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Correlation of Preinjection Values of Gonadotropins and Estradiol Level with Clinical and Radiologic Evidence of Sufficient Pubertal Suppression in Girls with Central Precocious Puberty

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Abstract

Background: In monitoring of precocious puberty treatment, less attention has been paid to the clinical signs and radiological evidence of puberty control. We evaluated the correlation of preinjection values of gonadotropins and estradiol level with clinical criteria of sufficient pubertal suppression in girls with central precocious puberty.

Materials and Methods: 34 patients with CPP were included. After 4-19 dose of depot Triptorelin, blood levels of Estradiol, LH and FSH was measured before next dose of drug. The growth velocity and the bone age advancement were calculated. Correlation of Estradiol and gonadotropins level with clinical and radiologic evidences of pubertal suppression determined.

Results: The mean age was 8.82±1.31 years. The mean LH ± SD was 1.02 ±0.53 IU/l (range 0.1-3.55 IU/l). LH/FSH ratio was 0.85±1.3 and 7 girls (20.5%) has LH/FSH ratio above 1. Serum LH level had significant correlation only with FSH (R = 0.589, P< 0.0001). The physical symptoms of puberty (breast tanner stage) were regressed well in 22 (52.9%) but in 12 (47.1%) cases were partially inhibited. Insufficient inhibition of physical signs of puberty was associated with higher growth rate of height (R: 0.422, P = 0.013) and higher BMI-SDS (R: -0.423, P: 0.008).

Conclusion: A preinjection value of gonadotropins and estradiol level has not correlation with other criteria of sufficient pubertal suppression in girls with central precocious puberty and is not useful for monitoring of treatment.

Keywords: Preinjection; Triptorelin; Puberty; Histrelin

Abbreviations: GnRH: Gonadotropin Releasing Hormone; CPP: Central Precocious Puberty; FSH: Follicle Stimulating Hormone; SDS: Standard Deviation Score.

Introduction

True precocious puberty is a common problem in girls [1-3]. Treatment of true precocious puberty is suppression of hypothalamic-pituitary- gonadal- axis. Gonadotropin-releasing hormone agonists (GnRHa) are the main stay of treatment for true precocious puberty [4-6]. GnRH agonists can improve final height in rapidly progressive precocious puberty [7]. Early diagnosis and treatment can delay sexual development until the normal age of pubertal onset, reduce family anxiety, and reduce the risk of sexual abuse in this group [8,9]. Biochemical methods (evaluation of LH, FSH, estradiol levels) or clinical score (evaluation of tanner stage, growth rate, skeletal maturation) can be used to evaluate appropriate response to GnRH analogue treatment. Intravenous gonadotropin stimulation test have been considered as the gold standard in assessing adequately suppressing central premature puberty, although not economically and temporally pleasing to the patient, therefore, biochemical methods to evaluate LH levels before or after injection

of gonadotropin analogues are used as alternative test in patients. Although years of LHRH stimulation testing have been recommended to detect insufficient puberty inhibition, recent studies have shown a poor concordance between LHRH stimulation test results and clinical signs of puberty inhibition and bone age progression [10]. Evidences suggest that unstimulated LH in the pubertal range is not a sign of insufficient puberty suppression, whereas concentrations in the pre-pubertal range may indicate adequate puberty inhibition. Therefore, due to the lack of relationship between biochemical measurements during treatment and final height, it is not recommended to evaluate routine biochemistry in all patients [5]. Clinical evaluation of adequate suppression of puberty is said to occur in a child with CPP treated with GnRH agonists including: (1) tanner stage regression or no progression) (2) skeletal maturity index ≤1 (bone age changes / chronological age changes) 3) growth rate < 2SDS for the same chronological age [11]. Much of the previous studies have focused on evaluating adequate suppression of puberty in patients with central precocious puberty (CPP) with a focus on the use of LH levels after GnRH agonist injection and comparing LH levels after IVGnRH stimulation test and has been less compared with clinical evidence of puberty inhibition. We evaluated the correlation of gonadotropins and estradiol levels before administration of next therapeutic dose triptorelin depot with clinical indicators of adequate suppression of puberty in girls with central early puberty.

