Purpose: Pubertal gonadotropin secretion shows circadian pattern and the luteinizing hormone (LH) levels tend to rise in later stages of puberty in girls. We studied the usefulness of basal LH in the evaluation of central precocious puberty with emphasis on the influence of sampling time.

Methods: Medical records of 334 girls that underwent gonadotropin-releasing hormone stimulation test (GnRHST) were reviewed. Auxological and laboratory data were compared between those with early morning (EM, before 10 AM) and late morning/afternoon (LM/A, after 10 AM) basal samples.

Results: Among those in sexual maturity rating (SMR) 2, EM samples showed higher basal LH ($P=0.004$) compared to LM/A samples, whereas those in SMR 3 showed no difference in LH levels between EM and LM/A samples. Among girls with pubertal response, EM group showed higher basal LH ($P=0.031$) and follicular stimulating hormone ($P=0.008$) than LM/A group. The EM basal LH was more closely related with the peak stimulated LH than the LM/A basal LH did ($r_s=0.871$ vs. $r_s=0.524$). The optimal basal LH cutoffs to predict a pubertal response to GnRHST were 0.11 IU/L with a sensitivity of 66.7% and a specificity of 78.7% in EM group, and 0.07 IU/L with a sensitivity of 60.0% and a specificity of 78.9% in LM/A group, respectively.

Conclusion: In girls with early stages of puberty, EM basal LH is a more sensitive screening tool than the LM/A basal LH. Diurnal variation should be considered in evaluating children with precocious puberty.

Keywords: Precocious puberty, Luteinizing hormone, Gonadotropin-releasing hormone

Introduction

Gonadotropin secretion at the onset of puberty shows marked circadian rhythm due to nocturnal gonadotropin secretion\(^1\). The increase of plasma luteinizing hormone (LH) during sleep is initially seen in children at sexual maturity rating (SMR) 2–3\(^2,3\). As puberty progresses, the daytime LH levels rise continuously until the diurnal rhythm is lost\(^4,5\). The early activation of hypothalamic-pituitary-gonadal (HPG) axis can result in central precocious puberty (CPP)\(^6\). The standard method to confirm CPP is to measure the gonadotropin response to gonadotropin releasing hormone (GnRH) administration\(^7\). However, the GnRH stimulation test (GnRHST) is inconvenient to patients because of multiple blood sampling and cost. Several studies suggested that the serum basal LH level can be useful in the screening of girls with suspected CPP\(^8-13\). However, because the circadian pattern of early pubertal gonadotropin secretion and the trend of serum LH levels to rise in later stages of puberty in girls, random daytime values of gonadotropins have limited usefulness in outpatient clinic setting. We studied the validity of basal LH for the screening of CPP in girls, with emphasis on the influence of sampling time.
Materials and methods

1. Subjects

Subjects were girls at 8 years of age or younger who visited the pediatric endocrinology clinic in Bundang CHA Medical Center due to precocious breast development and underwent the GnRHST between 2011 and 2014. After excluding those with peripheral precocious puberty or chronic illness, total 334 girls (240 girls in SMR 2, 91 girls in SMR 3, 3 girls in SMR 4 based on breast development) were included in the present study. This study was approved by the Institutional Review Board of CHA Bundang Medical Center (CHAMC 2016-09-036-001). Written informed consent was obtained from all patients.

Participants were classified into early morning (EM) group when basal sampling before the administration of GnRH was performed before 10 AM, and children in whom the basal sampling was performed after 10 AM was classified into late morning/afternoon (LM/A) group considering the circadian rhythm of gonadotropin. To compare the basal and stimulated gonadotropin levels between girls with similar stages of pubertal development, children were stratified by SMR and their response to GnRHST.

To compare the EM and LM/A data in the same patient, subgroup analysis was performed in 16 girls (all of whom were in SMR 2) who underwent GnRHST on different time range, within 4 weeks after initial basal sampling. In 12 girls, initial basal sampling was performed after 10 AM, and GnRHST including EM basal sample was performed before 10 AM, after 13.8±7.0 days. Initial basal sampling was performed before 10 AM in 4 girls, followed by GnRHST including LM/A basal sample after 10 AM, after 10.0±6.2 days.

2. Methods

We reviewed the medical records of the subjects retrospectively. Clinical data at the time of GnRHST, such as chronological age, bone age, height, body weight, body mass index (BMI), SMR, parental height, and laboratory profiles, were collected. The standard deviation score (SDS) of the height, body weight and BMI were calculated using the 2007 Korean National Growth Charts. Bone age was measured using the Greulich–Pyle method. Auxological and biochemical data were compared between EM and LM/A.

