Diagnostic efficacy of pelvic ultrasound in central precocious puberty in girls: a retrospective cohort study

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Research Article

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Abstract

Background: Differentiating central precocious puberty (CPP) patients from immature normal cases and CPP-like patients “isolated premature adrenarche (IPA) and isolated premature thelarche (IPT)” is important for beginning of treatment. Although the GnRH stimulation test is considered the gold standard for diagnosis of CPP, Because of its wide limitations, our study targets to evaluate pelvic sonography parameters as a contributory tool for CPP diagnosis.

Methods: We consecutively enrolled 183 cases (93 CPP, 16 IPT, 12 IPA and 62 of age-matched normal controls) in our study over four years. All cases are of Persian ethnicity classified by clinical and laboratory findings and are followed up for at least 2 years. Pelvic sonography parameters included uterine fundus, body and cervix anteroposterior diameter, fundus/cervix ratio, uterine length and transverse diameter, uterine volume, endometrial thickness, ovarian volumes and diameter of the largest follicle are evaluated in all classified groups. One-way ANOVA, POST HOC and receiver operating characteristic (ROC) analysis was used to compare the study groups.

Results: Our study found that all sonography parameters differ significantly between CPP and normal control cases, also a significant difference is found between CPP compared to IPT or IPA cases in all parameters except in cervix anteroposterior diameter, ovarian volumes and diameter of the largest follicle. In order of best parameters for differentiating CPP compared to study groups, uterine volume (a cut-off of 1.40 ml had a sensitivity of 75.27% and a specificity of 75.56%), transverse diameter (a cut-off of 13.5 mm had a sensitivity of 72.04% and a specificity of 71.11%) and F/C ratio (a cut-off of 0.98 had a sensitivity of 78.49% and a specificity of 70%) was selected. Our study also classified sonography parameters as of equal diagnostic value to uterine volume (as the best diagnostic parameter with area under the curve of 0.826) and not equal diagnostic value to uterine volume.

Conclusions: Pelvic Sonography parameters may improve the diagnosis of CPP patients and can have a contributory role in distinguishing treatment needed from other patients. The best diagnostic parameter and its cut-off value could change according to different ethnicities and studies.

Background

Girl’s precocious puberty is defined as development of secondary sexual characteristics, growth spurts, and psychosocial changes before the age of 8 years in white or Caucasian people and before the age of 7 years in black or African American people (1-3). Precocious puberty is classified into two main groups which is defined as gonadotropin dependent precocious puberty (GDPP) or gonadotropin independent precocious puberty (GIPP)(4). Conditions such as gonadal, adrenal endocrine disorders, exogenous hormone consumption, pseudo precocious-puberty and peripheral precocious puberty are classified as GIPP group(4). On the other hand GDPP group which is called central precocious puberty (CPP) is caused by hypothalamic-pituitary-gonadal (HPG) axis activity and includes 58-90% of the precocious puberty cases(4). CPP is mostly caused by idiopathic reasons and in rare cases brain abnormalities such as

