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Sensitivity and specificity of using pelvic ultrasonographic parameters combined with basal gonadotropin levels to diagnose central precocious puberty in Thai girls

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Abstract

Background: The criterion standard gonadotropin-releasing hormone (GnRH) stimulation tests to diagnose central precocious puberty (CPP) are time-consuming, inconvenient, and expensive.

Objectives: To determine predictive cut-off values codetermined by ultrasonographic parameters and basal gonadotropin levels in girls with premature sexual development and compare them results of criterion standard tests in a study of diagnostic accuracy.

Methods: Retrospective review of hormonal investigations and ultrasonographic uterine and ovarian parameters in a consecutive sample of girls at a single center, tertiary care hospital in Bangkok, Thailand.

Results: We separated data from 68 girls (age range 2–12 years) into 2 groups based on their response to a GnRH analogue agonist stimulation test. A "prepubertal response" group included girls with premature thelarche and thelarche variants (n = 18, 6.37 ± 1.77 years) and a "pubertal response" group, including girls with CPP (n = 50, 8.46 ± 1.46 years); excluding patients with pathological causes (n = 0). The basal level of luteinizing hormone (LH) had the largest area under receiver operating characteristic curves (AUC) of 0.84; 95% confidence interval [CI] 0.74–0.93) compared with basal levels of follicle stimulating hormone (AUC 0.77; 95% CI 0.64–0.90) or estradiol (0.70; 95% CI 0.56–0.85). An optimal cut-off of 0.25 IU/L LH was related to a pubertal response to GnRH analogue agonist stimulation tests with 75.0% sensitivity, 88.9% specificity, 94.7% positive predictive value (PPV), and 57.1% negative predictive value. Uterine and ovarian cut-off volumes of 3.5 cm³ and 1.5 cm³ were related to a pubertal response with 88.6% and 76.2% PPV, respectively. A uterine width cut-off of 1.7 cm combined with a basal LH cut-off of 0.25 IU/L increased specificity and PPV to 100%.

Conclusion: Combining uterine and ovarian ultrasonographic parameters with basal gonadotropin levels, especially uterine width and basal LH level, appears useful for diagnosis of CPP.

Keywords: diagnostic imaging; gonadotropins; pelvis; puberty, precocious; ultrasonography

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Premature sexual development in girls is conventionally defined as any sexual characteristics occurring before the age of 8 years. The etiology can be generally classified as central precocious puberty (CPP) or peripheral precocious puberty (PPP). CPP is characterized by early activation of hypothalamic–pituitary–gonadal (HPG) axis, which increases growth velocity and the development of secondary sexual characteristics. The cause of CPP in most girls is idiopathic. A small proportion of girls with CPP have an underlying central nervous system (CNS) lesion such as a CNS tumor, or as a result of CNS surgery or irradiation, meningitis, or encephalitis. By contrast, the HPG axis is not activated in PPP. Pathological sources of sex hormone secretion are located outside the HPG axis and include ovarian and adrenal tumors [1]. CPP may cause early epiphyseal maturation with compromised final height as well as psychological stress [2, 3]. Treatment of girls with CPP depends on multiple factors including the age of the child, tempo of puberty, effect of CPP on the child's behavior, effect on parents, and final height prognosis [4]. However, a girl with the onset of puberty at around 8 years of age, presenting with a rapid progression of puberty, accelerated bone age advancement, and a decline in predicted adult height, may need to be treated as for CPP.

There are other, benign forms of premature sexual development in girls, which include premature thelarche (PT) and thelarche variants (TVs) [4, 5]. PT is typically diagnosed during the first few years of life and usually resolves spontaneously. The pathophysiology of this condition remains obscure. TV is generally diagnosed in girls who have clinical presentation somewhere between PT and CPP. Activation of the HPG axis cannot be demonstrated in either PT or TV and treatment is not required for these conditions [4, 5].

Activation of the HPG axis can be demonstrated by a rise of serum luteinizing hormone (LH) level after a stimulation test with 100 μg of gonadotropin-releasing hormone (GnRH) intravenously [6], which we call "pubertal response." Despite its high specificity, this criterion standard test is time-consuming, laborious, and causes inconvenience to patients due to the requirement of several blood samples. In case of the unavailability or commercial limitation of the standard intravenous GnRH test, there are alternative criterion standard tests to diagnose CPP by showing a pubertal response if peak LH level is >6 IU/L after subcutaneous injection of 100 μg triptorelin, a dectapeptide agonist analogue of GnRH, or peak LH level is >10 IU/L 2 h after intramuscular injection of 3.75 mg leuprorelin, also a peptide analogue of GnRH, which acts as a GnRH receptor agonist [7–9].

