GnRH analog is ineffective in increasing adult height in girls with puberty onset after 7 years of age: a systematic review and meta-analysis

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Abstract

Objective: We assessed the effectiveness of puberty blockade with a gonadotropin-releasing hormone (GnRH) analog in increasing adult height (AH) in girls with puberty onset between 7 and 10 years of age.

Methods: We performed a systematic review and included controlled studies in which girls with early puberty (EP) were assigned to the GnRH analog or no treatment groups. The primary outcome analyzed was AH. Search strategies were applied to the MEDLINE, EMBASE, LILACS and CENTRAL databases.

Results: We identified 1514 references, and six studies fulfilled our eligibility criteria. Two studies were randomized and four were not randomized. At the baseline of each trial, height, chronological age, bone age, predicted AH (PAH) and target height (TH) were equal between the groups. All studies used intramuscular triptorelin every 28 days in the intervention groups. The mean duration of the therapy was 2 years. Meta-analysis of AH among the six studies (comprising 332 girls) showed no significant difference between the groups (mean difference=0.50 cm, 95% confidence interval=−0.72 to 1.73 cm, $I^2=0\%$). In a sub-group analysis based on PAH (<155 cm and <TH; <TH, but >155 cm and equal to TH), there was no difference in average AH between the groups. The quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation approach was low.

Conclusion: We found no evidence from controlled experimental and observational studies that compared with no treatment, the use of GnRH analogs improved AH in girls with EP.

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Introduction

Early puberty (EP) is defined as puberty occurring at the normal age of pubertal development, where the appearance of Tanner stage 2 or 3, with or without sexual hair, which is associated with advanced bone age (BA), accelerated growth velocity and activated hypothalamic–pituitary–gonadal axis, would occur during the first half of the normal distribution of pubertal onset (1, 2). Although various age intervals have been mentioned in the literature for EP, based on the report by Lebrethon and

Bourguignon (3), Mul *et al.* (1) proposed to consider EP as puberty onset in girls between 8 and 10 years of age in Europe and at 7–9 years of age in the United States.

Conversely, precocious puberty (PP) is defined as the appearance of secondary sexual characteristics before 8 years of age in girls and before 9 years of age in boys. In a historical series of girls with severe forms of PP, lack of treatment has been associated with a mean adult height (AH) of 152 cm and loss of height of

approximately 10 cm (4). Because of these data, parents and pediatricians are concerned about the potential loss of height in girls with EP.

However, because EP is considered as normal puberty development, girls with this diagnosis are not expected to have a reduction in AH as well as other maladjustments found in some girls with PP. An observational study following the growth and pubertal development of 104 Thai girls with EP in Thailand reported that at the final visit, these girls attained AH according to their parental height (5).

In some girls, EP can be accompanied with rapid pubertal development, reaching Tanner stage 3 before 10 years of age, which is significantly earlier than the median age for reaching this stage in normal girls (11.9 ± 1.0 years) (6). Some authors consider this situation, i.e., combined early and fast puberty, to be a state of so-called sexual precocity for age, a condition that is very similar to central PP (CPP) and with the possibility of reduction in AH, and a form of psychosocial embarrassment for the girls (7). Meanwhile, Lazar *et al.* (8) analyzed data on 126 girls with that diagnosis and showed that girls treated with a gonadotropin-releasing hormone (GnRH) analog and untreated girls achieved a similar mean AH, which was not significantly different from their respective mean target heights (THs).

At the same time, the search for puberty blockade in healthy girls who have just had their eighth birthdays and whose pubertal evolution is compatible with EP is common in clinical practice. Many physicians are also concerned that these children may not reach their TH range ($TH \pm 1.5$ standard deviation (S.D.)), and consequently, many girls with normal puberty considered as having EP have received puberty blockade with GnRH analogs worldwide.

Thus, under the hypothesis that there is no difference on AH with the usage of GnRH analogs, we assessed whether puberty blockade with GnRH analogs is effective in increasing AH in girls with EP compared with that in those undergoing no treatment.

Methodology

A systematic review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions (9) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (10). Its protocol was registered in the International Prospective Register of Systematic Reviews, under CRD42017064599.