Materials and Methods

In a cross-sectional study, we included all girls with precocious puberty symptoms and idiopathic central puberty confirmed by clinical examinations and hormonal tests and who had the indication for GnRH agonist therapy. The inclusion criteria were as follows: I) the child met the diagnostic criteria of ICPP, referring to the "Recommendations on the diagnosis and treatment of central (true) precocious puberty" (Chinese Medical Association, 2017 edition) [12-14]. (II) Parental consent signed. Exclusion criteria include irregular use of depot triptorelin, thyroid dysfunction, growth hormone deficiency, chronic diseases, and developmental disorders. The weight, height, and pubertal stage were determined at first and three-month intervals. At the same time of day (afternoon) height was measured using the Harpenden stadiometer, weight was measured using a SECA scale, and BMI (weight in kilograms divided by the square of height) and BMI standard deviation score (BMI-SDS) was calculated for all children. The target height (in centimeters) was obtained with the formula: (total height of parents minus 13) / 2. Marshall-Tanner method was used for Sexual maturation staging [15]. Bone age determined by Bayley-Pinneau method and adult height predicted by Greulich-Pyle method [16,17]. Treatment protocol was to treat all patients at first by depot Triptorelin 3.75 mg IM every 28 days, and in the cases with insufficient suppression of puberty, injection intervals reduced to 25 and then to 21 days if needed. Within 6-12 months after beginning treatment, in a fast morning state, a blood sample was drawn for LH, FSH, and Estradiol level one hour before depot Triptorelin injection. Serum levels of hormones were measured by radioimmunoassay. According to the breast Tanner stage, patients were divided into two groups: Group A: well suppressed and Group B: partially suppressed. Growth rate expressed as centimeters per year. Statistical analysis was done with SPSS, version 16.0 (SPSS software Inc, Chicago, IL, USA). P values lesser than 0.05(two-sided) considered as statistically significant.

Results

Thirty-four children with CPP who were treated with triptorelin were included. The mean age was 8.93±1.2 years. The mean age at the diagnosis of CPP was 7.4 years. At the time of the study, Triptorelin 3.75 mg was used for 25 children (76.5%) every 28 days, six children (14.7%) every 25 days, and 3 (8.8%) children every 21 days. Dose intervals were not significantly related to age, BMI-SDS, and height. Seven cases (20.6%) were obese; BMI-SDS have no significant correlation with age (P: 0.349) and bone age (P: 0.598) (Table 1).

Variable	Total	Group A	Group B	P-value
Number	34	22	12	-
Age	8.82± 1.31	8.7±1.3	9.2±1	NS
Weight	35.9± 8.9	32.4± 7.1	40.8± 7.5	0.03
Height (cm)	135± 8.2	132±7.9	140± 6.6	0.007
Height SDS	1± 1.8	.73± 2	1.5± 1.1	0.024
BMI-SDS	.84 ±1.09	.58 ±1.08	1.32 ±.97	0.025
Growth velocity(cm/year)	5.2±2.4	4.7±2.3	6.8±2.1	0.024
Bone age (year)	10.6± 1.4	10.5±1.4	11.2±1.2	NS

Bone maturity rate (year /year)	1.01± .62	1.05±.73	.94±.36	NS
LH (IU/L)	1.02±.9	1.01±.78	1.02±1.1	NS
FSH (IU/L)	1.9 ±1.8	1.5±1.3	2.08±2	NS
Estradiol (pg/ml)	42± 52	53±46	71±92	NS
PAH changes (cm)	1.61±4.4	.75 ±4.7	3.2±3.5	NS

Table 1: General characteristics and comparison of two groups of clinically well-suppressed and partially suppressed puberty. **LH**: Luteinizing Hormone, **FSH**: Follicular stimulating hormone, **SDS**: standard deviation score