Previous studies showed that basal LH level or basal LH/follicle stimulating hormone (FSH) ratio can be used as alternative ways to diagnose CPP with sensitivity and specificity of 69.1%–94% and 50.5%–100%, respectively [10–12].

Pelvic ultrasound, which is a rapid, noninvasive, and inexpensive procedure, might serve as a helpful tool to diagnose precocity. However, this is an observer-dependent tool, which needs to be performed by an experienced radiologist. In addition, uterine size and shape reflect an estradiol effect, irrespective of the cause. Thus, uterine enlargement and maturation are not diagnostic for CPP, and can be seen with CPP, but are not normally seen in PT [13]. By contrast, ovarian volume and the presence of follicles reflect gonadotropin activity [14–16]. Previous studies were performed to determine the pelvic ultrasonographic parameters in combination with optimal basal hormonal values to help diagnose CPP, but the results in recent data varied and are considered controversial because either different methods for the GnRH receptor stimulation test or different assays for the hormonal measurement were used [9].

The present study aimed to determine the predictive cut-off values for ultrasonographic parameters combined with basal hormonal gonadotropin levels and to compare their sensitivity and specificity with that of the criterion standard GnRH receptor stimulation tests used to diagnose CPP.

Methods

After approval by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University (IRB No. 102/60, certificate of approval No. 387/2017), we retrospectively reviewed the medical records of 68 girls (age range 2–12 years) who presented consecutively from January 2010 to January 2014 with premature secondary sexual development at the Pediatric Endocrinology Unit at King Chulalongkorn Memorial Hospital, a tertiary referral, teaching hospital of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. The present study was conducted in compliance with the contemporary revision of the Declaration of Helsinki, The Belmont Report, CIOMS guidelines, and the International Conference on Harmonization in Good Clinical Practice. The girls had breast development before 8 years of age, except for 5 who had breast development just after 8 years of age, but with rapid progression of puberty and accelerated bone age, which we call "rapidly progressive puberty." The patients were classified as being in a pubertal response group if the peak level of LH was >6 IU/L in a GnRH receptor stimulation test using the GnRH analogue agonist, triptorelin acetate (Diphereline, Ipsen Pharma Biotech) or LH was >10 IU/L 120 min after a stimulation test using the GnRH analogue agonist leuprorelin acetate (Enantone, Takeda). Otherwise they were classified as being in a "prepubertal response" group. Clinical data including age at presentation, bone age at presentation, and pelvic ultrasonography parameters were noted. Pelvic ultrasound

scans were performed as routine practice by 2 pediatric radiologists at our hospital.

Exclusion criteria for the present study were premature sexual development caused by any identified pathological etiology, such as brain tumor or cranial irradiation, congenital adrenal hyperplasia, sex-hormone secreting tumor, or patients who took any medicines that might interfere with hormonal values.

Pubertal development was ascertained according to the method described first by Marshall and Tanner [18]. Radiological assessment of bone age was determined according to the atlas by Greulich and Pyle [19].

The GnRH receptor stimulation test was performed by injecting 100 μg of triptorelin acetate subcutaneously followed by measurements of LH, FSH, and estradiol levels at 40 and 60 min after injection [8], or in the case of patients who did not undergo this test, 3.75 mg leuprorelin acetate was injected intramuscularly followed by measurements of LH level at 120 min [5]. LH, FSH, estradiol levels were measured by electrochemiluminescence assay (ECLIA) on a Cobas e411 instrument (Roche Diagnostics) with a minimum limit detection of 0.1 mIU/mL for LH and FSH and 5 pg/mL for estradiol, and with a maximum limit detection of 200 mIU/mL for LH and FSH, and 4300 pg/mL for estradiol. Interassay coefficients of variation were 1%–2.1% for LH, 1.7%–3.3% for FSH, and 1.85%–2.6% for estradiol as specified by the manufacturer (Roche Diagnostics).