tumors, trauma, infections and malformations are the main causes of HPG axis activity(5). Although the CPP cases occur at a younger age, the pattern of natural maturation stages, such as thelarche, pubarche and menarche, occurs the same as normal people (6). The main concerns about CPP are premature bone maturation, reduced final patient height, and physiological stress which is imposed on the patients (6, 7). That's why timely initiation of CPP treatment with GnRH (gonadotropin releasing hormone) agonists is of great value for patients (8). Distinguishing CPP cases from isolated premature thelarche (IPT) and isolated premature adrenarche (IPA) is clinically important because despite the onset of sexual characteristics similar to CPP, they don't accelerate bone maturation and does not require treatment with GnRH agonists(9). Furthermore, differentiating CPP cases from pseudo-precocious puberty and exogenous obesity, which its prevalence has been increasing in recent years, is important. it is possible that in cases of obesity, bone age may be higher than normal, but there is no other evidence of puberty and therefore does not require treatment with GnRH agonists(10). Clinical diagnosis of CPP is based on physical examination, bone age, and growth rate(11). GnRH stimulation test as the gold standard is used to differentiate CPP patients from other cases which are considered suspicious and borderline, but despite its high specificity, it has disadvantages such as low sensitivity, time consuming and requires multiple blood sampling(12). Pelvic ultrasonography (US) is almost always requested in cases of clinical suspicion of any type of precocious puberty(13). Pelvic US has an advantage of being non-invasive, accessible, radiation-free and inexpensive, and it is a useful diagnostic tool for assessing a female's pelvic(13). Pelvic US gives detailed information about uterine and ovarian size, fundus to cervical ratio, endometrial thickness, follicle size and distribution of the ovaries. Pelvic US can also help to diagnose cysts and pelvic masses(13). Numerous studies have been performed on increasing the volume of the ovaries and uterus and increasing the size and number of follicles during the years leading up to puberty (14-16). Also numerous attempts have been made to use the US to distinguish normal girls from girls with precocious puberty (14-16). But still the diagnostic value of pelvic US parameters remains unclear. Some studies report overlapping values of pelvic US parameters between CPP and other groups(14) and in other studies pelvic US parameters are useful for differentiating CPP from normal individuals, nevertheless different studies determine different cut-off points for sonography parameters(15, 16).

This study aimed to evaluate the usefulness of pelvic ultrasonography and its parameters in differentiating girls with CPP from normal individuals with or without suspicious characteristics. Therefore, in this study an attempt is made to compare the parameters of the pelvic ultrasonography between the CPP, IPT, IPA and normal individuals to determine safe cut-off limits for each of the parameters.

Methods

Study population

The cases of this study were female patients of Persian ethnicity with eight or less than eight years old who were referred to the Endocrinology department of our hospital (Tehran Ali Asghar children's hospital)

for evaluation of precocious puberty from 2015 to 2019 years. Four groups are labeled as control, IPT, IPA, and CPP groups with exclusion criteria of CNS abnormalities related endocrinological abnormalities such as adrenal, gonadal, and thyroidal abnormalities, iatrogenic or exogenous hormonal contact, and also patients with no proper follow-up. The study was confirmed by the local ethics committee and written informed parental consent, following the revised Helsinki declaration, was given to all participants. All of the cases mentioned below are clinically and axiologically followed and confirmed for at least two years.

- Control group

Sixty-two girls ≤ 8 years old are included in this group after the exclusion of 3 of them due to noted exclusion criteria (no proper follow-up). The inclusion criteria for the control group were as follows: (1) 8 or less than 8 years for chronological age, (2) children without secondary sexual characteristics, (3) children within 2 SD of bone age and normal height velocity, (4) children who have hormonal assessments and pelvic ultrasonography in our hospital.

- CPP (central precocious puberty) group

Ninety-three ≤ 8 years old are included in this group after the exclusion of 4 of them due to noted exclusion criteria (two of them have hypophyseal microadenoma, one has hypothyroidism and one uses estrogen cream treatment for labial adhesion in infancy). The inclusion criteria for the CPP group were as follows: (1) 8 or less than 8 years for chronological age, (2) children with secondary sexual characteristics, (3) children with more than 2 SD of bone-chronological age and accelerated height velocity, (4) children who have confirmed precocious puberty with GnRH stimulation test, (5) children who have pelvic ultrasonography in our hospital.

- IPT (isolated premature thelarche) group

Sixteen girls ≤ 8 years old are included in this group after the exclusion of 1 of them due to adipose tissue of breast instead of real thelarche. The inclusion criteria for the IPT group were as follows (1) 8 or less than 8 years for chronological age, (2) children with breast development in the absence of any other signs of puberty, (3) children within 2 SD of bone age and normal height velocity, (4) children who have hormonal assessments and pelvic ultrasonography in our hospital.