Basal serum samples for LH, follicular stimulating hormone (FSH) and estradiol (E₂) were drawn immediately before the administration of 100 μg of GnRH (Relefact LH-RH; Sanofi-Aventis, Frankfurt, Germany). After injection, blood samples for LH and FSH were collected at 30, 45, and 60 minutes. Serum LH and FSH concentrations were measured using a chemiluminescence immunoassay (CLIA) (ADVIA Centaur XP Systems, Siemens, Germany). The sensitivity of the FSH and LH assays were 0.3 IU/L and 0.07 IU/L, respectively. The percent coefficients of variation for replicate analysis were <4% for both assays in the 0.3–200 IU/L for FSH and 0.07–200 IU/L for LH. E₂ was also measured by CLIA (UniCel Dxi 800 system, Beckman Coulter, Brea, CA, USA). A peak stimulated LH concentration of ≥ 5.0 IU/L on the GnRHST was regarded as a pubertal response and <5.0 IU/L was classified a prepubertal response.

3. Statistical analysis

All data were provided as the mean±standard deviation. Statistical analyses were performed by IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). Student t-test was used to compare values between the 2 groups. In subgroup analysis, Wilcoxon signed rank test was used to compare values and Spearman rank correlation was used to evaluate the relationships between basal serum LH and peak stimulated value. Multiple logistic regression models were fit with a pubertal response to GnRHST and BMI SDS, the basal gonadotropin value (LH and FSH) and E₂.

Receiver operating characteristic (ROC) curves were constructed to evaluate the sensitivity and specificity at each level of LH based on predicted probability, and area under the curve (AUC) with 95% confidence interval (CI) was measured for each curve. Youden’s J index (sensitivity+specificity–1) was used to determine the optimal cut off point of basal serum LH from the ROC curve for each assay to differentiate girls with CPP from prepubertal girls. For these cutoff points, specificity and sensitivity were then recalculated to evaluate the cutoff point efficacy. P-value of <0.05 was considered statistically significant.

Table 1. Comparison of biochemical characteristics in subjects stratified by sexual maturity rating

| Characteristic | SMR 2 (n=128) | SMR 3 (n=38) |
|----------------|--------------|--------------|
| Age (yr)       | 7.7±0.5      | 7.7±0.5      |
| Height SDS     | 0.9±0.9      | 0.8±0.9      |
| BMI SDS        | 0.3±0.9      | 0.3±0.9      |
| BA–CA (yr)     | 1.6±1.2      | 1.4±0.7      |
| Basal LH (IU/L)| 0.32±0.56    | 0.15±0.27    |
| Peak LH (IU/L) | 9.26±7.47    | 10.41±8.62   |
| Basal FSH (IU/L)| 3.4±1.8    | 2.8±1.2     |
| Peak FSH (IU/L)| 17.0±6.1   | 16.7±5.3    |
| Basal LH/FSH   | 0.07±0.10    | 0.05±0.09    |
| Peak LH/FSH    | 0.56±0.42    | 0.61±0.46    |
| Estradiol (pg/mL)| 8.7±15.3  | 6.0±13.9    |

Values are presented as mean±standard deviation.

Subjects were classified into EM and LM/A group considering the circadian rhythm of gonadotropin. To compare the basal and stimulated gonadotropin levels between girls with similar stages of pubertal development, children were stratified by SMR and their response to GnRHST.

Participants were classified into early morning (EM) group when basal sampling before the administration of GnRH was performed before 10 AM, and children in whom the basal sampling was performed after 10 AM was classified into late morning/afternoon (LM/A) group. To compare the EM and LM/A data in the same patient, subgroup analysis was performed in 16 girls who underwent GnRHST on different time range, within 4 weeks after initial basal sampling. In 12 girls, initial basal sampling was performed after 10 AM, and GnRHST including EM basal sample was performed before 10 AM, after 13.8±7.0 days. Initial basal sampling was performed before 10 AM in 4 girls, followed by GnRHST including LM/A basal sample after 10 AM, after 10.0±6.2 days.