The ultrasound scanner used was either a Logiq E9 (GE Healthcare) or iU22 (Philips Healthcare) system. All of the patients were scanned with a full bladder, which served as an acoustic window through which the pelvic organs could be examined. Uterine measurements included length, width (transverse diameter), thickness (anteroposterior diameter) of uterine fundus and uterine cervix, and uterine volume—calculated using an ellipsoid formula: V (cm^3) = longitudinal diameter (cm) × transverse diameter (cm) × anteroposterior diameter (cm) × 0.5236. Ovarian measurements included length, width, thickness, and volume—calculated using the same ellipsoid formula. The mean values of each parameter for both ovaries were calculated and used for analysis.

Magnetic resonance imaging (MRI) of pituitary and hypothalamic areas was performed in every patient diagnosed with CPP and rapidly progressive puberty to exclude CNS abnormality.

We used the Standards for Reporting of Diagnostic Accuracy Studies (STARD) statement checklist when writing our report [20].

Statistical analysis

SPSS for Windows (version 17.0) was used to analyze raw data. An analysis of variance (ANOVA) was performed to compare means between pubertal and prepubertal response groups. All data are expressed as means ± standard deviation (SD); $P < 0.05$ is considered significant. Sensitivity and specificity of hormonal and ultrasonographic parameters at each level were determined using receiver operating characteristic (ROC) curves by visual inspection, and the area under the curve (AUC) is reported.

Results

Of the 68 patients, 50 (74%) with a mean age at presentation of 8.46 ± 1.46 years were classified into a pubertal response group. This group included girls with CPP and rapidly progressive puberty. No pathological causes of CPP were identified. We classified 18 girls (26%) with a mean age at presentation of 6.37 ± 1.77 years into a prepubertal response group. This group included girls with PT or TVs (**Figure 1**). The clinical and demographic characteristics of girls in both groups are shown in **Table 1**. Neither chronological age nor bone age was different between the 2 groups. The girls in the pubertal response group had a significantly greater uterine length, thickness, and volume than those in the prepubertal response group. Ovarian ultrasonographic parameters, including bilateral ovarian volume in girls in the pubertal response group, but not bilateral ovarian length, thickness, or width, were significantly greater than those in girls in the prepubertal response group. Basal and peak LH, basal FSH, and basal estradiol levels were significantly higher in girls in the pubertal response group than the levels in girls in the prepubertal response group.

