gonadotropin-releasing hormone analogs (GnRHas) are the treatment of choice for children with CPP. Treatment aims to halt physical maturation, to prevent an early menarche, to retard skeletal maturation, to improve final adult height, to avoid psychosocial/behavioural sequelae, and to relieve the parents of the associated anxiety (8-11).

Good predictors of height outcomes include younger chronological age (CA), younger bone age (BA), greater height standard deviation score for CA at initiation of therapy (11-14) and a higher predicted adult height using Bayley-Pinneau tables (15). A suppression of luteinizing hormone (LH) to < 3 mIU/mL in patients on GnRHa therapy may be a reasonable target in patients on GnRHa therapy (16).

Although GnRHa therapy appears to be both well tolerated and effective in pediatric patients; there are no widely accepted guidelines for how long to continue treatment with a GnRHa for CPP. Individual practice varies widely among endocrinologists. Furthermore, conflicting results have been published on the long-term effects of GnRHa therapy in patients with CPP. These included a higher incidence of polycystic ovary syndrome (PCOs), changes in body composition, metabolic profiles and bone mineral density (16-21). Moreover, short term side effects such as headaches, hot flushes, mood swings and injection site reactions (rashes, bruising and sterile abscess formation) have been reported in the literature.

Therefore, we reviewed the current literature focusing on the long-term effects and the significant adverse drug reactions (ADRs) observed during treatment with GnRHa in patients with CPP. As long-term studies of male CPP patients are scarce, this review mainly addresses female CPP patients.

## Gonadotropin releasing-hormone analogs (GnRHa)

First synthesized in 1980, GnRHa desensitize and down-regulate GnRH-receptors, suppress gonadotropin secretion, and eventually reduce gonadal hormones to pre-pubertal levels (9,11,22,23).

Basically, the native GnRH molecule is modified at least at the glycine 6 position, where it is substituted by another amino acid resulting in a super-agonistic effect. Prolonged exposure of the pituitary to a GnRHa paradoxically results in inhibition of gonadotropin secretion.

In 1986, the first long-term study of daily GnRHa treatment in 27 children (21 female and 6 male), treated for 2-4 years, showed a reduction of growth velocity to pre-pubertal levels, improved the advancement of skeletal maturation, and increased the predicted adult height (PAH) (24,25).

GnRHa are available as rapid-acting or long-term depot preparations. The long-acting preparations available include: leuprolide, triptorelin and goserelin,

given every 3-4weeks or as a long-acting depot at 10 to 12-weekly intervals. The monthly (leuprolide 3.75 mg or triptorelin 3.75 mg) or 3-month depot leuprolide 11.25 mg are the most common formulation used to treat CPP as they cause a steady release of the drug without relevant side effects (1-4,8).

All these preparations are synthetic analogues of naturally occurring gonadotropin releasing hormone (GnRH) which possess greater potency than the natural hormone.

All depot preparations are available as lyophilized powder along with separate reconstituting fluid in a composite syringe. It is important to inject the preparation immediately after re-constitution, to avoid solidification and injection failure. Injection should always be administered deep intramuscularly, preferably in the gluteal region.

In the United States a histrelin implant that causes pubertal suppression for more than a year has been approved and successfully used. While short-acting intranasal preparations such as nafarelin are available for daily administration, these are less efficient and there are significant difficulties with compliance, which limit their use substantially as a first-line treatment.

In Europe, triptorelin depot is widely used at 28-day intervals, even though some authors have reported shorter frequency intervals of administration (21- 26 days). It is usually administered at a dose of 3.75 mg (approximately 60-75 μg/kg) for children weighting more than 20 kg; and a half dose has been employed in patients weighting less than 20 kg. Some authors have used higher doses (100-120 μg/kg/21-25 days) (26).

Leuprolide depot is used at different doses in Europe (3.75 mg/28 days) and in the USA (7.5- 15 mg/28 days) (21,27). The dose of leuprolide required for gonadal suppression is unclear, with higher doses employed in the USA (7.5 mg monthly) compared to European countries (3.75 mg monthly). This was addressed in a trial comparing the effect of 7.5 mg leuprolide monthly against 11.25 mg and 22.5 mg, 3-monthly, in girls with gonadotropin dependent precocious puberty (28). The study demonstrated that at 6 months, greatest suppression was observed in the 22.5 mg group, but the effects were similar at 1 year. Thus, the initial use of higher-dose leuprolide may be worthwhile, particularly in girls weighing more than 30 kg.