Criteria for eligibility

We included randomized and non-randomized controlled studies that adopted the PICO (P=Patients, I=Intervention, C=Comparison and O=Outcomes) structure noted below:

- *Patients:* We considered girls as having EP based on the appearance of Tanner stage 2 or 3 between 7 and 10 years of age, with or without sexual hair and associated with some evidence of activation of the hypothalamic–pituitary–gonadal axis.
- *Intervention:* The intervention group comprised girls whose puberty was blocked using a long-action GnRH analog in its different forms (triptorelin, nafarelin, leuprolide, goserelin and buserelin).
- *Comparison:* Placebo or no treatment.
- *Outcomes:* The primary outcome analyzed was the average AH. Secondary outcomes were whether the girls reached their TH range, pubertal height gain, adverse events, quality of life and psychosocial impact.

Exclusion criteria

We excluded studies that included girls with some organic conditions identified as the cause of PP, clinical signs of rapidly progressing puberty (a change in the Tanner stage in <3 months) or puberty onset before 7 years and studies in which the groups were significantly different in terms of height, chronological age (CA), BA, TH and predicted AH (PAH) at the baseline visit.

Identification of the studies

Four general and adaptive search strategies were created for the electronic health databases: EMBASE (by Elsevier, 1980–2018), MEDLINE (by PubMed, 1966–2018), LILACS (by Virtual Health Library, 1982–2018) and Registry of Controlled Clinical Studies of the Cochrane Collaboration (CENTRAL–Cochrane; [Supplementary data](#), see section on [supplementary data](#) given at the end of this article). There was no restriction regarding language or year of publication. Databases were searched on May 25, 2016, and updated on January 25, 2018.

Eligible studies were also surveyed in the Trip Medical Database, SCOPUS, Web of Science and CINAHL. We also looked for unpublished studies among Ph.D. or master degree theses, [ClinicalTrials.gov](#) website and Brazilian Registry of Clinical Trials (ReBec).

We used the Endnote software for downloading all references, removing duplicates and facilitating the selection process.

Assessment of eligibility of the studies

Two reviewers (I A F and F B) independently selected the titles and abstracts identified during the literature search. Potentially eligible studies for inclusion in the review were read completely and subsequently assessed in terms of appropriateness of the proposed PICO structure. Whenever there was disagreement in the selection process, a consensus was reached by discussion with the project coordinator (V S N N).

For the studies selected for inclusion, both reviewers used a standardized extraction form so that all information regarding each study (number of patients, average age, study design, inclusion and exclusion criteria, intervention nature, outcomes analyzed, monitoring time and risk of bias) might be computed.

Risk of bias

For each selected randomized and prospective non-randomized clinical study, the risk of bias was evaluated according to the criteria described in the Cochrane Reviewers Handbook (9), which considers seven domains: the process of randomization, concealing allocation, blinding of participants and researchers, blinding of outcome assessors, whether the losses were included in the final analysis, selective reporting of outcomes and others.

For each selected observational study, the risk of bias was evaluated according to the criteria described by the Newcastle–Ottawa Scale (NOS) for case–control studies, which considers three domains: selection (four items), comparability (one item) and exposure (three items) (11).

Synthesis and analysis of data: meta-analysis

Similar outcomes measured in at least two studies were plotted in a meta-analysis using the software Review Manager 5.3 (the Cochrane Community). Continuous data are expressed as means and s.d.s. Differences between means with 95% CIs were used as an estimate of the intervention effect. We chose the random effect model as the analytic model in the meta-analysis. The inverse variance method was used for weighing the estimates of the effect among the studies included. Inconsistencies among the study results were verified by visual inspection of the forest graph (absence of overlap of CIs of the estimates of the effects in the individual studies) and by the Higgins inconsistency test in which $I^2 > 50\%$ indicated a moderate probability of heterogeneity.

Quality of the evidence

The quality of evidence of estimation of the effect of the intervention on outcomes that could be plotted in the meta-analysis was generated in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group (12).