ROC curves of each ultrasonographic and hormonal parameters were constructed to determine the AUC and the optimal cut-off values with high sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to differentiate between the pubertal response and prepubertal response groups. Based on ROC curves (**Figure 2**), the basal level of LH had the largest AUC (0.84; 95% confidence interval (CI) 0.74–0.93; **Figure 2A**) compared with the basal levels of FSH (AUC 0.77; 95% CI 0.64–0.90; **Figure 2B**) and estradiol (0.70; 95% CI 0.56–0.85; **Figure 2C**). An optimal cut-off of 0.25 IU/L basal LH related to the pubertal response group was associated with 75.0% sensitivity, 88.9% specificity, 94.7% PPV, and 57.1% NPV. For ultrasonographic parameters, uterine volume had the largest AUC (0.83; 95% CI 0.72–0.95) (**Figure 2D**) compared with uterine width (**Figure 2E**), length (**Figure 2F**), thickness (**Figure 2G**), and bilateral ovarian volume (**Figure 2H**). A cut-off of 3.5 cm^3 uterine volume was associated with 73.8% sensitivity, 66.7% specificity, 88.6% PPV, and 42.1% NPV (**Table 2**).
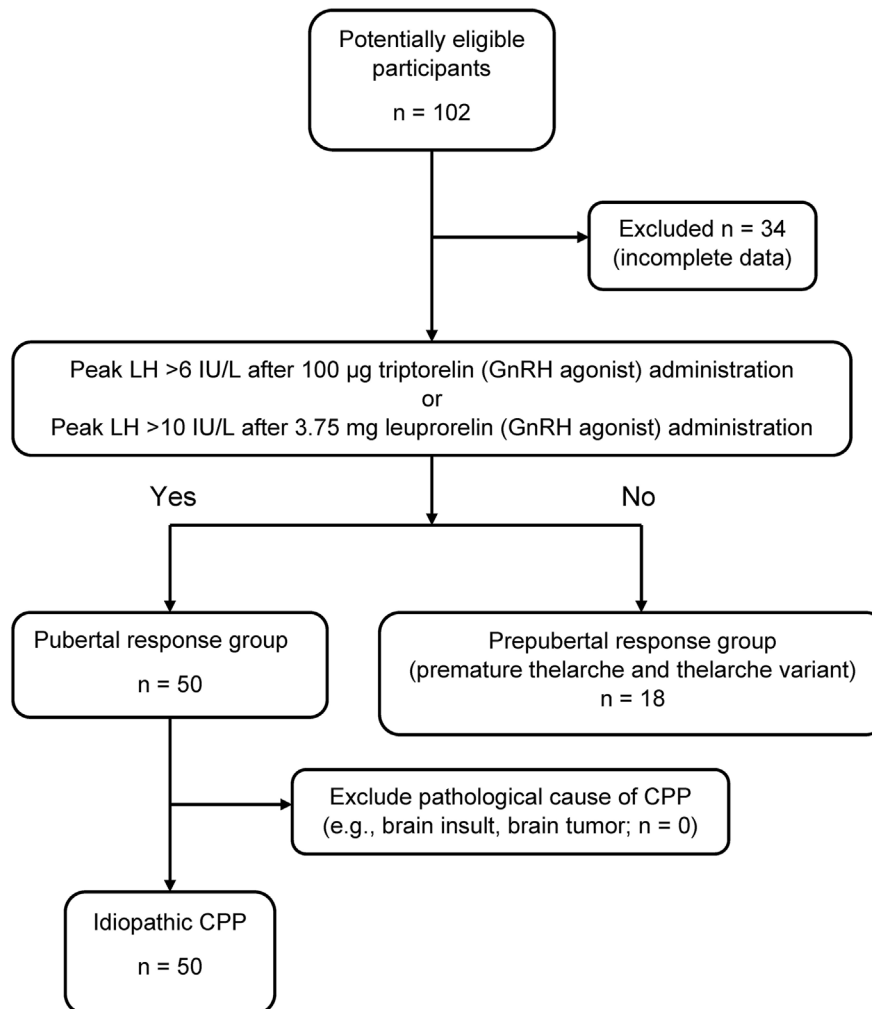
Figure 1. Flow diagram showing the flow of participants though the study. CPP, central precocious puberty; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

The sensitivity, specificity, PPV, and NPV increased if ultrasonographic parameters were combined with basal hormonal levels (**Table 3**). Moreover, the uterine volume at a cut-off of 3.0 cm³ or uterine length at a cut-off of 3.5 cm combined with the basal level of LH at a cut-off of 0.25 IU/L increased specificity to 91.7% and 94.1%, and PPV 96.3% and 96.0%, respectively. Notably, if we combined uterine width at a cut-off of 1.7 cm with basal level of LH at a cut-off of 0.25 IU/L, specificity and PPV increased to 100%.

Discussion

High basal level of gonadotrophin might be a useful tool for diagnosing CPP as shown in many previous studies, but the cut-off level varies [11, 21–23]. Low or suppressed gonadotrophin levels are normally seen in girls with PT, TV, or PPP.

Previous studies demonstrated the clinical application of basal LH level for a diagnosis of CPP with various results. Neely et al. [12] suggested that basal LH levels >0.3 IU/L by immunochemiluminometric assays had 100% specificity for CPP. Lee et al. [11] suggested that a basal LH level of 1.1 IU/L is an optimal cut-off point to distinguish girls with CPP from a prepubertal group with 69% sensitivity and 50.5% specificity with an AUC of 0.620 (95% CI 0.581–0.660), compared with 75% sensitivity and 88.9% specificity with an AUC of 0.84 (95% CI 0.74–0.93) as found in the present study. Binay et al. [24] recommended a basal LH level of 0.12 IU/L with 79.3% sensitivity and 91.8% specificity with an AUC of 0.854 (95% CI 0.769–0.916).