Results on goselerin depot (10,8 mg, 3 monthly) are mainly from the United Kingdom and limited to girls (56 females and 6 males) (29).

## Long-term Effects

### *a. Linear growth during the treatment*

A recent consensus document of 30 experts from Europe, the USA and Canada concluded that the efficacy of GnRHa in increasing adult height is undisputed only in girls <6 years old with early-onset CPP (9) but does not improve final height in girls beyond 8 years of age, and there is only modest improvement in final adult height (FAH) in girls aged 6-8 years (30,31). Carel et al. (32) also pointed out that continuing GnRHa treatment beyond 11 yr of age in girls did not improve FAH and could may potentially decrease it.

During treatment with GnRHa, it is frequently observed that height velocity decreases, even below pre-pubertal levels. The effects of GnRHa treatment on the growth hormone (GH)-IGF axis remain controversial. To compensate for the reduced spontaneous or stimulated secretion of GH and IGF-1 during GnRHa therapy, it would be logical to add recombinant human GH (rhGH) in combination with GnRHa.

Several groups have studied the effect of the addition of rhGH to GnRHa in children with CPP. The overall analysis of the data failed to indicate any benefit of combined therapy, while " individual reports suggested that in specific instances combined therapy may be beneficial in preserving or reclaiming growth potential and improving adult height " (33).

Nevertheless, a recent meta-analysis searched randomized controlled trials (RCTs) and clinical controlled trials (CCTs) adopting GnRHa therapy and GnRHa plus rhGH combination therapy to treat CPP girls. A total of six RCTs (162 patients) and six CCTs (247 patients) were included. Compared to the GnRHa therapy group, "the combination therapy group achieved taller final height, greater progression of final height compared with target height and larger height gains. No severe adverse effects to treatment were reported" (34).

### *b. Weight changes during treatment*

Several reports have demonstrated that treatment with GnRHa in patients with CPP was associated with an increase risk of obesity but others have not confirmed these observations.

In summary, to date the reported results on changes in the BMI values of CPP patients before, during and after treatment are inconsistent. Table 1 summarizes the data reported in the literature from 1991 to 2019. Therefore, long-term prospective controlled research is required to evaluate the weight changes in these subjects.

### *c. Metabolic changes*

Currently there is a relatively little research concerning changes in body composition and metabolic profiles in CPP patients following GnRHa treatment. It seems that in the normal-weight group there are no

**Table 1.** Review of body mass index (BMI) changes before, during and after GnRHa treatment

| Authors and references | Results |
|---|---|
| Kamp GA et al. J Clin Endocrinol Metab. 1991;72:301-7. | The increased BMI SDS during treatment seems to be a transient phenomenon. |
| Boot AM et al. J Clin Endocrinol Metabol. 1998;83:370–3. | The Authors performed dual-energy x-ray absorptiometry (DEXA) before and during treatment with GnRHa in girls with CPP and early puberty. Their findings showed that BMI SDS, fat mass, and percent of body fat for chronological age increased during GnRHa therapy. |
| Heger S et al. J Clin Endocrinol Metab. 1999;84:4583-90. | Many CPP patients were obese prior to GnRHa treatment but experienced no changes in BMI SDS following treatment.<br>The BMI SDS before treatment correlated strongly with the BMI SDS after treatment discontinuation. |
| Palmert MR et al. J Clin Endocrinol Metab. 1999;84:4480-8. | Obesity occured at a high rate among children with CPP, but did not appear to be related to long term pituitary-gonadal suppression induced by GnRHa administration. |
| Feuillan PP et al. J Clin Invest. 2001; 24:734-6. | The increased BMI, at initial presentation and during therapy, persisted after discontinuation of therapy and progressed to frank obesity. |
| van der Sluis IM et al. J Clin Endocrinol Metab. 2002;87:506-12. | After an initial increase of percentage body fat during treatment, percentage body fat decreased and normalized within 1 yr after cessation of treatment. |
| Arrigo T et al. Eur J Endocrinol. 2004;150:533-7. | 23.8% of CPP patients were obese prior to GnRHa treatment but experienced BMI decreases after at least 2 years of treatment. |
| Paterson WF et al. Clin Endocrinol (Oxf). 2004;61:626-34. | The mean BMI SD scores of CPP patients increased from 0.93 to 1.2. The frequency of overweight increased from 41% to 59%, and the frequency of obese patients increased from 28% to 39%. |
| Traggiai C et al. Eur J Endocrinol. 2005;153:463-4. | The Authors compared 29 ICPP girls with 45 healthy girls with normal onset puberty. Regarding BMI SDS few changes were observed during the first year of therapy, while an increasing trend was observed at the end of therapy and a complete recovery after 2.5 years of the end of therapy. |
| Pasquino AM et al. J Clin Endocrinol Metab. 2008;93:190-5. | CPP patients maintained their previous BMI SDS during treatment regardless of the overall increase in BMI after GnRHa treatment. |

