Gonadotropin-Releasing Hormone Testing in Premature Thelarche

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Abstract

Premature thelarche (PT) is characterized by isolated breast development in girls prior to 8 years of age. In addition, there is neither growth spurt nor advanced bone age. It has been suggested that luteinizing hormone (LH) response to gonadotropin-releasing hormone (GnRH) alone is adequate to distinguish central precocious puberty from PT. However, LH response to GnRH is greater in infancy than that in childhood. Therefore, gonadotropin response to GnRH in girls with isolated premature breast development in different age group was studied.

Thirty-six girls with isolated PT (aged 0.25-8 years) were evaluated. They were classified into 2 groups; aged < 4 years (group A: mean age 1.57 ± 0.87 years, n = 13) and ≥ 4 years (group B: mean age 6.97 ± 0.94 years, n = 23). Initial evaluation included X-ray bone age, pelvic sonography and GnRH testing. Patients were followed for at least 1 year to confirm that no patient had progression into puberty.

Bone ages in both groups were within mean ± 2 SD in all patients. Pelvic sonography was performed in all patients which revealed no abnormality of ovaries and uterus. Pubertal response to GnRH stimulation is characterized by peak LH of > 20 IU/L or Δ LH of > 15 IU/L which is generally greater than peak follicle stimulating hormone (FSH) or Δ FSH, respectively. Mean peak LH and Δ LH in group A were 13.0 ± 6.06 and 11.4 ± 5.92 IU/L whereas those in the group B were 8.5 ± 4.10 and 6.3 ± 3.49 IU/L. Therefore, LH response to GnRH in group A was significantly higher than that in group B ($p < 0.05$). In addition, the mean peak FSH and Δ FSH in group A were 120.5 ± 45.87 and 109.9 ± 42.09 IU/L whereas those in the group B were 48.7 ± 24.05 and 39.9 ± 23.69 IU/L. Therefore, FSH response to GnRH in group A was significantly greater than that in group B ($p < 0.001$).

LH response to GnRH alone can distinguish prepuberty from puberty in girls > 4 years of age. However, in prepubertal young girls with PT aged < 4 years, pubertal LH response can occur, i.e. peak LH > 20 IU/L. Hence, the greater FSH response to GnRH than that of LH would confirm the diagnosis of premature thelarche in this group. Therefore, the evaluation of FSH response to GnRH is beneficial to distinguish puberty from prepuberty in young girls.

Key word : Premature Thelarche, Gonadotropin-Releasing Hormone

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Premature thelarche (PT) is a benign self-limited condition of young girls in which there is isolated breast development before 8 years of age; the highest prevalence is during the first 2 years of life. When PT occurs, there is history of neither a growth spurt nor advanced skeletal maturation. Other symptoms of puberty do not occur and there is no development of additional secondary sexual characteristics[1-3]. In contrast, central precocious puberty (CPP) is a process initiated by activation of hypothalamic-pituitary-gonadal axis resulting in the development of secondary sexual characteristics [3,4]. Therefore, there is a rise of luteinizing hormone (LH), follicle stimulating hormone (FSH) and sex steroids in CPP. Gonadotropin-releasing hormone (GnRH) testing is a standard method for differentiating precocious puberty from PT[3,5-7]. The majority of CPP occurs between ages 6 and 8 years. The pubertal response to GnRH in females in these ages is well characterized i.e. peak LH > 7-10 IU/L by immunoradiometric assay (IRMA), peak LH > 15 IU/L by radioimmunoassay (RIA), peak LH/peak FSH > 0.66 IU/IU (IRMA)[6,8]. However, the data on pubertal response to GnRH in girls less than 4 years of age are limited. In this study, evaluation of LH and FSH responses to GnRH stimulation in girls with PT was compared between groups aged < 4 years and ≥ 4 years. The LH and FSH responses to GnRH in the younger group were significantly greater than those of the older.