Uterine parameters demonstrated by pelvis ultrasonography, such as uterine size and shape, reflect the effect of estrogen exposure alone regardless of the causes and are not specific to CPP. By contrast, ovarian volume and the presence

Table 1. Clinical and laboratory characteristics of the girls with a prepubertal (PT, TV) or pubertal response (CPP) to a GnRH stimulation test

Parameter	Prepubertal response (n = 18)	Pubertal response (n = 50)	P
	Mean (SD)	Mean (SD)	
Chronological age (years)	6.37 (1.77) range 2–8.2	8.46 (1.46) range 4.8–11	0.41
Bone age (years)	7.91 (2.05) range 4–11	10.43 (1.88) range 6.8–12	0.85
Uterine length (cm)	3.34 (0.64)	4.25 (1.18)	0.007*
Uterine thickness (cm)	0.95 (0.39)	1.53 (0.71)	0.001*
Uterine width (cm)	1.49 (0.60)	2.43 (0.96)	0.31
Uterine volume (cm^3)	2.56 (1.53)	10.96 (11.58)	0.001*
Bilateral ovarian length (cm)	1.31 (0.31)	1.48 (0.43)	0.20
Bilateral ovarian thickness (cm)	1.09 (0.30)	1.32 (0.44)	0.15
Bilateral ovarian width (cm)	1.30 (0.31)	1.43 (0.37)	0.53
Bilateral ovarian volume (cm^3)	1.69 (0.71)	2.77 (2.06)	0.01*
Basal LH (IU/L)	0.22 (0.35)	2.63 (3.99)	0.001*
Basal FSH (IU/L)	1.34 (1.51)	2.90 (1.97)	0.03*
Basal E2 (pg/mL)	51.9 (54.6)	134.6 (182.2)	0.049*
Peak LH (IU/L)	4.33 (2.75)	41.29 (36.19)	<0.001*
Peak FSH (IU/L)	9.45 (4.49)	13.19 (5.61)	0.28
Peak E2 (pg/mL)	53.9 (45.6)	139.7 (196.3)	0.10

CPP, central precocious puberty; E2, estradiol; FSH, follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PT, premature thelarche; SD, standard deviation. Comparisons between groups were made using an independent *t* test. *$P < 0.05$.

of follicles that reflect gonadotrophin activity might be more useful for diagnosing CPP. Previous studies showed that the cut-off values for ovarian volume vary from 1 cm^3 to 3.35 cm^3 [14–16, 24, 25]. The present study found a cut-off of ovarian volume at 1.5 cm^3 with an AUC of 0.66 (95% CI 0.52–0.81). For uterine length, the cut-off values reported varied from 3 cm to >4 cm [13, 14, 26–28]. It is consistent with our present data that uterine length at a cut-off of 3.5 cm was associated with a relatively large AUC (0.72; 95% CI 0.60–0.85) and 62% sensitivity, 64.7% specificity, 83.8% PPV, and 36.7% NPV. For other uterine parameters, such as volume, the cut-off reported in the literature varied from 1.96 cm^3 to 3 cm^3 [13, 25]. In the present study, compared with other uterine parameters, a uterine volume with a cut-off of 3.5 cm^3 had the largest AUC (0.83; 95% CI 0.72–0.95), but its sensitivity (73.8%) and specificity (66.7%) were not remarkable. Moreover, other investigators report the use of uterine parameters including length, thickness, volume or the anteroposterior diameter of the cervix, but not uterine width as was included in our study [13, 24, 25, 29]. In the present report, we show the usefulness of a uterine width cut-off of 1.7 cm, which had 83.7% sensitivity, 58.3% specificity, and 87.8% PPV, with an AUC of 0.80 (95% CI 0.66–0.94) for the screening of sexual precocity.

To avoid a time-consuming and costly GnRH receptor stimulation test, combining uterine parameters, which reflect estradiol effects, and the level of basal gonadotropin, which suggests the extent of activation of the HPG axis, might be a more practically useful tool with which to diagnose CPP.