Results

Selection of studies

The search strategies yielded 1514 references; after removing duplicates, 1382 studies remained. We selected 33 studies, with a high probability of inclusion in this review, for complete reading (Fig. 1). After completely reading these references, six studies met our eligibility criteria and therefore were included in this review (2, 8, 13, 14, 15, 16). A total of 27 studies were excluded for the following reasons: six studies did not have controls; two used historical control groups (17, 18); five were retrospective studies on CPP (19, 20, 21, 22, 23); in two studies, the control group consisted of patients with normal evolution at puberty (24, 25); in three studies on EP (26, 27, 28) and six studies on CPP, the control group had a predicted AH significantly greater than that in the intervention group (29, 30, 31, 32, 33, 34) and three studies on CPP included girls with puberty onset at <7 years of age (35, 36, 37).

The six studies included involved a total of 332 girls. Two studies were randomized (2, 16), three were non-randomized prospective controlled studies (13, 14, 15) and one was an observational controlled study (8). Eligibility criteria for the included studies and baseline characteristics of study participants are presented in Tables 1 and 2, respectively.

At the baseline of each trial, height, CA, BA, PAH and TH were not statistically different between the intervention and comparison groups. In two studies, the included girls presented with mean PAH of <155 cm and <mean TH at diagnosis (8, 16). In the study conducted by Chiavaroli *et al.* (13), the patients had mean PAH < mean TH, but >155 cm. In three studies (2, 14, 15), the PAH was equal to TH. PAH was calculated by the method used by Bayley and Pinneau (38).

Regarding the type of GnRH agonist, all studies used intramuscular triptorelin every 28 days in the intervention group, whereas the comparison groups did not receive treatment. The mean duration of intervention was 2 years in most studies, and follow-up lasted until achievement of AH.

Figure 1

Flowchart for identifying eligible studies.

Risk of bias among the included studies

For randomized and non-randomized prospective studies, the risks of bias in the five included studies are presented in Fig. 2. For the observational study, applying NOS, Lazar *et al.* (8) achieved three stars for the selection domain, two for comparability and three for exposure, resulting in a total of eight stars (maximum nine).

Meta-analysis

The only outcomes that could be plotted in the meta-analysis were AH and final BMI. Meta-analysis of AH

among the six studies showed no significant difference between the groups (mean deviation (MD)=0.50 cm, 95% CI=−0.72 to 1.73 cm, $I^2=0\%$). We performed a sub-group analysis according to PAH (<155 cm and <TH, <TH but >155 cm and equal to TH); in all these analyses, there were no differences in AH between the groups (Fig. 3).

Three studies assessed BMI at discontinuation of the GnRH treatment and at the final study visit. In the studies by Chiavaroli *et al.* (13) and Lazar *et al.* (8), at discontinuation of the suppressive treatment, the treated girls showed higher BMI than the untreated girls; however, during AH measurement, no significant difference was

Table 1 Characteristics of the included studies: inclusion and exclusion criteria, intervention, control, follow-up time and outcomes.