The physical symptoms of puberty (breast Tanner stage) were regressed well in 22 (52.9%), but in 12 (47.1%) cases, they were partially inhibited. Significant correlations of clinical and radiologic evidence of pubertal suppression with together and gonadotropins levels are expressed in Table 2. Estradiol levels have not correlated with age, LH, FSH, growth velocity, breast tanner stage, bone maturation rate, PAH changes, or with duration of triptorelin administration. All cases had serum LH concentrations lower than 3.55 IU/L. Three patients had LH levels above 2.5 IU/L, and only one had clinically suppressed puberty. Also, serum FSH concentrations were less than or equal to 6.5 IU / L in all cases. Seven (20.5%) patients had an LH/FSH ratio greater than 1, of whom five had clinically suppressed puberty. The mean LH / FSH ratio is 0.85±1.3. The LH correlation was only significant with FSH (P = 0.001, R = 0.589).Serum estradiol concentrations in 10 cases (29.4%) were less than 10 pg/mL and 10-20 pg/mL (11.7%) in 4 cases. Fourteen cases (41.2%) had estradiol levels of 20-50 pg/mL and in two cases (5.8%) was 50-100 pg/mL. Four cases (11.7%) had estradiol levels above 100 pg/mL. Of the 34girls, 23 (70.6%) had a bone maturity rate (BMR) of less than one year per calendar year, and 10 (29.4%) had a BMR of more than one year per calendar year. BMR had a significant but inverse relationship with age (R=-0.398, P=0.02) but no relationship with height growth velocity and BMI-SDS. Predicted adult height (PAH) changes were calculated in 28 children. Fourteen (50%) had PAH changes less than ±3 cm, while 10 (35.7%) had increased PAH by more than 3 cm, and 4 (14.3%) had decreased PAH by more than 3 cm. PAH changes have no significant relationship with age, bone age, height growth velocity, BMI-SDS, LH, FSH, Estradiol level, and BMR. BMR and PAH changes have no significant association with physical symptoms of pubertal inhibition.

Variable	Variable	R	P-value
Growth Rate	Breast tanner stage suppression	-0.42	0.013
	BMI-SDS	0.325	0.037
	Height SDS	0.256	0.025
	Bone age changes	0.312	0.015
BMI-SDS	Growth Rate	0.325	0.037
	Breast tanner stage suppression	-0.42	0.008
	Height SDS	0.232	0.04
	Bone age changes	0.382	0.026
	Advanced bone age	0.377	0.028
Breast tanner stage suppression	BMI-SDS	-0.42	0.008
	Growth Rate	-0.42	0.013
LH	FSH	0.589	0.001
Bone age changes	Age	-0.48	0.004
	Bone age	-0.34	0.05
	BMI-SDS	0.382	0.026
	Growth Rate	0.312	0.015

Table 2: Significant Correlations of Clinical and Radiologic Evidence of Pubertal Suppression with together and Gonadotropins.