2. Methods

We reviewed the medical records of the subjects retrospectively. Clinical data at the time of GnRHST, such as chronological age, bone age, height, body weight, body mass index (BMI), SMR, parental height, and laboratory profiles, were collected. The standard deviation score (SDS) of the height, body weight and BMI were calculated using the 2007 Korean National Growth Charts. Bone age was measured using the Greulich–Pyle method. Auxological and biochemical data were compared between EM and LM/A.

Basal serum samples for LH, follicular stimulating hormone (FSH) and estradiol (E₂) were drawn immediately before the administration of 100 μg of GnRH (Relefact LH-RH; Sanofi-Aventis, Frankfurt, Germany). After injection, blood samples for LH and FSH were collected at 30, 45, and 60 minutes. Serum LH and FSH concentrations were measured using a chemiluminescence immunoassay (CLIA) (ADVIA Centaur XP Systems, Siemens, Germany). The sensitivity of the FSH and LH assays were 0.3 IU/L and 0.07 IU/L, respectively. The percent coefficients of variation for replicate analysis were <4% for both assays in the 0.3–200 IU/L for FSH and 0.07–200 IU/L for LH. E₂ was also measured by CLIA (UniCel Dxi 800 system, Beckman Coulter, Brea, CA, USA). A peak stimulated LH concentration of ≥ 5.0 IU/L on the GnRHST was regarded as a pubertal response and <5.0 IU/L was classified a prepubertal response.

3. Statistical analysis

All data were provided as the mean±standard deviation. Statistical analyses were performed by IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). Student t-test was used to compare values between the 2 groups. In subgroup analysis, Wilcoxon signed rank test was used to compare values and Spearman rank correlation was used to evaluate the relationships between basal serum LH and peak stimulated value. Multiple logistic regression models were fit with a pubertal response to GnRHST and BMI SDS, the basal gonadotropin value (LH and FSH) and E₂.

Receiver operating characteristic (ROC) curves were constructed to evaluate the sensitivity and specificity at each level of LH based on predicted probability, and area under the curve (AUC) with 95% confidence interval (CI) was measured for each curve. Youden’s J index (sensitivity+specificity–1) was used to determine the optimal cut off point of basal serum LH from the ROC curve for each assay to differentiate girls with CPP from prepubertal girls. For these cutoff points, specificity and sensitivity were then recalculated to evaluate the cutoff point efficacy. P-value of <0.05 was considered statistically significant.
Results

1. Characteristics of subjects stratified by SMR

The descriptive statistics for auxological and biochemical data of participants stratified by SMR, and further divided by EM and LM/A groups are shown in Table 1. Whereas the differences of basal serum LH and FSH between EM and LM/A samples were significant in girls with SMR 2 (P=0.004 for LH and P=0.001 for FSH), there was no significant difference in basal LH and FSH levels between EM and LM/A samples in those with SMR 3 (Table 1). LM/A basal LH level in girls with SMR 3 was significantly higher than in those with SMR 2 (P=0.040).

2. Characteristics of subjects classified by response to GnRHST

There was no significant difference in auxological data between prepubertal and pubertal response groups, except that prepubertal EM group showed higher BMI SDS compared to pubertal EM group (P=0.005) (Table 2). The basal and stimulated levels of gonadotropins in pubertal response group were higher than those of their prepubertal response counterparts (Table 2). In prepubertal response group, basal FSH in the EM group was higher than LM/A (P=0.005). Among pubertal response group, the basal LH, FSH and E₂ were significantly higher in the EM group than LM/A group (P=0.031, P=0.008, and P=0.020, for LH, FSH, and E₂, respectively).

3. Subgroup analysis to compare EM and LM/A data in the same patient

A subgroup analysis was undertaken in 16 girls to compare the correlation between EM basal LH and peak LH vs. LM/A basal LH and peak LH. Subjects for subgroup analysis did not show significant difference in auxological data as compared with the total study group (age, 7.8±0.5 years; height SDS, 0.9±0.9; BMI SDS, 0.4±0.9). Eleven girls (69%) in the subgroup showed prepubertal response to GnRHST. In the subgroup, EM samples showed significantly higher levels of basal serum LH (0.51±0.60 IU/L vs. 0.18±0.18 IU/L, P=0.008), FSH (3.8±1.9 IU/L vs. 2.7±1.1 IU/L, P=0.015) and E₂ (8.6±14.2 pg/mL vs. 3.4±8.5 pg/mL, P=0.043) levels than LM/A samples (Fig. 1). In Spearman correlation analysis, the EM basal LH was more...
Kang YS, et al. • Diurnal variation of gonadotropin levels in early stages of puberty