As demonstrated in the present study, the sensitivity, specificity, PPV, and NPV were increased after we combined ultrasonographic parameters with basal hormonal levels. Especially if we combine uterine width at a cut-off of 1.7 cm with basal LH level at a cut-off of 0.25 IU/L, specificity and PPV increased to 100%. Therefore, this might be a useful clinical tool to help us differentiate girls with pubertal response from girls with a prepubertal response without a using GnRH receptor stimulation test. Furthermore, if we combined uterine width at a cut-off of 1.7 cm with a basal FSH level at a cut-off of 1.5 IU/L, the specificity was 91.7% and PPV was 96.3%. Similarly, when uterine volume at a cut-off of 3 cm^3 was combined with a basal LH level at a cut-off of 0.25 IU/L, the specificity was 91.7%, and PPV was 96.3%. Moreover, uterine length at a cut-off of 3.5 cm combined with basal LH level at a cut-off of 0.25 IU/L, increased specificity to 94.1% and PPV to 96.0%. This implies that a girl with a basal level of LH <0.25 IU/L and a prepubertal uterus is unlikely to have CPP.
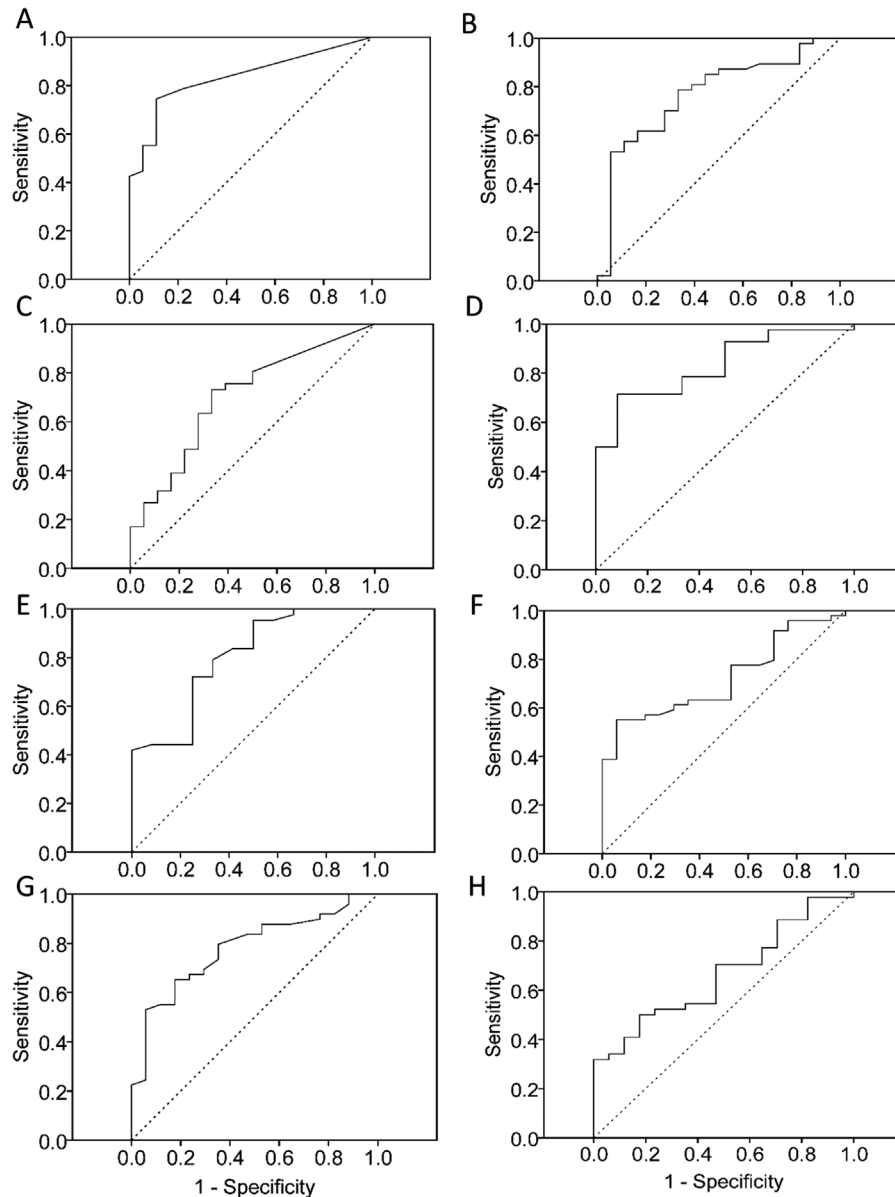
Figure 2. Receiver operating characteristic curves for various ultrasonographic and hormonal parameters. **A.** Basal luteinizing hormone. **B.** Basal follicle stimulating hormone. **C.** Basal estradiol. **D.** Uterine volume. **E.** Uterine width. **F.** Uterine length. **G.** Uterine thickness. **H.** Bilateral ovarian volume. Solid lines indicate the variable parameter and dashed lines indicate a reference line. Diagonal segments are produced by ties.