- IPA (isolated premature adrenarche) group

Twelve girls ≤ 8 years old are included in this group after the exclusion of 2 of them due to CAH (congenital adrenal hyperplasia) diagnosis. The inclusion criteria for the IPT group were as follows: (1) 8 or less than 8 years for chronological age, (2) children with pubic and/or axillary hair appearance in the absence of any other signs of puberty, (3) children within 2 SD of bone age and normal height velocity, (4) children who have hormonal assessments and pelvic ultrasonography in our hospital.

Study design

All patients' secondary sexual characteristics were examined precisely and were assessed according to Tanner staging (3). Height and weight measurements and also height velocity (height gained within a year) are measured on a minimum of a six-month interval and interpreted as whether accelerated or not (17). Bone age was evaluated from the non-dominant hand radiographs and defined by Greulich scoring (18). The hormonal evaluation included basal levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E2) as well as GnRH-stimulated LH and FSH levels are measured using radioimmunoassay. Stimulated LH and FSH levels are measured after 30 and 60 min of GnRH agent injection. Stimulated LH level of ≥5 IU/L was considered diagnostic for CPP in patients with pubertal characteristics (19).

Pelvic ultrasonography was done by the Radiology Department of Tehran Ali Asghar children's hospital by the same radiologist. Philips EPIQ 7 Ultrasound Machine equipped with a 7.5-MHz linear array transducer and a 5-MHz convex array transducer was used for evaluation of patients. All patients were examined with a full bladder in a completely calm condition. Ultrasonography parameters included uterine fundus AP(anteroposterior) diameter (mm), uterine body AP diameter (mm), uterine cervix AP diameter(mm), F/C ratio(uterine fundus AP diameter divided by the cervix AP diameter), uterine length(mm), uterine transverse diameter(mm), uterine volume – calculated by the ellipse formula: V *(*ml*)* = uterine length(mm) × transverse diameter(mm) × AP diameter(mm) × 0.5236, endometrial thickness(mm), left ovarian volume(ml), right ovarian volume(ml), average maximal diameter of largest follicle in both ovaries(mm). The volume of each ovary was calculated by using the same ellipse formula as for the uterus.

Statistics

The categorical variables were presented as frequency and percent and continuous data were reported as mean and standard deviation (SD). The one-way analysis of variance (One-way ANOVA) was used to compare the mean of continuous variables between the study groups including CPP, IPT, IPA, and control group. Moreover, the POST HOC analysis using the Tukey test was used for pairwise comparisons between the study groups, if the initial ANOVA test was statistically significant. The Receiver–operating characteristics (ROC) analysis was used to determine the best cut-off point for ultrasonography parameters and its corresponding sensitivity, specificity, Positive Likelihood Ratio (LR+), and Negative Likelihood Ratio (LR-) for identifying patients with central precocious puberty (CPP). Furthermore, the equality of ROC area for ultrasonography parameters against the uterine volume ROC curve as a gold standard was assessed using the "Rocgold" command in Stata software. The Stata software version 12 (Stata Corp, College Station, TX) was used for statistical analysis, and a p-value less than 0.05 was considered as significant findings.

Results

Among a total of 183 children, 62 were classified as the control group (33.87%), 93 as CPP group (50.81%), 16 as IPT group (8.74%), and 12 as IPA group (6.55%).

- Comparison of the demographic characteristics and hormonal laboratory values between groups

One-way analysis of variance and post hoc analysis used for comparison of demographic characteristics, and although there is no significant difference in chronological age and BMI of classified groups, girls with different groups had a significant difference in bone age ($p<0.001$) and height ($p=0.003$), in a way which, CPP group showed a significantly higher bone age (107.76±19.81 month) and taller height (129.53±8.97 cm) against other groups (Table 1). In one-way analysis of variance, the hormonal laboratory values showed significant differences in baseline LH ($p<0.001$), baseline FSH ($p=0.024$), and estradiol ($p<0.001$) levels between classified groups, but in pairwise post-hoc analysis this difference is only significant between CPP and control group, and there is no significant pairwise difference between IPA group or IPT group with other classified groups (Table 1). Also vitamin D levels are compared and no significant difference is observed between classified groups (Table 1).

