# Basal Luteinizing Hormone/Follicle Stimulating Hormone Ratio in Diagnosis of Central Precocious Puberty

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**Abstract**

**Background :** Precocious puberty is characterized by breast development in girls prior to 8 years old and may have acne, adult odor, growth spurt and menstruation. Conventionally, gonadotropin releasing hormone (GnRH) stimulation test is a gold standard for diagnosis of central precocious puberty but it is a time-comsuming procedure that is not practical on an out patient basis.

**Objective :** To evaluate the basal luteinizing hormone (LH)/follicle stimulating hormone (FSH) ratio in diagnosis of central precocious puberty in order to save time and cost.

**Subjects and Method :** The GnRH stimulation tests were performed on 51 girls with breast development before 8 years old. The 51 girls were divided into 2 groups, 24 girls with central precocious puberty (CPP) and 27 girls with premature thelarche (PT), and the clinical data and GnRH stimulation tests data were compared between the 2 groups. The authors also compared the clinical data and GnRH stimulation tests data between 13 girls with PT and 12 girls with thelarche variants (TV) who developed puberty approximately 1 year later as confirmed by GnRH stimulation test.

**Results :** Girls with CPP had a large bone age and chronological age ratio and advancement of breast staging. Girls with TV had a greater level of basal luteinizing hormone (LH), peak LH and 120 min estradiol than girls with PT. Basal luteinizing hormone and follicle stimulating hormone (FSH) ratio greater than 0.2 can be used to diagnose CPP with 75 per cent sensitivity, 85 per cent specificity, 82 per cent positive predictive value (PPV) and 82 per cent negative predictive value (NPV)

**Conclusion :** Girls with CPP have a basal LH/FSH ratio greater than 0.2 and this can be used as a cut-off point for the diagnosis CPP.

**Key word :** Central Precocious Puberty, Premature Thelarche, Thelarche Variants, Follicular Stimulating Hormone, Luteinizing Hormone, Bone Age and Chronological Age

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Girls with breast development before 8 years of age can be divided into 3 groups including true or central precocious puberty (CPP), pseudo or peripheral precocious puberty (PPP), and incomplete precocious puberty such as premature thelarche (PT)[1]. Usually the growth rate in girls who have central precocious puberty and peripheral precocious puberty is rapid, while in premature thelarche it is normal. In central precocious puberty, pubertal development is normal except for its early occurrence. This is the result of early activation of pulsatile GnRH secretion and subsequent pituitary gland secretion of both LH and FSH. Central precocious puberty is idiopathic in more than 75 per cent of girls. Secondary causes of CPP may be as diverse as hydrocephalus, central nervous system infections, head trauma, cerebral palsy or hypothalamic tumors. CPP is also a common consequence of radiation therapy of brain tumors near the hypothalamus. In peripheral precocious puberty, only one type of sexual characteristic develops early, not occurring in the normal sequence of puberty. Disorders associated with PPP include McCune Albright syndrome, ovarian tumors, and adrenal tumors. Incomplete forms of precocious puberty are relatively benign. An ovarian follicle may secrete sufficient estrogen to stimulate breast and uterine endometrial growth leading to premature thelarche, which is self-limited and a non-progressive state. Approximately 10 per cent of children who have apparent premature thelarche will progress to central precocious puberty[2]. Careful follow-up of girls with PT is very important because some of them may develop puberty called thelarche variants (TV) which need appropiate treatment with GnRH agonist for a good height prognosis.

GnRH stimulation test is a gold standard for diagnosis of central precocious puberty, but it is cumbersome, costly, and time-consuming. To decrease these problems, there have been many studies to evaluate the use of basal LH for diagnosis central precocious puberty with a reported range of sensitivity and specificity depending on the assay for LH detection and the cut-point of basal LH. Moreover, it has been suggested that the basal luteinizing hormone and follicle stimulating hormone ratio greater than 0.2 can be used for the diagnosis CPP[3].