5. ROC curve analysis to validate basal LH as a predictor of pubertal response

ROC curves to verify the validity of basal LH as a predictor of pubertal response were constructed in each sample groups. In EM group, the AUC of basal LH was 0.773 (95% CI, 0.704–0.841; \( P < 0.001 \)) and that in LM/A group was 0.732 (95% CI, 0.641–0.823; \( P < 0.001 \)) (Fig. 3). The optimal cutoff value of basal LH related with a pubertal response was 0.11 IU/L in EM group. The sensitivity and specificity of basal LH≥0.11 IU/L in the EM group was 66.7% and 78.7%, respectively. In LM/A group, the optimal basal LH cutoff was 0.07 IU/L and the sensitivity and specificity of this cutoff to predict a pubertal response was 61.7% and 76.5%, respectively.

Discussion

A pulsatile LH secretory pattern during sleep, but not while the children are awake, is the first change in LH secretion at the early puberty\(^2,3\). Sleep associated LH release in the peripubertal period results from increased sensitivity of the pituitary gonadotropins to GnRH\(^17\). Third-generation assays demonstrate that LH increases during sleep to approach peaks in the lower adult range, above 1.0 U/L, and then decrease during the day to 0.6 U/L or less in early puberty\(^18,19\). Later on, a constant pulsatile secretion of LH during day and night occurs in pubertal children\(^4,5\) and in adults\(^20,21\).

Boys at an early stage of puberty show that the timing in the changes of serum LH closely resembled that of FSH. In contrast, in girls, LH levels tend to rise in the later stages of puberty than that of FSH\(^22,23\). Therefore, girls in the early phase of HPG axis activation commonly do not show definite LH elevation in the afternoon. In our study, the basal levels of serum LH and FSH in the LM/A group were significantly lower than those in the EM group in girls with pubertal response to GnRHST. Especially, girls in SMR 2 showed significant difference in basal LH and FSH levels between EM and LM/A samples.

To perform the GnRHST for every patients with suspected CPP is relatively invasive and time-consuming. Among previous studies that evaluated the validity of basal serum LH levels

Table 3. Multiple logistic regression analysis of factors affecting the pubertal response of the gonadotropin-releasing hormone stimulation test

| Model | Variable | Coefficient (\( \beta \)) | Standard error | \( P \)-value |
|-------|----------|--------------------------|----------------|--------------|
| EM model (n=181, \( R^2 =0.195 \)) | BMI SDS | -0.137 | 0.033 | <0.001 |
| | Basal LH | 0.161 | 0.073 | 0.029 |
| | Basal FSH | 0.054 | 0.023 | 0.021 |
| | Estradiol | -0.002 | 0.002 | 0.437 |
| LM/A model (n=153, \( R^2 =0.157 \)) | BMI SDS | -0.087 | 0.036 | 0.018 |
| | Basal LH | 0.125 | 0.092 | 0.177 |
| | Basal FSH | 0.087 | 0.025 | 0.001 |
| | Estradiol | -0.004 | 0.002 | 0.069 |

EM, early morning; LM/A, late morning/afternoon; BMI, body mass index; SDS, standard deviation score; LH, luteinizing hormone; FSH, follicular stimulating hormone.
for effective screening of CPP, some studies conducted blood sampling in the EM before 10 AM, and the others did not describe the time of blood sampling. Rosenfield et al. suggested that sleep LH correlated with LH after stimulation of GnRHα across the pubertal transition. Our subgroup analysis suggested that basal serum LH in the EM is more strongly correlated with peak stimulated LH than that in the late morning or afternoon. Multiple regression analysis in our study showed that the basal LH level in the EM was a significant predictor of pubertal response whereas that in the late morning or afternoon samples was not.

The EM basal FSH level was significantly higher than the LH level in prepubertal boys and girls. In girls, FSH levels rise during the early stages of puberty. Diurnal variation in serum FSH level is less than that of LH. Spontaneous FSH levels might provide more valuable data about pubertal status and more stable data with less prominent night-day variation. However, serum FSH levels rise about 2.5 fold, in contrast with LH levels increase less prominently. The present study showed that the basal LH level in the EM was a significant predictor of pubertal response whereas that in the late morning or afternoon samples was not.