*(continued)*

**Table 1** *(continued).* Review of body mass index (BMI) changes before, during and after GnRHa treatment

| Authors and references | Results |
|---|---|
| Glab E et al. Pediatr Endocrinol Diabetes Metab. 2009;15:7-11. | No significant correlation between overweight and obesity at the end of treatment and the duration of the therapy, and with the duration of CPP before introduction of GnRHa therapy was observed. |
| Magiakou MA et al. J Clin Endocrinol Metab. 2010;95:109-17. | No difference in the BMI SDS between GnRHa-treated group and a nontreated group was observed. Therefore, it appears likely that GnRHa treatment is not associated with an increase in fat mass |
| Ko JH et al. Horm Res Paediatr. 2011;75: 174–9. | The Authors assessed the percentage of body fat with DEXA method, at baseline and after one year of GnRHa therapy in 121 Korean girls and concluded that GnRHa therapy does not increase the prevalence of obesity in girls with CPP. |
| Yoon JY et al. J Korean Soc Pediatr Endocrinol.2011;16:165- 71. | BMI z-score increased from 0.26 ± 1.03 to 0.4 ± 0.89 during a year of GnRHa treatment. |
| Wolters B et al. Horm Res Paediatr. 2012;78:304-11. | Patients who were normal-weight at the start of the GnRHa treatment, exhibited an increase in BMI z-score (0.08±1.02 at baseline vs. 0.40±0.85 at the end of treatment vs. 0.41±0.89 at 6-month follow-up). In the overweight group, there was an insignificant change in BMI z-score (2.01±0.69 at baseline vs. 2.03 ± 0.54 at the end of treatment vs. 1.9 ± 0.51 at 6 months after the end of treatment). |
| Lee SJ et al. Chonnam Med J. 2012; 48:27-31. | BMI z-score of a Korean girl with CPP significantly increased from 0.58± 1.18 to 0.96 ± 0.83, after 18 months of GnRHa treatment. |
| Sorensen K et al. Eur J Endocrinol. 2012;166:903-10. | A year of GnRHa treatment increased BMI from 18.1 to 18.6 kg/m2. |
| Karamizadeh Z et al. Acta Med Iran. 2013;51:41–6. | GnRHa therapy cause central obesity and hyperlipidemia. The maximum weight gain of was observed at sixth months of therapy. |
| Gillis D et al. J Pediatr. 2013; 163: 532–6. | 34 girls with CPP treated with a GnRHa were evaluated before, and the end of treatment until menarche. Changes of BMI-SDS was not significant in neither group. |
| Anik A et al. Indian J Endocrinol Metab. 2015;19:267-71. | GnRHa treatment did not induce significant changes in BMI z-score for chronological age, but it increased BMI z-score for bone age. The percentage of overweight/ obese CPP patients increased from 59.4% to 65.7%, after a year of treatment. |
| Arani KS and Heidari F. Int J Endocrinol Metab. 2015 July; 13(3): e23085. DOI: 10.5812/ijem.23085v2 | The prevalence of obesity was significantly different between study groups at baseline and at sixth and 12th months of therapy (P = 0.11, P = 0.068, and P = 0.052, respectively). |
| Chemaitilly W et al. Clin Endocrinol (Oxf). 2016;84:361-71. | Obesity was more prevalent at the last follow-up than at the completion of GnRHa or the puberty onset (37,7%, 22,6% and 20,8%, respectively, P = 0.03). |
| Park J et al. Ann Pediatr Endocrinol Metab.2017; 22:27-35. | GnRHa treatment increased BMI z-score within a year of treatment, regardless of the subject's obesity status. |
| Arcari AJ et al. J Pediatr Endocrinol Metab. 2019;32:181-6. | An increase of BMI in girls with normal weight was observed. |

changes in insulin resistance, whereas a tendency to develop an insulin resistance was detected in patients who at the start of the treatment were overweight or obese (Table 2). Different diagnostic criteria, race/ethnicity, age at follow-up, and potential for bias make comparison of studies difficult, but concern continues for long-term endocrine and metabolic outcomes (35,36). Therefore, long-term prospective controlled research is required to evaluate the changes in obesity and insulin resistance in subjects with CPP.