Additional tests are needed for the evaluation of precocious puberty, and these include skeletal age and ultrasonography of the pelvis to assess for evidence of ovaries and uterus responsiveness to pulsatile GnRH secretion occuring in central precocious puberty. Magnetic Resonance Imaging of the pituitary and hypothalamus and tumor markers including β-human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) for excluding a tumor can complete the CPP evaluation.

The objective of the present study was to evaluate the basal LH/FSH ratio in the diagnosis of central precocious puberty in order to save cost and time, and to find the predictors for development of CPP in girls with premature thelarche.

## SUBJECTS AND METHOD

GnRH stimulation tests were performed on 51 girls with breast development before 8 years old and they were all treated at the Endocrinologic Unit, Department of Pediatrics, King Chulalongkorn Memorial Hospital between 1999 and 2002. Girls who had breast tanner stage greater than 3 and menstruation were excluded from the study. Because they had puberty already, the gonadotropin levels are not necessary for differentiating CPP from PT. Girls who had PPP were also excluded.

GnRH stimulation tests were performed by collecting FSH, LH at 0, 30, 60, 90, 120 min and estradiol at 0 and 120 min after giving synthetic GnRH (Relisorm 100 μg) intravenously[4]. Serum FSH, LH and estradiol levels were measured by fluoroimmunoassay. Pelvic ultrasonography was performed to exclude ovarian tumor and functional ovarian cyst. The bone age was estimated by the Greulich and Pyle method. Tumor markers including β-hCG and alpha-fetoprotein (AFP) were measured.

After that, the girls were divided into 2 groups including :

1. Central precocious puberty (CPP) : Girls who presented with early breast development and had a peak LH level greater than 10 IU/L or peak LH/FSH ratio greater than 1.

2. Premature thelarche (PT) : Girls who presented with early breast development and had a peak LH level lower than 10 IU/L or peak LH/FSH ratio lower than 1.

Then the authors compared the clinical data, GnRH stimulation tests data between group 1 (CPP) and group 2 (PT). Nonparametric *t*-test was used to compare the patient between 2 groups and $p < 0.05$ was considered significant.

## RESULTS

There were 24 girls in the CPP group, they all had accerelated height velocity and advanced bone age. There were 27 girls in the PT group, 7 of them

had accerelated height velocity and 5 had advanced bone age. The clinical data comparing the 2 groups are shown in Table 1. The mean of breast tanner stage of CPP was 2.70 ± 0.09 and PT was 2.10 ± 0.06 (p = 0.01) and BA/CA ratio of CPP was 1.26 ± 0.03 and PT was 1.22 ± 0.05 (p = 0.02) and other clinical data were not significantly different.

GnRH stimulation tests data are shown in Table 2.

**In group 1 (CPP)**

The mean basal LH was 3.67 ± 0.66 IU/L, basal FSH was 5.16 ± 0.42IU/L, basal estradiol was 112.77 ± 22.73 pmol/L, peak LH was 40.52 ± 4.84 IU/L, peak FSH was 16.13 ± 1.20 IU/L,120 min estradiol was 119.21 ± 19.11 pmol/L,basal LH/FSH ratio was 0.63 ± 0.97, 30 min LH/FSH ratio was 2.67 ± 0.23 and peak LH/FSH ratio was 2.53 ± 0.20.

**In group 2 (PT)**

The mean basal LH was 0.40 ± 0.10 IU/L, basal FSH was 3.47 ± 0.52 IU/L, basal estradiol was 59.19 ± 8.46 pmol/L, peak LH was 5.80 ± 0.46 IU/L, peak FSH was 12.77 ± 0.73 IU/L, 120 min estradiol was 65.72 ± 9.39 pmol/L, basal LH/FSH ratio was 0.13 ± 0.03, 30 min LH/FSH ratio was 0.67 ± 0.09 and peak LH/FSH ratio was 0.52 ± 0.07.

Table 3 shows that the basal LH/FSH ratio of 0.2 has better sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) than other cut-off points.