PATIENTS AND METHOD

Patients

We retrospectively reviewed 36 girls with PT who were evaluated in Endocrine Clinic at the Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand, between August 1994 and December 1996. Their ages ranged from 3 months to 8.0 years. They were classified into 2 groups: group A, aged < 4 years (n = 13) and group B, aged ≥ 4 years (n = 23). Premature thelarche was diagnosed based upon the criteria: isolated breast development without other signs of puberty before 8 years of age, bone age (BA) within mean ± 2 SD of chronologic age, normal growth velocity, no progressive breast development and no growth spurt at a 12-month follow-up. The degree of breast development was assessed according to the stages given by Marshall and Tanner[9]. Bone age was determined according to the method of Greulich and Pyle[10]. Growth velocity was determined from the height increment during follow-up. Diagnostic evaluation included GnRH testing, X-ray bone age and ultrasound examination of the uterus and ovaries. GnRH testing was performed by administering intravenously 100 μg of GnRH (Relisorm L®, Laboratories Serono S.A., Switzerland) and serum LH and FSH were obtained at 0, 30, 60, 90 and 120 minutes. Serum estradiol (E_2) was obtained at 0 and 120 minutes. Serum alpha fetoprotein (AFP) levels were determined at baseline.

Hormone assays

Serum LH, FSH, and E_2 were measured by enzyme linked immuno-sorbent assays (ELISAs) by commercial kits (Enzymun-Test®LH, Enzymun-Test®FSH and Enzymun-Test®Oestradiol, Boehringer Mannheim Gmbh, Mannheim, F.R.G.). The Imx® AFP assay is a microparticle enzyme immunoassay (MEIA) manufactured by Abbott Laboratories diagnosis.

Statistical analysis

All data are expressed as mean ± SD. Comparison between 2 groups was performed by using analysis of variance and Student *t*-test. The Δ level means the difference between peak and basal levels following GnRH test. A p value of < 0.05 was considered significant difference.

RESULTS

The mean age ± SD in group A was 1.57 ± 1.87 years and that in group B was 6.97 ± 0.94 years. All patients had bone age within mean ± 2 SD for chronological age. Pelvic sonography was performed in all patients which revealed neither abnormality of ovaries and uterus nor ovarian cysts.

Fig. 1 and 2 illustrate LH and FSH responses (mean ± SD) following GnRH stimulation in girls with PT. The means basal LH ± SD in group A and B were 1.5 ± 0.83 and 2.2 ± 2.11 IU/L, whereas those of FSH were 10.6 ± 5.58 and 8.8 ± 6.92 IU/L. The mean basal LH and FSH levels were not significantly different in both groups (p > 0.05). The mean LH and FSH concentrations at 30, 60 and 90 minutes of group A were significantly greater than those of group B (p < 0.05). The mean Δ LH in group A and B (Fig. 3) were 11.4 ± 5.92 and 6.3 ± 3.49 IU/L, which were significantly different (p = 0.002). Moreover, the mean Δ FSH in group A was 109.9 ± 42.09 IU/L which was significantly greater than that of group B (39.9 ± 23.69 IU/L) (p = 0.000)

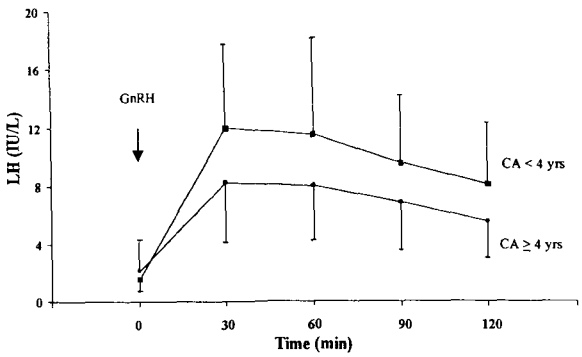

Fig. 1. LH response (mean ± SD) following GnRH stimulation in girls with premature thelarche, comparison between 2 groups; aged < 4 years (n = 13) and aged ≥ 4 years (n = 23).

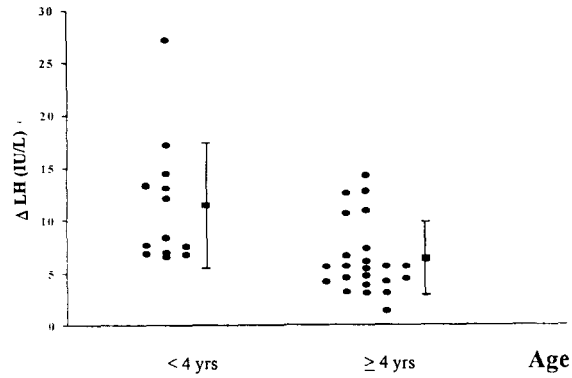

Fig. 3. Δ LH levels (IU/L) in girls with isolated premature thelarche; group A (n = 13, aged < 4 years) compared with group B (n = 23, aged ≥ 4 years).