Ref./study design	Inclusion criteria	Exclusion criteria	n/intervention/dose/mean period of the treatment	Control, n*	Follow-up time	Outcomes
(2)(RDZ)	Early puberty, defined as breast development between 7.5 and 8.5 years, associated to advanced BA, growth velocity > 1.5 s.d. score	Growth hormone deficiency, congenital adrenal hyperplasia, learning disorder, hydrocephalus, cerebral palsy, organic illness in hypophysis and gonads	23/ Triptorelin 3.75mg/ i.m. every 4 week/25 months (12-40 months)	23	I=A mean of 33 months (16-69 months) after treatment. C=A mean of 41 months (31-81 months)	Mean adult height, growth after menarche, adult height compared to adult height prognosis and target height, adult height compared to first evaluation height, adverse events
(13) (non-RDZ)	Early puberty, defined as onset of secondary sex characteristics between 8 and 10 years for Caucasian girls. Breast stage Tanner 2 or 3, with or without sexual hair for not longer than 6 months, pubertal uterine and ovarian development at pelvic ultrasonography, peak LH response > 5IU/L after exogenous GnRH therapy, recent increase in growth velocity, and BA > 1 year above the chronological age with a predicted final height less than genetic target height	Use of any medication or presented congenital anomalies, psychomotor delay, organic brain disorders, and autoimmune diseases; onset of secondary sex characteristics before 8 years, disorders of androgen excess, congenital adrenal hyperplasia or other endocrinopathies, and being born prematurely or small for gestational age	25/ Triptorelin/ i.m. 80 µg/kg every 28 days/ 1.9 ± 0.5 years	55**	Biannual until menarche. Final evaluation 2 or more years after menarche	Adult height, adult height compared to predicted height, BMI, blood pressure, lipid profile, fasting glucose and insulin, resistance, androgens dosage, FSH, LH, estradiol, progesterone, side effects
(16) (RDZ)	Advanced puberty defined by breast development (B2-B3) with or without pubic hair (P1-P3), between 8.4 and 10 years, since 3-6 months, uterine length greater than 35 mm at ultrasonography, peak plasma LH response to GnRH greater than 5IU/L, recent acceleration of growth rate, BA greater than 10.5 year; predicted adult height between -1 and -3 s.d.	Not reported	20 / Triptorelin 3.75mg/ i.m. every 4 week/2 years	10	Biannual evaluation for 2 years. All patients were followed until adult height	Growth velocity, bone maturation, total height gain, age at menarche, time from treatment to menarche, mean adult height, adult height compared to initial height and predicted height, chronological and bone age
(14) (non-RDZ)	Advanced puberty, onset of puberty between 7.5 and 8.5 years; breast stage >2; growth velocity >5 cm/year in the following year of breast development; BA ≥2 years in advance of CA; BA/CA ≥ 1 in the following year after breast development	Evidence of organic central nervous system disorders; adrenal or gonadal pathology	16/ Triptorelin/ i.m. 3.75mg/month for 1 year	16**	Until adult height	Adult height, height at the end of treatment, menarche age, growth peak, pubertal duration, weight gain, BMI variation, obesity
(15) (non-RDZ)	Early puberty, with symptoms beginning at 7-8.5 years of age (Tanner stage ≥2, activation of the hypothalamic-pituitary-gonadal axis)	Problems that could affect growth and puberty, such as growth hormone deficiency, thyroid pathology, adrenal and gonadal pathology, dysmorphic syndrome, skeletal dysplasia, chronic illness, learning disability, cerebral palsy, hydrocephalus, and those with a history of chronic drug use	18/ Triptorelin/ i.m. 3.75mg every 28 days/ 2 years	8**	Until adult height	Mean adult height
(8) (OBS)	Early puberty defined as appearance of first pubertal signs (breast buds and/or genital Tanner stage 2), with or without sexual hair, between ages 8 and 9 years; fast transition from Tanner stage 2 to 3, accompanied by a recent acceleration of growth velocity and bone maturation rate; laboratory findings appropriate for midpuberty at age less than 9.5 years	Girls born prematurely or who were small for gestational age, girls with chronic diseases, bone dysplasias, organic brain diseases, congenital adrenal hyperplasia	63/ Triptorelin maximal dose of 3.75 mg/ i.m. every 4 weeks/2-4 years	63**	Until adult height	Adult height, BMI

Ref., reference; BA, bone age; BMI, body mass index; C, control; FSH, follicle-stimulating hormone; I, intervention; i.m., intramuscular; LH, luteinizing hormone; RDZ, randomized; OBS, observational. * Controls had no treatment; ** No treatment (parents request)

found between the two groups. Llop-Vinolas *et al.* (14) found no significant differences in body fat mass, BMI and weight during treatment and at the end of the study. A meta-analysis of BMI at the final visit did not show any significant difference between the groups (MD=0.01, 95% CI=-0.35 to 0.37, $I^2=40\%$).

Results of outcomes that could not be plotted in the meta-analysis

No study assessed the social impact and quality of life of the girls studied. Chiavaroli *et al.* (13) assessed the presence of polycystic ovary syndrome (PCOS). For both criteria used (Androgen Excess Society (AES, 2006) and Rotterdam, 2003), the frequency of PCOS was higher in the treatment than in the comparison groups (36 and 14.5%; relative risk (RR)=2.48, 95% CI=1.08–5.66 and 56 and 23.6%; RR=2.37, 95% CI=1.32–4.27, respectively).

Only Lazar *et al.* (8) evaluated the number of girls who reached their TH range, with a non-significant difference; 70% of the treated and 67% of untreated girls achieved AH within or above their TH range ± 0.5 s.d.