***d. Bone mineral density (BMD) and bone markers***

Although suppression of ovarian activity has been associated with BMD reduction during GnRHa treatment (37), recent studies have shown no changes in bone mineralization among CPP patients who had received 3 years of GnRHa treatment (38). Antoniazzi et al. (39) reported that although the BMD decreased during GnRHa treatment, this was reversible and preventable with calcium supplementation. Furthermore, restoration of BMD after cessation of treatment has been also documented (26). As in normal girls and adolescents, exercise and adequate nutritional intake would be helpful for bone mass formation in CPP patients.

Regarding bone turnover markers in CPP patients, the 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, increased prior to GnRHa treatment but decreased during a 6-month treatment period and stabilized after treatment. Bone age-adjusted bone turnover markers were also normalized 2 years after treatment cessation. On the other hand, a report indicated that no changes in age- and bone age-adjusted BMD-SDS was observed during GnRHa treatment (40).

In brief, the long-term BMD studies in CPP patients proposed that although BMD levels decreased during GnRHa treatment, the bone mass was sufficiently preserved after treatment.

***e. Menarche, menstrual cycles and polycystic ovary syndrome (PCOS)***

Regarding reproductive function, studies indicate that menstruation occurs on average 16 months after the treatment of CPP is withdrawn (with a variation of 2 to 61 months). Regular ovarian cycles occur in 60% to 96% of the patients, and infertility has not been reported (9,26). However, there are concerns that PCOs may occur more often in those with CPP than in those with normal puberty (41). The reported frequencies vary and conflicting data on the long-term risk of developing PCOS in conjunction with CPP remain (Table 3).

PCOS is observed in 5%-10% of women of reproductive age and is characterized by anovulation, hyperandrogenism, and polycystic ovaries (42,43). Severe

**Table 2.** Review of the metabolic changes reported in patients with precocious puberty treated with GnRHa

| Authors and references | Results |
|---|---|
| Taşcilar ME et al. Turk J Pediatr. 2011;53:27-33. | An exaggerated elevation in trunk fat mass and insulin resistance (IR) in GnRHa-treated ICPP children was observed. |
| Sorensen K et al. Eur J Endocrinol. 2012;166:903-10. | Fasting insulin, first phase insulin release and mean plasma insulin during oral glucose tolerance test in CPP patients increased after a 52-week period of GnRHa treatment, whereas whole body insulin sensitivity index decreased, indicating an insulin resistance. |
| Park J et al. Ann Pediatr Endocrinol Metab.2017;22:27-35. | No changes were observed in QUICKI and HOMA-IR within a year of treatment in the normal-weight girls with CPP. |
| Arcari AJ et al. J Pediatr Endocrinol Metab. 2019;32:181-6. | GnRHa did not affect BMI, insulin index and lipid profile. However, an increase of BMI in girls with normal weight was observed. |