Additional evaluation of the PT group revealed, twelve girls out of 27 girls of the PT group developed puberty approximately 1 year later, defined as Thelarche variants (TV). A second GnRH stimulation test was performed, the result revealed pubertal response in all twelve girls. The authors compared

**Table 1. Clinical data of the 51 girls.**

| Group | Central precocious puberty | Premature thelarche | P-value |
|---|---|---|---|
| N | 24 | 27 | |
| Chronological age (yr) at onset of breast development | 7.01 ± 0.38 | 6.31 ± 0.46 | 0.25 |
| Chronological age (yr) at enrollment | 8.27 ± 0.37 | 7.36 ± 0.33 | 0.62 |
| Breast stage | 2.70 ± 0.09 | 2.10 ± 0.06 | 0.01* |
| Pubic hair | 1.20 ± 0.09 | 1.15 ± 0.08 | 0.45 |
| Height standard deviation score | 1.36 ± 0.28 | 1.31 ± 0.22 | 0.83 |
| Height standard deviation score for bone age | -0.46 ± 0.22 | -0.11 ± 0.24 | 0.47 |
| Weight standard deviation score | 1.70 ± 0.39 | 1.90 ± 0.34 | 0.62 |
| Bone age (yr) | 10.05 ± 0.40 | 8.64 ± 0.43 | 0.44 |
| Bone age/chronological age ratio | 1.260 ± 0.03 | 1.22 ± 0.05 | 0.02* |
| Predicted adult height (PAH) | 154.05 ± 1.57 | 155.52 ± 1.80 | 0.37 |

* $p < 0.05$

**Table 2. Serum LH, FSH, LH/FSH and estradiol in 51 girls.**

| Group | Central precocious puberty | Premature thelarche | P-value |
|---|---|---|---|
| Basal LH (IU/L) | 3.67 ± 0.66 | 0.40 ± 0.10 | < 0.01* |
| Basal FSH (IU/L) | 5.16 ± 0.42 | 3.47 ± 0.52 | 0.66 |
| Basal estradiol (pmol/L) | 112.77 ± 22.73 | 59.19 ± 8.46 | 0.04* |
| Peak LH (IU/L) | 40.52 ± 4.84 | 5.80 ± 0.46 | < 0.01* |
| Peak FSH (IU/L) | 16.13 ± 1.20 | 12.77 ± 0.73 | 0.01* |
| Basal LH/FSH ratio | 0.63 ± 0.97 | 0.13 ± 0.03 | < 0.01* |
| 30 min LH/FSH ratio | 2.67 ± 0.23 | 0.67 ± 0.09 | < 0.01* |
| Peak LH/FSH ratio | 2.53 ± 0.20 | 0.52 ± 0.07 | < 0.01* |
| 120 min estradiol (pmol/L) | 119.21 ± 19.11 | 65.72 ± 9.39 | 0.06 |

* $p < 0.05$

**Table 3. GnRH stimulation tests data.**

| Basal LH/FSH ratio | Sensitivity (%) | Specificity (%) | Positive predictive value (PPV,%) | Negative predictive value (NPV,%) |
|---|---|---|---|---|
| ≥ 0.10 | 91.17 | 51.85 | 62.86 | 87.50 |
| ≥ 0.15 | 87.50 | 70.37 | 72.41 | 86.36 |
| ≥ 0.20 | 79.17 | 85.19 | 82.61 | 82.14 |
| ≥ 0.25 | 70.83 | 85.19 | 80.95 | 76.67 |
| ≥ 0.30 | 62.50 | 85.19 | 78.95 | 71.88 |