Discussion

Recent recommendations for the treatment of central precocious puberty with GnRH agonists emphasize the less use of stimulatory tests and more use of unstimulated LH and lower frequency hormonal monitoring and use of other parameters such as linear growth rates, clinical symptoms, skeletal growth rate [5]. We examined the correlation between gonadotropins and Estradiol levels before administration of next therapeutic dose of triptorelin with clinical and radiologic evidences of adequate suppression of puberty in girls with central precocious puberty. The treatment with triptorelin is effectively improving adult height in girls with CCP [18-20]. The tanner stage, growth rate, level of LH, FSH and Estradiol and bone age progression can be used to assess the enough suppression of puberty [21]. The gold standard test for evaluation of sufficient suppression of puberty is the intravenous gonadotropin stimulation test [7,10,22] but, this test is time-consuming, high cost and requires multiple blood sampling. So, the levels of LH before or after injection of therapeutic dose of the GnRH analog have been used as alternative test for this purpose [1,20,23-26]. Prior studies had less addressing the correlation of gonadotropins and Estradiol level with clinical and radiologic evidences of adequate suppression of puberty [27,28]. In our study LH, FSH, and Estradiol level have not correlation with age, growth velocity, breast tanner stage, bone maturation rate, PAH changes or with duration of triptorelin administration. Three patients had LH level above 2.5 IU/L, only one of whom had clinically suppressed puberty. Lewis, et al. [19] showed random LH in children treated with histrelin implant does not fall to prepubertal values in more than one-half of cases in contrast to complete suppression of puberty documented by GnRH a stimulation test. Similar to our research, Lewis, et al. [19] noticed random LH and estradiol level are not predictive of growth velocity, pubertal progression, and bone age advancement. In the study of LEE, et al. [29] puberty suppression defined as basal LH less than .6 IU/L and stimulated peak LH less than 4 IU/L and basal or stimulated estradiol less than 13.6 pg/ml. A basal LH-level < 0.75 IU/L identified 85% of those who were suppressed, and a basal LH-level < 0.6 IU/L identified 80% of suppressed cases. In their study, inhibition of puberty has been diagnosed only on the basis of laboratory findings and and not based on the tanner stage of breast or bone age progression. While we find in clinical experience and this study that some of those children chemically diagnosed as unsuppressed puberty have well-controlled bone age and that their predicted final height has improved or not decreased despite high levels of LH or estradiol levels. PAH changes have not significant relationship with age, bone age, height growth velocity, bone maturity rate, BMI-SDS, LH, FSH and Estradiol level. Also other study revealed the peak LH level during GnRH stimulation test has not significant relation with clinically well suppressed or incompletely suppressed puberty. Kunz, et al. [30] evaluated usefulness of pre-injection LH levels in monitoring of treatment in central precocious puberty. The improvement of PAH was positively correlated with lower LH level before drug injection. During treatment with depot leuprolide acetate, Estradiol level was below the detection limits in 75% of cases and had not correlation with growth velocity or skeletal maturation rate [25]. Neely, et al. investigates the random LH level during GnRHa (histrelin implant) treatment. All of their patients had suppressed puberty. A strong positive correlation was found between the random LH and peak LH levels during leuprolide-stimulated test. Similar to our results unstimulated LH levels did not correlate with estradiol [31]. Estradiol is the main hormone that promotes breast growth, height growth acceleration and bone age progression during puberty. In our experience Estradiol level have not correlation with age, BMI-SDS, LH, FSH, growth velocity, breast tanner stage, bone maturation rate, PAH changes, or with duration of triptorelin administration. Also in previous our study Estradiol level did not correlate with growth velocity, bone age progression and with duration of triptorelin administration one hour after administration of triptorelin [32]. However, high levels of estradiol raise concerns about puberty progression and may be a reason for changing the treatment protocol especially in the presence of other evidences of pubertal inhibition. The relationship between obesity and early puberty has been shown in several studies [33,34]. Numerous studies have shown that obese children have more advanced bone age [34,35]. In our study, no association was found between BMI-SDS and age, levels of LH, FSH and estradiol. But our obese children were also taller at first and had higher height growth rates, had more frequent advanced bone age, and less inhibited in breast tanner staging, but the predicted final height changes were no different from those with normal weight. If this finding is confirmed in larger studies, it can be said that in the follow-up of obese children with precocious puberty, accelerated skeletal maturation and accelerated growth is due to obesity and does not lead to a decrease in the predicted final height and should not be add medicine dose based on this findings.

Limitations

We could not perform IV GnRH stimulation test due to unavailability of drug and so cannot compare the clinical evidence of puberty inhibition with this popular test.

Conclusion

Preinjection values of gonadotropins and estradiol level have not correlation with other criteria of sufficient pubertal suppression in girls with central precocious puberty and is not useful for monitoring of treatment.

Ethical Approval

The Ethics Committee approved the study of Kashan university of medical science (No: 94008), and informed consent was taken from all the patients.

References

1. Strich D, Kvatinsky N, Hirsch HJ, Gillis D (2013) Triptorelin depot stimulation test for central precocious puberty. J Pediatr Endocrinol Metab 26(7-8): 631-634.

2. Alessandri SB, Pereira FA, Villela RA, Antonini SRR, Elias PCL, et al. (2012) Bone mineral density and body composition in girls with idiopathic central precocious puberty before and after treatment with a gonadotropin-releasing hormone agonist. Clinics 67(6): 591-596.