**Table 3.** Review of PCOS prevalence in girls with precocious puberty before, during or after treatment with GnRHa

| Authors and references | Results |
|---|---|
| Boepple PA. In: Savage MO, Bourguignon J-P, Grossman AB, eds. Frontiers in paediatric neuroendocrinology. Oxford, London,Edinburgh, Cambridge, Carlton: Blackwell. 1994: pp. 23–9. | PCOS was reported in approximately half of the patients treated with GnRHa. |
| Bridges NA et al. Clin Endocrinol (Oxf) 1995; 42: 135-40. | The prevalence of PCOS among CPP patients was 24%, compared with 2% in an age-matched control group. |
| Lazar L et al. Eur J Endocrinol. 1995; 133: 403-6. | A significant number of girls with CPP develop PCO-like syndrome at a relatively young age. |
| Baek-Jensen AM et al. J Pediatr.1998; 132:105–8 | The Authors did not observe PCOS during or after treatment with GnRHa. |
| Heger S et al. J Clin Endocrinol Metab.1999; 84:4583–90. | No increased incidence of PCOS in GnRHa-treated patients with CPP compared with the normal population was reported. |
| Chiavaroli V et al. Eur J Endocrinol. 2010;163:55-62. | The prevalence of PCOS and hyperandrogenemia was significantly higher in GNRHa-treated adolescents than in untreated adolescents (36 and 14.5% respectively, P=0.04; 56 and 23.6% respectively, P=0.01). |
| Magiakou MA et al. J Clin Endocrinol Metab. 2010;95:109-17. | 21% of subjects evaluated between ages 16 and 32 had PCOS, using the National Institutes of Health criteria. |

insulin-resistant obesity, premature adrenarche, and sexual precocity in childhood are some of the known risk factors of PCOS (43,44).

In summary, the prevalence of PCOS among CPP patients varies depending on the characteristics of the patients, durations of treatment and follow-up period, and differences in the PCOS diagnosis standards. It is unclear whether this association is due to the hyperinsulinemia or premature adrenarche already present at CPP onset or a result of an abnormal hormonal response to GnRHa treatment (45). A comparison with a control group of CPP patients through a long-term evaluation from diagnosis to post-treatment adulthood is needed to determine the causative factors of PCOS in patients treated for PPC (45).

### *f. Psychosocial changes*

One of the most common concerns about PP in girls is the potential for adverse psychological consequences. Numerous studies have reported an association between early normal puberty and adverse psychological, behavioural, and social outcomes in girls (46-51).

Although many studies have examined early maturity or puberty, little is known about psychosocial changes in girls with CPP receiving treatment with GnRHa (Table 4). The available results are reassuring regarding concerns of adverse psychological consequences of early puberty in girls. However, long-term prospective studies are needed in order to further elucidate the psychological impact of PP on girls and their mothers.

## Adverse Drug Reactions (ADRs) associated with the use of GnRHa

Bone pain, micturition problems, hypersensitivity (itching, skin rash, fever), gynecomastia, flushing, depression, easy and quick to anger, headache, nausea, muscle pain, joint pain, excessive sweating, fatigue, sleep disturbances, pain at the injection site, predisposition to hypertension, and thrombosis are the adverse

**Table 4.** Review of psychosocial changes in girls with precocious puberty before and during treatment with GnRHa

| Authors and references | Results |
|---|---|
| Xhrouet-Heinrichs D et al. Acta Paediatr. 1997; 86:808–15. | Some behavioral and affective characteristics were observed in girls with PP. During treatment with long acting triptorelin, problematic behavior and functioning decrease slightly, particularly in the few girls showing breast regression. |
| Officioso A et al. J Pediatr Endocrinol Metab. 2000 Jul;13 Suppl 1:835-9. | Ten adolescent girls aged 14 years treated for ICPP were evaluated. All the adolescents had a negative body image compared with age-matched controls and expressed a strong inhibition of their femininity. Their poor body image was reflected by their low self-esteem.A psychological support was recommended. |
| Mul D et al. Acta Paediatr. 2001;90:965–71. | The psychological evaluation did not reveal any consistent abnormalities in adopted children with early puberty. Treatment with GnRHa with or without rhGH did not increase emotional and behavioural problems in adopted children, nor was their self-perception decreased. |
| Zheng F et al. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2008; 37: 289- 94. | The authors compared the psychological behavior of girls with ICPP before and after treatment by GnRHa. They found that the self-esteem scale, and body-esteem scale score in ICPP were significantly lower compared to controls (P <0.05). |
| Kim YJ et al. Ann Pediatr Endocrinol Metab 2013;18:173-8. | The psychological assessment did not exhibit a significant difference except with scores for sociability and behavior problems. |
| Choi MS et al. Ann Pediatr Endocrinol Metab. 2016; 21:155-60. | Patients with PP had distorted perception about their body image and breast development that seems to contribute to depression score. |
| Schoelwer MJ et al. Horm Res Paediatr. 2017; 88:347-53. | Girls with CPP completed psychological assessments at baseline and after 1 year along with their mothers. All girls were treated with GnRH analogs. Psychological measures were normal in all girls. |

drug reactions (ADRs) observed in adults (52-57). In children, the available evidences show that GnRHa in general are safe and effective long- term (58,59). However, some significant ADRs in children treated with GnRHa for CPP have been reported (60).