**Table 4. Initial clinical data of the 27 PT girls.**

| Group | Thelarche variants | Unchanged | P-value |
|---|---|---|---|
| N | 12 | 15 | |
| Chronological age (yr) at onset of breast development | 6.86 ± 0.43 | 5.58 ± 0.88 | 0.17 |
| Chronological age (yr) at enrollment | 7.55 ± 0.30 | 7.20 ± 0.56 | 0.61 |
| Breast stage | 2.13 ± 0.09 | 2.08 ± 0.08 | 0.74 |
| Pubic hair | 1.13 ± 0.13 | 1.17 ± 0.11 | 0.81 |
| Height standard deviation score | 1.57 ± 0.29 | 1.10 ± 0.33 | 0.31 |
| Height standard deviation score for bone age | -0.17 ± 0.34 | -0.06 ± 0.34 | 0.81 |
| Weight standard deviation score | 1.86 ± 0.52 | 1.93 ± 0.46 | 0.92 |
| Bone age (yr) | 9.28 ± 0.51 | 8.06 ± 0.65 | 0.16 |
| Bone age/chronological age ratio | 1.21 ± 0.06 | 1.23 ± 0.09 | 0.87 |
| Predicted adult height (PAH) | 154.47 ± 2.30 | 156.91 ± 2.97 | 0.52 |

Thelarche variants : GnRH stimulation test 1 year later showed the peak LH > 10 IU/L or peak LH/FSH ratio > 1)

girls with TV and PT with the initial clinical data and GnRH stimulation tests data.

The clinical data are shown in Table 4 including chronological age (CA) at onset, chronological age (CA) at presentation, breast staging, pubic hair, height standard deviation score (HtSDS), height standard deviation score for bone age (HtSDS for BA), weight standard deviation score (WtSDS), BA/CA ratio and predicted adult height (PAH) were not significantly different.

From Table 1, 2, 4 and 5, it was found that most of the GnRH stimulation tests data changed before the clinical data. This correlate with the authors' knowledge that timing of pubertal development usually occurs earlier than changing of laboratory data of GnRH stimulation test by approximately 6 months.

The initial GnRH stimulation tests data are shown in Table 5

### In the TV group

The mean basal LH was 0.61 ± 0.18 IU/L, basal FSH was 3.35 ± 0.53 IU/L, basal estradiol was 72.69 ± 15.97 pmol/L, peak LH was 7.44 ± 0.60 IU/L, peak FSH was 12.99 ± 0.86 IU/L, 120 min estradiol was 93.61 ± 18.92 pmpl/L, basal LH/FSH ratio was 0.18 ± 0.06, 30 min LH/FSH ratio was 0.76 ± 0.07 and peak LH/FSH ratio was 0.60 ± 0.07.

### In the PT group

The mean basal LH was 0.24 ± 0.06 IU/L, basal FSH was 3.57 ± 0.85 IU/L, basal estradiol was 48.39 ± 7.75 pmol/L, peak LH was 4.71 ± 0.51 IU/L, peak FSH was 12.62 ± 1.10 IU/L, 120 min estradiol was 48.99 ± 7.47 pmpl/L, basal LH/FSH ratio was 0.09 ± 0.02, 30 min LH/FSH ratio was 0.61 ± 0.14 and peak LH/FSH ratio was 0.47 ± 0.10.

## DISCUSSION

Girls presenting with early breast development before 8 years old have to have CPP from differentiated PT because these 2 conditions have different therapy and prognosis. PT does not require treatment but CPP can be treated effectively with GnRH agonist for improvement of final height[5]. Mills et al[6] described the natural history of 46 girls

**Table 5. Serum LH, FSH, LH/FSH and estradiol in 27 PT girls.**

| Group | Thelarche variants | Unchanged | p-value |
|---|---|---|---|
| Basal LH (IU/L) | 0.61 ± 0.18 | 0.24 ± 0.06 | 0.04* |
| Basal FSH (IU/L) | 3.35 ± 0.53 | 3.57 ± 0.85 | 0.84 |
| Basal estradiol (pmol/L) | 72.69 ± 15.97 | 48.39 ± 7.75 | 0.16 |
| Peak LH (IU/L) | 7.44 ± 0.60 | 4.71 ± 0.51 | < 0.01* |
| Peak FSH (IU/L) | 12.99 ± 0.86 | 12.62 ± 1.10 | 0.81 |
| Basal LH/FSH ratio | 0.18 ± 0.06 | 0.09 ± 0.02 | 0.14 |
| 30 min LH/FSH ratio | 0.76 ± 0.07 | 0.61 ± 0.14 | 0.45 |
| Peak LH/FSH ratio | 0.60 ± 0.07 | 0.47 ± 0.10 | 0.37 |
| 120 min estradiol(pmol/L) | 93.61 ± 18.92 | 48.99 ± 7.47 | 0.02* |