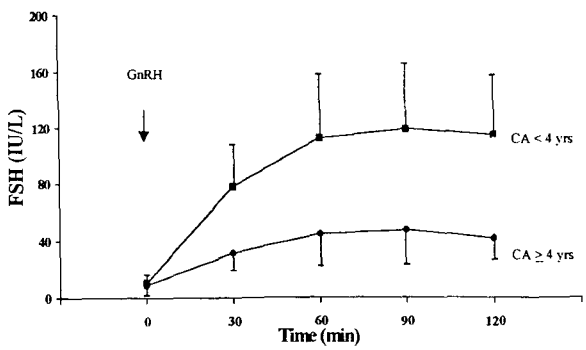

Fig. 2. FSH response (mean ± SD) following GnRH stimulation in girls with premature thelarche, comparison between 2 groups; aged < 4 years (n = 13) and aged ≥ 4 years (n = 23).

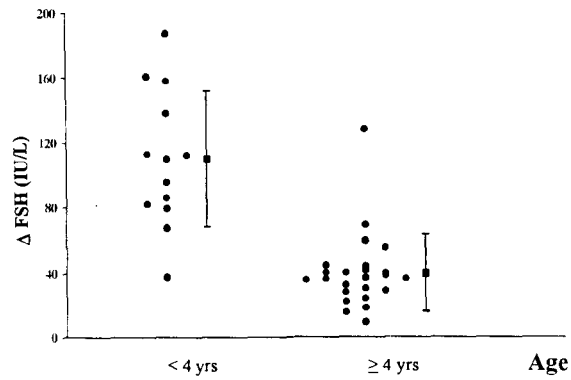

Fig. 4. Δ FSH levels (IU/L) in girls with isolated premature thelarche; group A (n = 13 aged < 4 years) compared with group B (n = 23 aged ≥ 4 years).

(Fig. 4). The mean peak LH concentrations following GnRH stimulation in group A and B were 13.0 ± 6.06 and 8.5 ± 4.1 IU/L (Fig. 5), which were significantly different (p = 0.012). The mean peak FSH concentrations in group A and B were 120.0 ± 45.87 and 48.7 ± 24.05 IU/L (Fig. 6) which were significantly different (p = 0.000).

In our laboratory, pubertal response to GnRH stimulation is characterized by peak LH of > 20 IU/L (ELISA) or Δ LH of > 15 IU/L which is generally greater than peak FSH or Δ FSH.

DISCUSSION

The results of this study clearly show that girls with isolated premature thelarche had a predominant FSH response to GnRH and the peak LH/peak FSH ratio after GnRH stimulation was less than 1.0. In contrast, girls with true puberty had LH response following GnRH stimulation greater than that of FSH[3,4,7,11,12]. In the present study, the levels of both LH and FSH following GnRH tests in children aged < 4 years were significantly greater than those of aged ≥ 4 years. Therefore, the criteria

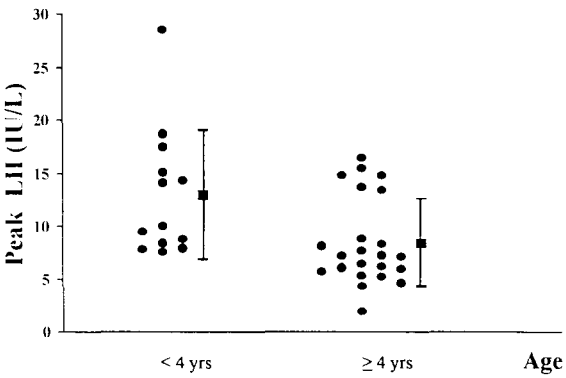

Fig. 5. Peak serum LH levels (IU/L) in girls with isolated premature thelarche; group A (n = 13 aged < 4 years) compared with group B (n = 23 aged ≥ 4 years).