ADRs are basically defined according to the World Health Organisation as: "any response to a drug which is noxious, and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function " (61).

Relevant studies indexed in Pubmed and Google Scholar were selected using the search terms: "precocious puberty/early puberty, GnRH analogue, GnRHa safety and adverse events". For the classification of ADRs severity we choose the Hartwig Siegel assessment scale (62).

### *a. Vaginal spotting/bleeding (Hartwig and Siegel severity scale: Level 1)*

Continuous stimulation of the pituitary gland results in a short period of pubertal stimulation, followed by down regulation of GnRH receptors, pituitary desensitisation and reduced gonadotropin synthesis. Therefore, the first injection of GnRHa is associated with a transient surge in LH and FSH resulting in a transient increase in estradiol levels, which then rapidly drops following down regulation of GnRH receptor, usually within a fortnight (63).

This transient surge in estradiol may result in vaginal spotting/ bleeding, in a small number of female patients, following the first injection due to discontinuation of the estrogen support of the proliferative and stable endometrium.

Eight of the 28 (28.5%) girls, aged 6.5-11 years, with idiopathic CPP treated by Yeshaya et al. (64) every 28 days with an intramuscular depot GnRHa developed vaginal bleeding after GnRHa administration. Of these, prolonged vaginal bleeding of 11-13 days occurred in four girls, three recurrent episodes occurred in one during the second injection, and in one other girl the 4th episode occurred after 6 months of treatment. The episodes resolved spontaneously and necessitated no further treatment.

However, other researchers have suggested the use of an anti-androgen [cyproterone acetate, given (usually) for the first six weeks of therapy at a dose of 70 mg/m$^2$/day], or a prostanoid receptor antagonist or a co-injection of depot medroxy-progesterone acetate (MPA) with the first dose of GnRHa (65,66).

### *b. Local side effects (Hartwig and Siegel severity scale: Levels 1 and 3)*

Local side effects, including pain at the injection site and flares usually are mild, although some may persist for several months and can leave significant scarring. Rare cases of subcutaneous nodules and sterile abscess (SAs) formation related to GnRHa, affecting the compliance with the treatment, have been observed (60, 67-69).

Lee et al (70) reported a prevalence of SAs formation in 4 out of 621 patients (0.6%) with CPP and early onset puberty, who were receiving monthly long-acting GnRHa (leuprolide acetate, triptorelin acetate) (70). In one patient, SAs occurred following leuprolide acetate depot therapy and also developed after a switching the treatment to triptorelin acetate depot. The fact that one patient had SAs formation following treatment with 2 different long-acting GnRHa can suggest that the cause could be attributed to the antibody formation against the same type of biodegradable polymers (lactic acid glycolic acid copolymer) present in the depot formulations (69,70).

### *c. Slipped capital femoral epiphyses (SCFE) (Hartwig and Siegel severity scale: Level 5)*

Slipped capital femoral epiphyses (SCFE) occur mainly in boys in late childhood or adolescence. The incidence is 0.33/100,000 to 24.58/100,000 children 8 to 15 years of age. The single most significant risk factor for SCFE is obesity. Other risk factors include male sex, periods of rapid growth, and prior radiation therapy. The average age of onset is 11.2 years in females and 12.0 years in males. Approximately 25% (range: 8-50%) of cases are bilateral. Delay in the diagnosis of SCFE is associated with higher rates of complications, including femoral head osteonecrosis (71,72).

Five events of SCFE associated with GnRHa occurred in children during or shortly after the drug discontinuation (70,73,76). Inman et al. (76) suggested that a lack of adequate sex hormone exposure at a " critical period " of bone formation may result in a weakened epiphysis that becomes susceptible to slipping. In addition, the increase in growth velocity after

**Table 5.** Hartwig and Siegel severity scale

| Level description |
|---|
| **Level 1:** An ADR occurred but required no change in treatment with the suspected drug. |
| **Level 2:** The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay |
| **Level 3:** The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed, and/or an antidote or other treatment was required. No increase in length of stay. |
| **Level 4:** Any level 3 ADR which increases length of stay by at least 1 day. |
| **Level 5:** Any level 4 ADR which requires intensive medical care. |
| **Level 6:** The adverse reaction caused permanent harm to the patient. |
| **Level 7:** The adverse reaction either directly or indirectly led to the death of the patient. |

stopping GnRHa , subsequently results in a reduction of the shearing force needed for the displacement of the epiphysis.