* $p < 0.05$

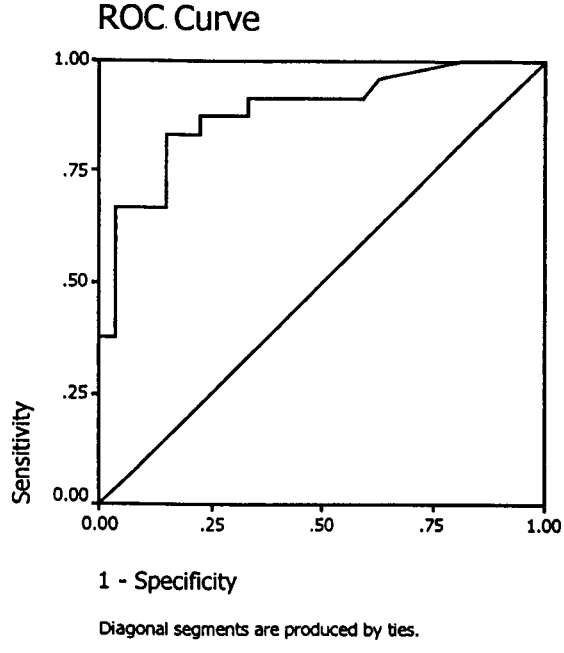


**Fig. 1. Basal LM/FSH ratio value, computations were made for cut-off levels of 0.1, 0.15, 0.2, 0.25 and 0.3.**

with PT. The majority had no change in breast development during 3-5 years of follow-up (57%), 11 per cent reported progressive breast enlargement with the development with no other symptoms, and 32 per cent reported disappearance of their breast development. From the present study, breast staging and BA/CA ratio are the clinical criteria differentiate these 2 conditions and the result also occurred in the GnRH stimulation tests data including basal LH, basal estradiol, peak LH, peak FSH, basal LH/FSH, 30 min LH/FSH and peak LH/FSH. In the same way, AM Pasquino et al[7] suggested that peak LH of CPP (30.8 mU/mL) was more significant than PT (10.5 mU/mL). Girls with PT need careful follow-up because some of them may develop early puberty, called thelarche variants (TV). In the present study, 12 girls out of 27 girls with PT develpoed puberty 1 year (6 months - 1 year) later and the important predictors were basal LH, peak LH and 120 min estradiol levels.

Conventionally, the GnRH stimulation test is the gold standard for diagnosis of CPP but because the GnRH stimulation test is time consuming and

costly. The previous studies used basal LH level to diagnose CPP. In VN Brito et al[8] suggested basal LH more than 0.7 IU/L can be used in diagnosis of CPP. Garibaldia et al[9] also used basal LH by IRMAs of more than 0.7 IU/L to diagnose CPP with 67 per cent of sensitivity. Neely et al[10,11] measured LH level by ICMAs and used a basal LH level more than 0.1 IU/L to diagnose CPP with 94 per cent sensitivity and 88 per cent specificity. Augsusingha et al[12] suggested that the peak LH minus basal LH was the best parameter to diagnose CPP. Normally, CPP has a peak LH/FSH ratio more than 1 from GnRH stimulation test. In the present study, the authors tried to use the basal LH/FSH ratio instead of peak LH/FSH ratio for diagnosis of CPP. Basal LH/FSH ratio of CPP was 0.63 ± 0.97 and PT was 0.13 ± 0.03 which was markedly different and the authors used the value of basal LH/FSH ratio of more than 0.2 to diagnose CPP with good sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPP) when compared with the other cut-off point including 0.1, 0.15, 0.25 and 0.3. S Wacharasindhu et al showed that a basal LH/FSH ratio more than 0.2 can be used to diagnose CPP with PPV of 87.3 per cent.