The EM basal FSH level was significantly higher than the LH level in prepubertal boys and girls. In girls, FSH levels rise during the early stages of puberty. Diurnal variation in serum FSH level is less than that of LH. Spontaneous FSH levels might provide more valuable data about pubertal status and more stable data with less prominent night-day variation. However, serum FSH levels rise about 2.5 fold, in contrast with LH levels increase less prominently. The present study showed that the basal LH level in the EM was a significant predictor of pubertal response whereas that in the late morning or afternoon samples was not.

The EM basal FSH level was significantly higher than the LH level in prepubertal boys and girls. In girls, FSH levels rise during the early stages of puberty. Diurnal variation in serum FSH level is less than that of LH. Spontaneous FSH levels might provide more valuable data about pubertal status and more stable data with less prominent night-day variation. However, serum FSH levels rise about 2.5 fold, in contrast with LH levels increase less prominently. The present study showed that the basal LH level in the EM was a significant predictor of pubertal response whereas that in the late morning or afternoon samples was not.

Several studies have not evaluated the diagnostic values considering diurnal fluctuation of LH levels. The present study showed that basal LH in the EM sample was more sensitive for screening CPP than in the late morning or afternoon sample. However, girls with basal LH under optimal cutoff in the late morning and afternoon still cannot be excluded from precocious puberty, because up to 30% of them showed pubertal response in GnRHST in our study.

The present study has some limitations. One of them is that the sensitivity of CLIA of gonadotropins in this study is lower than other studies using immunoochemiluminiometric assay, and the cutoff value was close from the detection limit. Another limitation is that the subgroup analysis was conducted in a small subgroup and blood samples were taken on different days with 4–28 days of intervals, under the assumption that the change in gonadotropin levels in this population are insignificant in 4 weeks. Further studies including a larger number of subjects with samples obtained on the same day are required.

In conclusion, EM basal LH level is more sensitive than late morning or afternoon LH for the initial laboratory screening of girls in early stages of puberty. Diurnal variation should be considered in evaluating girls with precocious puberty, especially in those with early stages of puberty.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Oerter KE, Uriarte MM, Rose SR, Barnes KM, Cutler GB Jr. Gonadotropin secretory dynamics during puberty in normal girls and boys. J Clin Endocrinol Metab
Kang YS, et al. • Diurnal variation of gonadotropin levels in early stages of puberty