3. Kim D, Sung-Yoon C, Se-Hyun M, Yi ES, Jung YJ, et al. (2012) Diagnosis and constitutional and laboratory features of Korean girls referred for precocious puberty. Korean J Pediatr 55(12): 481-486.

4. Seminara S, Nanni L, Generoso M, Mirri S, Leonardi V, et al. (2010) Effect of treatment with cyproterone acetate on uterine bleeding at the beginning of GnRH analogue therapy in girls with idiopathic central precocious puberty. Horm Res Paediatr 73(5): 386-389.

5. Krishna KB, Fuqua JS, Rogol AD, Klein KO, Popovic J, et al. (2019) Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium. Horm Res paediatr 91(6): 357-372.

6. Bertelloni S, Mucaria C, Baroncelli GI, Peroni D (2018) Triptorelin depot for the treatment of children 2 years and older with central precocious puberty. Expert Rev Clin Pharmacol 11(7): 659-667.

7. Nabhan ZM, Walvoord EC (2010) Treatment of Gonadotropin-Dependent precocious puberty. pp: 345-362.

8. Zenaty D, Blumberg J, Liyanage N, Jacqz-Aigrain E, Lahlou N, et al. (2016) A 6-Month Trial of the Efficacy and Safety of Triptorelin Pamoate (11.25 mg) Every 3 Months in Children with Precocious Puberty: A Retrospective Comparison with Triptorelin Acetate. Horm Res Paediatr 86(3): 188-195.

9. Fuqua JS (2013) Treatment and outcomes of precocious puberty: An update. Journal of Clin Endocrinol Metab 98(6): 2198-2207.

10. Demirbilek H, Alikasifoglu A, Gonc NE, Ozon A, Kandemir N (2012) Assessment of gonadotrophin suppression in girls treated with GnRH analogue for central precocious puberty; Validity of single luteinizing hormone measurement after leuprolide acetate injection. Clin Endocrinol 76(1): 126-130.

11. Lawson ML, Cohen N (1999) A single sample subcutaneous luteinizing hormone (LH)-releasing hormone (LHRH) stimulation test for monitoring LH suppression in children with central precocious puberty receiving LHRH agonists. J Clin Endocrinol Metab 84(12): 4536-4540.

12. Soriano-Guillen L, Argente J (2011) Central precocious puberty: epidemiology, etiology, diagnosis and treatment. An Pediatr (Barc) 74(5): 336 e1-336 e13.

13. Wang ZF, Gui-Jun L (2012) Value evaluation of follicle stimulating hormone and luteinizing hormone in the diagnosis of precocious puberty in girls by ROC curve analysis. Chinese Journal of Contemporary Pediatrics 14(6): 441-444.

14. Brito VN, Spinola-Castro AM, Kochi C, Kopacek C, Silva PCA, et al. (2016) Central precocious puberty: revisiting the diagnosis and therapeutic management. Archives of Endocrinol Metabolism 60(2): 163-172.

15. Allali S, Lemaire P, Couto-Silva AC, Prété G, Trivin C, et al. (2011) Predicting the adult height of girls with central precocious puberty. Medical Science Monitor 17(6): PH41-PH48.

16. Bar A, Linder B, Sobel EH, Saenger P, DiMartino-Nardi J (1995) Bayley-Pinneau method of height prediction in girls with central precocious puberty: Correlation with adult height. J Pediatr 126(6): 955-958.

17. Paxton ML, Lamont AC, Stillwell AP (2013) The reliability of the Greulich-Pyle method in bone age determination among Australian children. Journal of Medical Imaging and Radiation Oncology 57(1): 21-24.

18. Acharya SV, Gopal RA, George J, Bandgar TR, Menon PS, et al. (2009) Utility of single luteinizing hormone determination 3 h after depot leuprolide in monitoring therapy of gonadotropin-dependent precocious puberty. Pituitary 12(4): 335-338.