In conclusion, girls with CPP who have more advanced puberty and a basal LH/FSH ratio of more than 0.2 can be used as the cut-off point to diagnosis CPP.

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# การใช้อัตราส่วนระหว่าง LH และ FSH ที่ระดับ BASAL ในการวินิจฉัยภาวะเป็นสาวก่อนวัย

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**ที่มา** : ภาวะเป็นสาวก่อนวัย คือ มีการเปลี่ยนแปลงของเต้านมในเด็กผู้หญิงก่อนอายุ 8 ปี อาจพบร่วมกับการมีสิว การเพิ่มอัตราความสูง และมีประจำเดือน ซึ่งวิธีมาตรฐานในการวินิจฉัยภาวะเป็นสาวก่อนวัย central precocious puberty (CPP) คือ GnRH stimulation test ซึ่งเสียเวลา ค่าใช้จ่าย รวมทั้งไม่เหมาะสมในการทำในแผนกผู้ป่วยนอก

**วัตถุประสงค์** : เพื่อใช้อัตราส่วนระหว่าง LH และ FSH ที่ระดับ Basal ในการวินิจฉัยภาวะเป็นสาวก่อนวัย central precocious puberty (CPP) เพื่อลดค่าใช้จ่ายและเวลา

**วิธีการวิจัย** : เด็กผู้หญิงทุกคนที่มีปัญหาเป็นสาวก่อนวัยคือมีการเปลี่ยนแปลงของเต้านมก่อนอายุ 8 ปี ได้รับการทำ GnRH stimulation test และแบ่งออกเป็น 2 กลุ่มดังนี้คือ CPP จำนวน 24 คนและ premature thelarche (PT) จำนวน 27 คนจากนั้นเปรียบเทียบอาการทางคลินิกและข้อมูลของ GnRH stimulation test ว่าแตกต่างกันอย่างไร เมื่อติดตามผู้ป่วยกลุ่ม PT ประมาณ 1 ปีพบว่าผู้ป่วยจำนวน 12 คนในกลุ่มนี้เริ่มมีการเปลี่ยนแปลงเข้าสู่ภาวะวัยรุ่นและทำ GnRH stimulation test ซ้ำพบว่าผลเป็น CPP จึงเปรียบเทียบอาการทางคลินิกและข้อมูลของ GnRH stimulation test ว่าแตกต่างจาก PT อย่างไร

**ผลการวิจัย** : พบว่าเด็กหญิงในกลุ่ม CPP นั้นมีค่าอัตราส่วนของอายุกระดูกและอายุตามวันเกิดมากกว่าและลักษณะเต้านม (Breast tanner stage) ที่มากกว่าเมื่อเทียบกับ PT และในกลุ่ม PT นั้นพบว่า TV (Thelarche variants) มีค่า LH สูงสุดและที่ระดับ basal รวมทั้งระดับ estradiol ที่เวลา 120 นาทีสูงกว่า PT และสามารถใช้อัตราส่วนของ LH และ FSH ที่ระดับ Basal ในการวินิจฉัยภาวะเป็นสาวก่อนวัย central precocious puberty (CPP) ด้วย

**วิเคราะห์สรุปผล** : เด็กผู้หญิงที่มีปัญหาภาวะเป็นสาวก่อนวัย central precocious puberty (CPP) มีการเปลี่ยน-แปลงของร่างกายทางเพศมากกว่าและสามารถใช้อัตราส่วนของ LH และ FSH ที่ระดับ Basal มากกว่า 0.2 ในการวินิจฉัยภาวะเป็นสาวก่อนวัย

**คำสำคัญ** : ภาวะเป็นสาวก่อนวัย, พรีแมทชัวทีลาเก, ทีลาเกแวเรียน, ฟอลลิคิวล่าสติมูเลททิงฮอร์โมน, ลูติไนซิ่ง ฮอร์โมน, อายุกระดูก และอายุตามวันที่

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