1990;71:1251-8.
2. Jakacki RI, Kelch RP, Sauder SE, Lloyd JS, Hopwood NJ, Marshall JC. Pulsatile secretion of luteinizing hormone in children. J Clin Endocrinol Metab 1982;55:453-8.
3. Kulkin HE, Moore RG Jr, Sant妖 SJ. Circadian rhythms in gonadotropin excretion in prepubertal and pubertal children. J Clin Endocrinol Metab 1976;42:770-3.
4. Corley KP, Valk TW, Kelch RP, Marshall JC. Estimation of GnRH pulse amplitude during pubertal development. Pediatr Res 1981;15:137-62.
5. Penny R, Olambiwonnu NO, Frasier SD. Episodic fluctuations of serum gonadotropins in pre- and post-pubertal girls and boys. J Clin Endocrinol Metab 1977;45:307-11.
6. Lee PA. Central precocious puberty. An overview of diagnosis, treatment, and outcome. Endocrinol Metab Clin North Am 1999;28:901-18, xi.
7. Brito VN, Batista MC, Borges MF, Latronico AC, Kohek MB, Throne AC, et al. Diagnostic value of fluorometric assays in the evaluation of precocious puberty. J Clin Endocrinol Metab 1999;84:3539-44.
8. Lee DS, Ryoo NY, Lee SH, Kim S, Kim JH. Basal luteinizing hormone and follicular stimulating hormone: is it sufficient for the diagnosis of precocious puberty in girls? Ann Pediatr Endocrinol Metab 2013;18:196-201.
9. Mogensen SS, Aksoglaoe L, Mouritzen A, Sorensen K, Main KM, Gideon P, et al. Diagnostic work-up of 449 consecutive girls who were referred to be evaluated for precocious puberty. J Clin Endocrinol Metab 2011;96:1393-401.
10. Neely EK, Wilson DM, Lee PA, Stene M, Hintz RL. Spontaneous serum gonadotropin concentrations in the evaluation of precocious puberty. J Pediatr 1995;127:47-52.
11. Pasternak Y, Friger M, Loewenthal N, Haim A, Hershkovitz E. The utility of basal serum LH in prediction of central precocious puberty in girls. Endocr 2012;166:295-9.
12. Boyar RM, Wu RH, Roffwarg H, Kapen S, Weitzman ED, Hellman L, et al. Human puberty: 24-hour estradiol in pubertal girls. J Clin Endocrinol Metab 1976;43:1418-21.
13. Moon JS, Lee SY, Nam CM, Choi JM, Choe BK, Seo JW, et al. 2007 Korean National Growth Charts: review of developmental process and an outlook. Korean J Pediatr 2008;51:1-25.
14. Greulich WW, Pyle SI. Radiologic atlas of skeletal development of the hand and wrist. 2nd ed. Standford (CA): Stanford University Press, 1959.
15. Cared JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR. ESPE-IWPEs GnRH Analogs Consensus Conference Group, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123:e752-62.
16. Schisterman EF, Perkins NJ, Liu A, Bondell H. Optimal cutpoint and its corresponding Youden Index to discriminate individuals using pooled blood samples. Epidemiology 2005;16:73-81.
17. Grumbach M, Kaplan S. The neuroendocrinology of human puberty: an ontogenetic perspective. In: Grumbach M, Sizonenko P, editors. Control of the onset of puberty II. Baltimore: Williams and Wikins, 1990:1-68.
18. Mitamura R, Yano K, Suzuki N, Ito Y, Makita Y, Okuno A. Diurnal rhythms of luteinizing hormone, follicle-stimulating hormone, testosterone, and estradiol secretion before the onset of female puberty in short children. J Clin Endocrinol Metab 2000;85:1074-80.
19. Rosenfield RL, Bordini B, Yu C. Comparison of detection of normal puberty in girls by a hormonal sleep test and a gonadotropin-releasing hormone agonist test. J Clin Endocrinol Metab 2013;98:1591-601.
20. Midgley AR Jr, Jaffe RB. Regulation of human gonadotropins. X. Episodic fluctuation of LH during the menstrual cycle. J Clin Endocrinol Metab 1971;33:962-9.
21. Nankin HR, Troen P. Repetitive luteinizing hormone elevations in serum of normal men. J Clin Endocrinol Metab 1971;33:558-60.
22. Apter D, Pakarinena A, Vikho R. Serum prolactin, FSH and LH during puberty in girls and boys. Acta Paediatr Scand 1978;67:417-23.
23. Grumbach M. Onset of puberty. In: Berenberg SR, editor. Puberty, biologic and social components. Leiden: H.E. Stenfert Kroese, 1975:1-21.
24. Kaplan SL, Grumbach MM, Aubert ML. The ontogenesis of pituitary hormones and hypothalamic factors in the human fetus: maturation of central nervous system regulation of anterior pituitary function. Recent Prog Horm Res 1976;32:161-243.
25. Apter D, Bützow TL, Laughlin GA, Yen SS. Gonadotropin-releasing hormone pulse generator activity during pubertal transition in girls: pulsatile and diurnal patterns of circulating gonadotropins. J Clin Endocrinol Metab 1993;76:940-9.
26. Schroor EJ, van Weissenbruch MM, Engelbrecht M, Martens F, Meurs JM, Wennink JM, et al. Bioactivity of luteinizing hormone during normal puberty in girls and boys. Horm Res 1999;51:230-7.
27. Bordini B, Littlejohn E, Rosenfield RL. LH dynamics in overweight girls with premature adrenarche and slowly progressing sexual precocity. Int J Pediatr Endocrinol 2010;2010:Article ID 724696.
28. Kaplowitz PB. Link between body fat and the timing of puberty. Pediatrics 2008;121(3 Suppl):S208-17.
29. Shaw ND, Seminara SB, Welt CK, Au MG, Plummer L, Hughes VA, et al. Expanding the phenotype and genotype of female GnRH deficiency. J Clin Endocrinol Metab 2011;96:E566-76.
30. Davison KK, Susman EJ, Birch LL. Percent body fat at age 5 predicts earlier pubertal development among girls at age 9. Pediatrics 2003;111(4 Pt 1):815-21.
31. Lee JM, Appugliese D, Kaciroti N, Corwyn RF, Bradley RH, Lumeng JC. Weight status in young girls and the onset of puberty. Pediatrics 2007;119:e624-30.
32. Fu JF, Liang JF, Zhou XL, Prasad HC, Jin JH, Dong GP, et al. Impact of BMI on gonadorelin-stimulated LH peak in premenarchal girls with idiopathic central precocious puberty. Obesity (Silver Spring) 2015;23:637-43.