A limitation of the present retrospective study includes the fixed ultrasonographic data, and the different GnRH analogue agonists used during routine screening. The 2 different kinds of GnRH analogue agonists used in the present study may cause an overlapping result and are not equivalent to the use of intravenous GnRH to discriminate between pubertal and prepubertal responses. We also include data from girls with rapidly progressive puberty in the present study, and they may have a greater response to the GnRH receptor stimulation test. Ultrasonographic data are operator dependent and their reliability depends on the quality of pictures and

specification of ultrasonographic machinery. In addition, the pattern of ovarian follicles, which is a good reflection of gonadotrophic activity, was not recorded consistently. The widths of the uterus and ovary are not always easy to measure correctly as these measurements are dependent on the individual technique and experience of the radiographer. We acknowledge that the sample size in the present study is small, but it represents patients attending a tertiary center and university teaching hospital, and so for a single-center study is acceptable given the rarity of the idiopathic CPP. The patients whose data were included were all from

Table 2. Area under the ROC curve, cut off point, sensitivity, specificity, PPV, and NPV of each ultrasonographic and hormonal parameters

Parameter	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Basal LH (IU/L)	0.84	0.74–0.93	0.25	75.0	88.9	94.7	57.1
Basal FSH (IU/L)	0.77	0.64–0.90	1	85.4	55.6	83.7	58.8
Basal estradiol (pg/mL)	0.70	0.56–0.85	25	76.2	61.1	82.1	52.4
Uterine width (cm)	0.80	0.66–0.94	1.7	83.7	58.3	87.8	50.0
Uterine thickness (cm)	0.78	0.66–0.90	1	73.5	64.7	85.7	45.8
Uterine length (cm)	0.72	0.60–0.85	3.5	62.0	64.7	83.8	36.7
Uterine volume (cm³)	0.83	0.72–0.95	3.5	73.8	66.7	88.6	42.1
Bilateral ovarian volume (cm³)	0.66	0.524–0.805	1.5	71.1	41.2	76.2	35.0

AUC, area under the ROC curve; CI, confidence interval; FSH, follicle stimulating hormone; LH, luteinizing hormone; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

Table 3. Sensitivity, specificity, PPV, and NPV when combining uterine ultrasonographic and basal hormonal parameters

Uterine ultrasonographic parameter	Cut-off	Basal hormonal parameter	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Width (cm)	1.7	Basal LH	0.25	65.9	100	100	46.2
Width (cm)	1.7	Basal FSH	1.5	63.4	91.7	96.3	42.3
Volume (cm³)	3.0	Basal LH	0.25	65.0	91.7	96.3	44.0
Length (cm)	3.5	Basal LH	0.25	50.0	94.1	96.0	40.0
Thickness (cm)	0.9	Basal FSH	1	68.1	70.6	86.5	44.4
Width (cm)	1.7	Basal FSH	1	68.3	83.3	93.3	43.5
Width (cm)	1.7	Basal E2	25	69.4	83.3	92.6	47.6

E2, estradiol (pg/mL); FSH, follicle stimulating hormone (IU/L); LH, luteinizing hormone (IU/L); NPV, negative predictive value; PPV, positive predictive value.

Thailand and the findings may not be directly applicable to other populations. A multicenter study with a larger sample size and more diverse population, and studies of populations with other ethnicities, are warranted to verify our findings. Clinicians may correlate imaging results with other clinical clues, and in cases where there is doubt, a standard GnRH receptor stimulation test can still be useful.

Conclusion

To avoid time-consuming, invasive, and expensive GnRH receptor stimulation tests, combining ultrasonographic parameters and basal hormonal levels, especially uterine width and basal LH level, appears to be a useful alternative for diagnosis of CPP in routine clinical practice and consumes less time and cost.

Data sharing statement. Statistical summaries of data generated and analyzed for the present report are included in this published article. Further details of data that support the findings of the present study are also available in figshare, with identifier https://doi.org/10.6084/m9.figshare/13611716; and all the data are available from the corresponding author on reasonable request after deidentification from any patient whose data are included in this report.

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