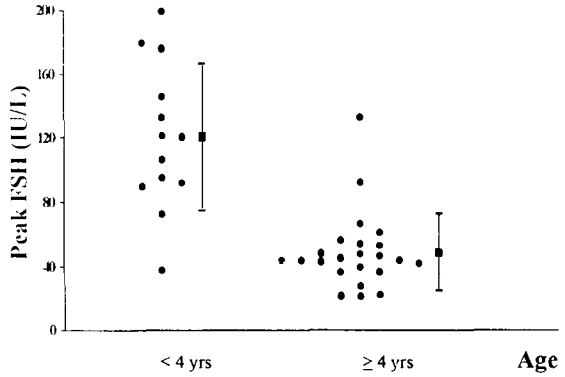

Fig. 6. Peak serum FSH levels (IU/L) in girls with isolated premature thelarche; group A (n = 13 aged < 4 years) compared with group B (n = 23 aged ≥ 4 years).

to differentiate pubertal *vs* prepubertal response to GnRH stimulation in infancy and toddler *vs* childhood period should be different, i.e. the cut-off point for pubertal LH response in infants should be greater than that in children. Nevertheless, it is important to follow them every 3 to 6 months for assessing pubertal progression and growth velocity because isolated premature thelarche may be an early sign of precocious puberty[1,2]. A long-term follow up study in girls with PT revealed regression of thelarche in 44 per cent after approximately 3 years and an overall progression into normal puberty at the appropriate time[4]. Recent retrospective study showed that majority of girls with PT had regression of breast volume during a period of 6 months to 6 years after diagnosis and about 10 per cent had persistent breast development until puberty[13].

In conclusion, LH response to GnRH stimulation alone is able to distinguish prepuberty from puberty in girls > 4 years of age. However, young girls < 4 years of age with PT can have pubertal LH response, i.e. peak LH > 20 IU/L or Δ LH >15 IU/L. Therefore, predominant FSH response to GnRH, i.e. greater than LH response, would confirm the diagnosis of PT in this group[11,14]. Hence, the evaluation of FSH response to GnRH stimulation is beneficial in differentiating puberty from prepuberty in young girls < 4 years of age.

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REFERENCES

1. Pasquino AM, Pucarelli I, Passeri F, Segni M, Mancim MA. Progression of premature thelarche to central precocious puberty. J Pediatr 1995; 126: 11-4.
2. Mills JL, Stolley PD, Davies J, Moshang J Jr. Premature thelarche: natural history and etiologic investigation. Am J Dis Child 1981; 135: 743-5.
3. Pescovitz OH, Hench KD, Barnes KM, Loriaux DL, Cutler GB Jr. Premature thelarche and central precocious puberty: the relationship between clinical presentation and the gonadotropin response to luteinizing hormone-releasing hormone. J Clin Endocrinol Metab 1988; 67: 474-9.
4. Illicki A, Prager R, Kauli R, Kaufman H, Schachter A, Laron Z. Premature thelarche: natural history and sex hormone secretion in 68 girls. Acta Paediatr Scand 1984; 73: 756-62.
5. Dickerman Z, Prager R, Laron Z. Response of plasma LH and FSH to synthetic LH-RH in children at various pubertal stages. Am J Dis Child 1976;130: 634-8.
6. Perignon F, Brauner R, Argyearopoulou M, Brunelle F. Precocious puberty in girls: pituitary height as an index of hypothalamo-pituitary activation. J Clin Endocrinol Metab 1992; 75: 1170-2.
7. Pohlenz J, Habermehl P, Wemme H, Grimm W, Schonberger W. The differentiation between premature thelarche and pubertas praecox on the basis of clinical, hormonal and radiological findings. Dtsch Med Wochenschr 1994; 119: 1301-6.
8. 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 1990; 71: 1251-8.
9. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969; 44: 291-303.
10. Greulich WW, Pyle SI. Radiographics atlas of skeletal development of the hand and wrist. 2nd ed. Stanford: Standford University Press, 1959.
11. Verrotti A, Ferrari M, Morgese G, Chiarelli F. Premature thelarche; a long-term follow-up. Gynecol Endocrinol 1996; 10: 24-7.
12. Pelzer V, Von Difurth M, Wendel U. Diagnostic differentiation between precocious puberty and premature thelarche using ultrasonography and the stimulated LH/FSH quotient. Geburtshilfe Frauenheikd 1990; 50: 964-8.
13. Van Winter JT, Noller KL, Zimmerman D, Melton LJ III. Natural history of premature thelarche in Olmsted County, Minnesota, 1940 to 1984. J Pediatr 1990; 116: 278-80.
14. Aritaki S, Takagi A, Someya H, Jun L. A comparison of patients with premature thelarche and idiopathic true precocious puberty in the initial stage of illness. Acta Paediatr Jpn 1997; 39: 21-7.