Quality of evidence

Applying GRADE to the primary outcome (AH), it was necessary to rate the quality of evidence in two domains: risk of bias and imprecision. The same results were observed as that for the frequency of PCOS. Therefore, the quality of evidence for these two items was low and very low, respectively (Supplementary Table 1).

Discussion

To present the best available evidence for helping clinicians in making decisions, we conducted a systematic review for comparing the effect of no treatment with the use of GnRH analogs on AH in girls with EP.

Six studies (total, 332 girls) were included. Meta-analysis of AH showed MD of 0.5 cm and 95% CI of -0.72 to 1.73 cm, i.e., there was no significant difference in AH between the groups studied. Even in the three studies in which the girls had PAH < TH, there were no differences in AH (MD=0.59, 95% CI=-0.86 to 2.04, $I^2=0\%$).

Although we were unable to assess the number of children in each group who attained their TH range using meta-analysis, it is important to note that, except for the study by Chiavaroli *et al.* (13) in the other included studies, the average AH of girls in the treatment and control groups was similar to or greater than TH (Table 2).

Table 2 Characteristics of the girls in the included studies at the baseline and visits (achievement of AH).

Study	Initial height	Chronological age	Adult height	Predicted adult height	Target height	Bone age
(2)	I 134.9 $\pm$ 6.8	8.5 $\pm$ 0.6	158.1 $\pm$ 6.2	157.8 $\pm$ 9.1	158.0 $\pm$ 7.6	10.6 $\pm$ 0.8
	C 135.5 $\pm$ 5.9	8.4 $\pm$ 0.5	158.6 $\pm$ 6.0	159.3 $\pm$ 5.4	158.8 $\pm$ 3.9	8.4 $\pm$ 0.5
(16)	I 135.2 $\pm$ 4.2	9.3 $\pm$ 0.5	157.6 $\pm$ 3.9	154.1 $\pm$ 3.9	157.6 $\pm$ 4.2	10.9 $\pm$ 0.5
	C 136.1 $\pm$ 4.2	9.4 $\pm$ 0.3	156.1 $\pm$ 5.3	155.2 $\pm$ 3.7	157.8 $\pm$ 4.7	10.9 $\pm$ 0.3
(13)	I 136.3 $\pm$ 3.8	8.9 $\pm$ 0.2	157.4 $\pm$ 5.2	157.4 $\pm$ 3.6	160.2 $\pm$ 4.0	11.0 $\pm$ 0.6
	C 138.1 $\pm$ 3.8	9 $\pm$ 0.2	157.2 $\pm$ 4.8	160.1 $\pm$ 3.8	161.7 $\pm$ 3.6	11.1 $\pm$ 0.5
(14)	I 132.0 $\pm$ 6.9	8.1 $\pm$ 0.2	161.2 $\pm$ 5.7	-----	155.4 $\pm$ 5.3	10.44 $\pm$ 0.9
	C 136.2 $\pm$ 5.7	8.1 $\pm$ 0.1	160.5 $\pm$ 5.1	-----	156.5 $\pm$ 5.5	10.83 $\pm$ 0.3
(15)	I -----	8.09 $\pm$ 0.42	159 $\pm$ 4.32	160.5 $\pm$ 5.53	158.4 $\pm$ 4.98	9.42 $\pm$ 0.87
	C Only SDS	8.83 $\pm$ 1.04	158.3 $\pm$ 5.6	161.6 $\pm$ 4.06	158.9 $\pm$ 3.65	9.98 $\pm$ 2.05
(8)	I 131 $\pm$ 5.67	8.34 $\pm$ 0.32	157.26 $\pm$ 6.16	152.89 $\pm$ 6.55	157.67 $\pm$ 4.88	9.7 $\pm$ 0.65
	C 132.8 $\pm$ 5.9	8.5 $\pm$ 0.4	156.66 $\pm$ 5.7	152.7 $\pm$ 6.32	157.96 $\pm$ 5.29	10.0 $\pm$ 0.77

I, intervention; C, comparison; --, no information provided; SDS, standard deviation scores; * Start.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bouvattier 1999	?	?	?	?	+	?	?
Cassio 1999	-	-	?	?	-	?	?
Chiavaroli 2010	-	-	?	?	+	?	+
Llop-Viñolas 2001	-	-	?	?	+	?	?
Savas-Erdeve 2016	-	-	?	?	+	?	+

Figure 2

Risk of bias summary. Review authors' judgments about each risk of bias item for each included study. *Yellow circles* indicate uncertainty. *Green and red circles* indicate low and high risk of bias, respectively. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-18-0473>.