***d. Pseudotumor Cerebri (PTC) (Hartwig and Siegel severity scale: Levels 5)***

Pseudotumor cerebri (PTC), also known as idiopathic intracranial hypertension, is a disorder with increased intracranial pressure and associated headaches, papilledema, vision changes, or pulsatile tinnitus in the setting of normal imaging and cerebrospinal fluid (CSF) studies. Children of both genders are affected equally before puberty (77). Males (aged 12 to 15 years) have an annual incidence of 0.8 per 100,000; females aged 12 to 16 years have an annual incidence of 2.2 per 100,000 (78). PTC can be classified as either primary (when there is no clear causal factor) or secondary to cerebral venous thrombosis or changes in the composition of the CSF. Proposed mechanisms involve the vascular, hormonal, and cellular systems. The first-line treatment is acetazolamide. The most concerning complication of PTC is permanent vision loss because of compression of the optic nerve secondary to elevated intracranial pressure (77).

Pseudotumor cerebri (PTC) secondary to use of leuprolide acetate is an extremely rare event with only two cases reported in the literature (79,80).

*Summary of case 1 presentation reported in the literature (Reference 79)*

A 9-year-old girl with PP was treated with leuprolide acetate (3.75 mg). After the 4th dose, she presented headache and hypertension (130-155/85-110 mmHg). There were no causes underlying the hypertension such as cardiac, renal, or endocrine. Neurological examination was normal except for bilateral papilledema. Cranial magnetic resonance imaging was normal and the orbital section of MRI revealed bilateral optic nerve enlargement. Cerebrospinal fluid (CSF) opening pressure was elevated. Triptorelin therapy was stopped and acetazolamide was started. The patient improved and the CSF pressure and fundoscopic examinations returned to normal (79).

*Summary of case 2 presentation reported in the literature (Reference 80)*

A 9-year-old girl with PP was treated with leuprolide acetate (3.75 mg). After 4 month, she complained of holocranial headache, transient visual obscuration followed by progressive visual loss. After 6 months, she persisted with holocranial headache and progressive visual loss associated with ocular deviation. Neuro-opthalmological examination revealed severe visual loss and bilateral papilledema. Cerebrospinal fluid (CSF) analysis showed opening pressure of 45 cm H2O. The most likely diagnosis was PTC associated with leuprolide acetate. Treatment was started immediately with oral acetazolamide and leuprolide was discontinued. Unfortunately, acetazolamide induced a metabolic acidosis. A ventriculoperitoneal shunt was performed to control intracranial pressure as an alternative to acetazolamide treatment. The follow-up of 18 months showed CSF pressure of 14 cm H2O, stabilization of visual acuity and resolution of papilledema (80).

***e. Hypertension (HTN) (Hartwig and Siegel severity scale: Levels 5)***

According to the instructions for GnRHa use, issued by the manufacturer, arterial hypertension is considered an infrequent complication (81).

Hypertension has been reported in girls with CPP (82-85) and in girls with gender dysphoria (86), likely due to loss of the vaso-protective properties of estrogens (87). The authors concluded that although estrogen depletion may play a role in the pathogenesis of triptorelin-induced HTN, this aspect should be further investigated. Furthermore, clinicians should be aware of the possibility, although rare, of HTN developing during triptorelin administration in childhood, specifically in patients at increased risk of HTN, such as those with Williams-Beuren syndrome (Table 6) (83).

***f. Anaphylactic reactions (Hartwig and Siegel severity scale: Levels 5)***

Anaphylaxis is defined by the European Academy of Allergy and Clinical Immunology (EAACI)