การทดสอบ gonadotropin-releasing hormone ในผู้ป่วยเต้านมโตก่อนวัย

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Premature thelarche (PT) คือภาวะที่เด็กหญิงมีการเจริญเติบโตของเต้านมเพียงอย่างเดียวก่อนอายุ 8 ปี โดยไม่มีอัตราการเจริญเติบโตเร็วกว่าปกติ และอายุกระดูกไม่ล้ำหน้ากว่าอายุจริง การวินิจฉัยโรคหาความแตกต่างระหว่างผู้ป่วย PT และ precocious puberty สามารถใช้ระดับฮอร์โมน LH ที่ตอบสนองต่อ GnRH เป็นตัวบ่งชี้ได้ แต่ในภาวะปกติระดับฮอร์โมน LH ในเด็กเล็กมีค่ามากกว่าในเด็กโต ดังนั้นการวิจัยนี้จึงมุ่งศึกษาถึงระดับฮอร์โมน gonadotropins ที่ตอบสนองต่อ GnRH ในผู้ป่วย PT ในกลุ่มอายุแตกต่างกัน

จำนวนผู้ป่วย PT ทั้งหมด 36 ราย อายุระหว่าง 3 เดือน - 8 ปีได้แบ่งออกเป็น 2 กลุ่ม กลุ่ม A มีอายุน้อยกว่า 4 ปีโดยมีอายุเฉลี่ย 1.57 ± 0.87 ปี จำนวน 13 ราย กลุ่ม B มีอายุมากกว่า 4 ปี โดยมีอายุเฉลี่ย 6.97 ± 0.94 ปี จำนวน 23 ราย ผู้ป่วยทั้ง 2 กลุ่มได้รับการตรวจหาอายุกระดูก (bone age), pelvic sonography การทดสอบ GnRH และติดตามดูความเปลี่ยนแปลงทางเพศทุติยภูมิต่อไปอีกอย่างน้อย 1 ปี เพื่อยืนยันว่าผู้ป่วยไม่เข้าสู่ puberty

ผลการทดสอบของผู้ป่วยทั้ง 2 กลุ่ม อายุกระดูกอยู่ใน mean ± 2SD ไม่พบความผิดปกติของรังไข่และมดลูก ผลการทดสอบ GnRH พบว่าผู้ป่วยที่เข้าสู่ puberty ระดับ LH สูงสุดจะมีค่ามากกว่า 20 IU/L หรือผลต่างของระดับ LH สูงสุดกับค่าเริ่มต้นก่อนทำการทดสอบ GnRH (Δ LH) >15 IU/L และจะมีค่ามากกว่าระดับ FSH สูงสุดหรือ Δ FSH ตามลำดับ ผลจากการวิจัยในผู้ป่วยกลุ่ม A ค่าเฉลี่ย ± ค่าเบี่ยงเบนมาตรฐานของระดับฮอร์โมนต่างๆ พบว่าระดับ LH สูงสุด 13.0 ± 6.06, Δ LH 11.4 ± 5.92 IU/L; ระดับ FSH สูงสุด 120.5 ± 45.87, Δ FSH 109.9 ± 42.09 IU/L ผู้ป่วยกลุ่ม B ระดับ LH สูงสุด 8.5 ± 4.1, Δ LH 6.3 ± 3.49 IU/L; ระดับ FSH สูงสุด 48.7 ± 24.05, Δ FSH 39.9 ± 23.69 IU/L

สรุปการตอบสนองของ LH เพียงอย่างเดียวต่อการกระตุ้นด้วย GnRH สามารถแยกระหว่าง prepuberty และ puberty ได้ในเด็กโตอายุมากกว่า 4 ปี สำหรับเด็กเล็กที่อายุน้อยกว่า 4 ปีการตอบสนองของ LH จะมากกว่าในเด็กโต คือระดับ LH สูงสุดอาจมากกว่า 20 IU/L ดังนั้นการใช้ระดับ LH อย่างเดียวในการวินิจฉัยว่าผู้ป่วยเข้าสู่ puberty จึงอาจมีความผิดพลาดได้ การตอบสนองของ FSH ซึ่งจะมีค่ามากกว่าการตอบสนองของ LH จึงช่วยในการวินิจฉัยโรค PT ได้โดยเฉพาะในกลุ่มที่มีอายุน้อยกว่า 4 ปี

คำสำคัญ : Premature Thelarche, Gonadotropin-Releasing Hormone

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