Three studies analyzed BMI of the participants at the final visit. Although there was no significant difference between the intervention and control groups, Chiavaroli *et al.* (13) reported that GnRH treatment tended to increase the body weight and significantly increased the risk of PCOS during adolescence. However, as this study was non-randomized and used a control group in which parents requested their daughters not be treated, causality could not be proven. In addition, other studies on girls treated in childhood with GnRH analogs for CPP have demonstrated normal BMI, body composition and ovarian function during early adulthood and no increase in PCOS frequency (21, 39).

Our systematic review had other limitations, with the main one being related to the study design.

Without randomization, we could not evaluate any unknown factor that would interfere with the outcome results. However, because of parents' concerns about possible adverse events of a new intervention in their children, we must consider the fact that clinical trials in children are observed less frequently in the literature. For this reason, it has been common for the control group to comprise patients whose parents refuse intervention. No study evaluated other important outcomes, such as quality of life and psychosocial impact related to EP or GnRH analog therapy.

In our registered protocol, we informed that we would include observational studies in the absence of experimental studies. As we did not find large and well-conducted randomized studies to result in a high or moderate quality of evidence, we combined the results of experimental studies with those of the single observational study available in the literature and that met our eligibility criteria (8).

Two published systematic reviews exist regarding the effectiveness of GnRH analogs in improving AH in girls. In 2014, Li *et al.* (40) aimed to evaluate the effect of GnRH therapy with and without added growth hormone (GH). They included five studies without GH; in two studies (also included in our review), the effect of GnRH treatment was compared with nontreatment in patients with EP (2, 16); in two studies on EP, the groups had different PAH (31, 36) and in one study, CPP was evaluated (37). With moderate heterogeneity ($I^2=54.23\%$), their overall analysis revealed a significant difference in AH and PAH, favoring GnRH therapy. However, of the five studies included in that meta-analysis, three reported no difference between the groups and in only the two studies that favored GnRH treatment, girls from the intervention and control groups had different prognoses regarding AH or had pubertal development before 7 years of age (31, 37). However, they did not include the four studies that were included in our review (8, 13, 14, 15).

The second published systematic review evaluated only patients with EP (41). However, the investigators included controlled (five were also included in our review (8, 2, 13, 15, 16)) and uncontrolled studies and concluded that GnRH analogs did not widely change the growth outcome. Compared with our review, in the previously published review, the investigators only searched for eligible studies in PubMed and included only studies published in English (they did not include the study conducted by Llop-Viñolas *et al.* (14)). They did not present a previously registered protocol, they did not apply a tool for assessing the risk of bias in the included studies, and they did not

Figure 3

Meta-analysis of AH with sub-group analysis according to the predicted AH (PAH) and TH showing no difference between the groups. Experimental: GnRH analog treatment; Control: no treatment. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-18-0473>.

evaluate the quality of evidence of their results. In the meta-analysis, they plotted the outcome AH as an s.d. score. As the unit of AH is intuitively interpretable (cm) and to promote easy comprehension among clinicians, we plotted the average AH of each group in each study, and MD between the intervention and control groups was presented in the meta-analysis. We also presented a meta-analysis of AH according to PAH.

Conclusion

Implications for practice

We did not find any evidence from controlled experimental and observational studies that compared with no treatment, GnRH analog treatment increases AH in girls with EP independent of the prognosis of AH on baseline visit (PAH ≤ TH).

Implications for research

As in experimental and observational studies, girls with EP achieved their TH independent of puberty blockade. We do not believe that new randomized studies with GnRH therapy will provide different results regarding AH.

However, observational studies are needed for evaluating if EP has a negative impact on the quality of life and other psychosocial aspects of girls with this condition.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-18-0473>.

Declaration of interest

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

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