19. Lewis KA, Eugster EA (2013) Random luteinizing hormone often remains pubertal in children treated with the histrelin implant for central precocious puberty. J Pediatr 162(3): 562-565.

20. Brito VN, Latronico AC, Arnhold IJP, Mendonca BB (2004) A single luteinizing hormone determination 2 hours after depot leuprolide is useful for therapy monitoring

of gonadotropin-dependent precocious puberty in girls. J Clin Endocrinol Metab 89(9): 4338-4342.

21. Ghaffari M, Shiasi K (2011) Evaluation of Therapeutic Response to Triptorelin Acetate in Girls with Central Precocious Puberty in Kashan University Pediatric Endocrinology Clinic from 2011 to 2017. 1: 106-111.

22. Kandemir N, Demirbilek H, Ozon ZA, Gonç N, Alikaşifoglu A (2011) GnRH stimulation Test in precocious puberty: Single sample is adequate for diagnosis and dose adjustment. J Clin Res Pediatr Endocrinol 3(1): 12-17.

23. Benetti-Pinto CL, Camargo LBN, Magna LA, Garmes HM, Petta CA (2008) Predictive factors for height gain in idiopathic central precocious puberty treated with GnRH analogues. Rev Bras Ginecol Obstet 30(12): 609-613.

24. Prasad HK, Khadilkar VV, Jahagirdar R, Khadilkar AV, Lalwani SK (2012) Evaluation of GnRH analogue testing in diagnosis and management of children with pubertal disorders. Indian J Endocrinol Metab 16(3): 400-405.

25. Kunz GJ, Sherman TI, Klein KO (2007) Luteinizing hormone (LH) and estradiol suppression and growth in girls with central precocious puberty: is more suppression better? Are pre-injection LH levels useful in monitoring treatment? J Pediatr Endocrinol Metab 20(11): 1189-1198.

26. Bhatia S, Neely EK, Wilson DM (2002) Serum luteinizing hormone rises within minutes after depot leuprolide injection: implications for monitoring therapy. Pediatrics 109(2): E30.

27. Salerno M, Maio SD, Gasparini N, Mariano A, Macchia V, et al. (1998) Central precocious puberty: A single blood sample after gonadotropin-releasing hormone agonist administration in monitoring treatment. Horm Res 50(4): 205-211.

28. Ostojic SM (2013) Prediction of adult height by Tanner-Whitehouse method in young Caucasian male athletes. QJM 106(4): 341-345.

29. Lee PA, Luce M, Bacher P (2016) Monitoring treatment of central precocious puberty using basal luteinizing hormone levels and practical considerations for dosing with a 3-month leuprolide acetate formulation. J Pediatr Endocrinol Metab 29(11): 1249-1257.

30. Cook JS, Doty KL, Conn PM, Hansen JR (1992) Assessment of depot leuprolide acetate dose-adequacy for central precocious puberty. J Clin Endocrinol Metab 74(5): 1206-1209.

31. Neely EK, Silverman LA, Geffner ME, Danoff TM, Gould E (2013) Random unstimulated pediatric luteinizing hormone levels are not reliable in the assessment of pubertal suppression during histrelin implant therapy. Int J Pediatr Endocrinol 2013(1): 20.

32. Kobra SA (2017) Correlation of Gonadotropins and Estradiol Level 1 Hour after Depot Triptorelin with Clinical Criteria of Adequate Pubertal Suppression in Girls with Central Precocious Puberty. J Pediatri Endocrinol 2(1): 1016.

33. Colmenares A, Gunczler P, Lanes R (2014) Higher prevalence of obesity and overweight without an adverse metabolic profile in girls with central precocious puberty compared to girls with early puberty, regardless of GnRH analogue treatment. Int J Pediatr Endocrinol 2014(1): 5.

34. Marcovecchio ML, Chiarelli F (2013) Obesity and growth during childhood and puberty. World Rev Nutr Diet 106: 135-141.

35. Chonchaiya W, Wacharasindhu S, Trinavarat P, Mahayosnond A (2008) Is the severity of obesity associated with poor prediction of adult height and height gain? Asian Biomedicine 2(6): 471-476.