**Table 6.** Summary of patients with central precocious puberty developing arterial hypertension during GnRHa treatment

| Authors and references | Results |
|---|---|
| Calcaterra V et al. Indian J Pediatr. 2013;80:884-885. | A 7-year-old girl with triptorelin-treated CPP, who developed reversible HTN with secondary concentric left ventricular hypertrophy, requiring transient antihypertensive therapy. |
| Siomou E et al. Pediatr Nephrol. 2014;29:1633–1636 | A 10-year-old girl with a Williams-Beuren syndrome and CPP who developed HTN with triptorelin treatment. In that case, blood pressure totally normalized, without any anti-hypertensive medication once GnRHa was discontinued. |
| Palma L et al. J Pediatr Endocrinol Metab. 2018 Aug 8. pii: /j/jpem. ahead-of-print/jpem-2018-0210/ jpem-2018-0210.xml. doi: 10.1515 /jpem-2018-0210 | A girl with CPP who developed HTN from treatment with GnRH-a (triptorelin). HTN subsided once triptorelin was interrupted. Consequently, the Authors hypothesized that the hypertension was related to triptorelin treatment. |
| Sifaki L et al. Front Pediatr. 2019 Mar 19;7:74. doi: 10.3389/ fped. 2019.00074. | A 10-year-old girl with CPP during treatment with triptorelin, developed an asymptomatic stage II HTN. Initial workup showed no renal, thyroid, or electrolytes abnormalities. A complete normalization of her blood pressure was obtained without any medication. |

as a severe, life-threatening generalised or systemic hypersensitivity, characterised by its rapid onset with life-threatening airway, breathing and/ or circulatory problems (88).

The incidence of anaphylaxis in children worldwide varied widely, ranging from 1 to 761 per 100 000 person-years for total anaphylaxis and 1 to 77 per 100 000 person-years for food-induced anaphylaxis. Gender and ethnicity are demographic risk factors associated with anaphylaxis in children (89).

Whilst drug-induced anaphylaxis is more commonly reported in adulthood, less is known about the role of drugs in pediatric anaphylaxis. Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the main elicitors in drug-induced anaphylaxis in children. Anaphylactic reactions to GnRHa agonists are exceedingly rare (90-92).

*Summary of case 1 presentation reported in the literature (Reference 93)*

An 8-year-old girl who was diagnosed with CPP was receiving triptorelin acetate treatment uneventfully for 6 months. To evaluate the efficacy of the treatment, an LH-RH stimulation test with gonadorelin acetate was planned. Within 3 min after intravenous administration of gonadorelin acetate, she lost consciousness and tonic seizures began in her hands and feet. She was immediately treated with epinephrine (0.01 mg/kg; 1:1000), high flow supplemental oxygen (6-8 L/min), IV diphenhydramine (1 mg/kg), and IV methylprednisolone (1 mg/kg). Her vital signs recovered within 30 min. When her medical history was more deeply investigated, her parents recalled that there were several skin reactions along with pruritus after a previous gonadorelin acetate injection. A skin test with gonadorelin acetate was planned during the follow-up, however, it could not be performed due to the unwillingness of her parents (93).

*Summary of case 2 presentation reported in the literature (Reference 70)*

An 8.4-year-old girl with CPP was treated with triptorelin acetate depot SC injected at four-week intervals. Immediately after the sixth injection, she developed dizziness, headache, whole body redness, and chest tightness. Subsequently, she lost consciousness. Blood pressure (BP) could not be measured at that time. All the above symptoms were relieved within several minutes without any particular treatment. Anaphylaxis was considered to have occurred (70).

In conclusion, although the occurrence of anaphylactic reactions to GnRHa are very rare, it can have serious practical implications. Therefore, clinicians should be aware of the potential association of GnRH analogs with systemic reactions, should recognize that recurrent anaphylaxis may occur due to the long half-life of these therapeutic agents in tissue and recommend GnRHa administration under proper conditions, even if there is no history of previous systemic hypersensitivity reactions.

## Conclusions

Since 1981, GnRHa administration has been the standard treatment for CPP. GnRHa suppress LH and FSH and thereby induce a marked inhibition of gonadal activity. This treatment is generally considered to be safe and well tolerated in children and adolescents. The most commonly reported drug reactions were pain, swelling, and urticaria at the injection site. Most events were mild, and there was no interruption in study procedures from these ADRs. Nevertheless, whatever is the frequency of these side-effects, clinicians using these treatments should be aware of the possibility of significant local and general ADRs that can lead to treatment withdrawal in the most severe cases.

We hope that our review may provide the necessary data in order to enable clinicians to administer GnRHa in the safest and most appropriate way. Further studies are necessary to identify the mechanisms of development of potential adverse drug reactions related to GnRHa therapy in CPP and the potential risk of causing prolonged QT, as reported in adults (94).

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