Table 1 location

- Comparison of pelvic ultrasonography parameters

According to our one-way analysis of variance and post hoc analysis, CPP patients had significantly ($p<0.001$) increased uterine fundus AP diameter, uterine body AP diameter, F/C ratio, uterine length, uterine volume, endometrial thickness, transverse uterine diameter compared to other classified groups. Three parameters including uterine cervix AP diameter, left ovarian volume and right ovarian volume, only showed significantly higher values in CPP patients compared to control and IPA groups, whereas no significant differences are found between CPP patients and IPT patients in recent noted three parameters despite having higher values in CPP patients compared to IPT patients (Table 2). The average maximal diameter of the largest follicle only had a significant difference between CPP patients (5.00±6.08 mm) compared to the control group (2.60±2.46 mm) and when comparing this parameter in IPA and IPT groups with each other or with control or CPP groups, no significant difference was evident (Table 2). All sonographic parameters had no significant differences in control, IPA, IPT groups when compared to each other according to pairwise post-hoc analysis (Table 2).

Table 2 location

- ROC analysis and cut off value determination for sonographic parameters

ROC analysis was done with each pelvic sonography parameter as an independent measurement between CPP patients and other groups (Figure 1).Among all parameters three of them showed acceptable and excellent sensitivity and or specificity for identifying CPP patients from other groups. Uterine volume was one of these parameters which identified CPP patients from other groups by a cut off of 1.40 ml (sensitivity=75.27%, specificity=75.56%, AUC=0.826 and SE=0.030). The other two parameters which had acceptable sensitivity and specificity were transverse uterine diameter (cut off of 13.5mm, sensitivity=72.04%, specificity=71.11%, AUC=0.780 and SE=0.034) F/C ratio (cut off of 0.98, sensitivity=78.49%, specificity=70%, AUC=0.788 and SE=0.034) (Table 3). ROC analysis was also done

between CPP patients and only control group (Figure 2). In this analysis same three parameters were found to be most practical among the others. First of them was uterine volume with cut off of 1.40 ml (sensitivity=75.27%, specificity=74.19%, AUC=0.826 and SE=0.032). The other two parameters were transverse uterine diameter (cut off of 13.5mm, sensitivity=72.04%, specificity=72.58%, AUC=0.778 and SE=0.037) F/C ratio (cut off of 1, sensitivity=77.42%, specificity=69.35%, AUC=0.769 and SE=0.039) (Table 4).

Table 3 and 4 location

Figure 1 and 2 location

- Checking the equality of the ROC area of each parameter against a "gold standard" ROC curve

According to our study and most other studies, uterine volume had a significant and constant value as a diagnostic parameter for recognizing CPP patients. Among all parameters, the best parameter was uterine volume, as selected by the highest value of area under the ROC curve and had acceptable sensitivity and specificity. That is why we check the equality of the ROC area of other sonography parameters compared to the ROC area of uterine volume. As a result area under the ROC curve of all parameters except uterine body AP diameter, uterine cervix AP diameter, and average maximal diameter of the largest follicle of both ovaries had no significant difference with the gold standard curve, which means all sonography parameters except noted parameters above had equal diagnostic value compared to the gold standard at both study designs (CPP toward others and CPP toward only control group) (Table 5).

Table 5 location

Discussion

The gold standard of CPP diagnosis is the GnRH-stimulation test, which has different cut-off values according to different investigations (19-21). Moreover, this test is a relatively high cost and time-consuming test, also despite its high specificity, it has a low sensitivity (16-23). Meanwhile, pelvic sonography is a useful, non-invasive, and relatively low-cost method for assessing female pelvic parameters (uterus and ovaries)(13). In this study we used clinical and laboratory data for the classification of cases. All cases were classified in either one of the control, IPA, IPT, or CPP groups. The criteria proposed by Kim et al. (19), according to which a stimulated LH level of ≥5 IU/L is considered as the gold standard to the diagnosis of CPP patients. In addition, at least two years of follow-up of the patients is done to lower the possibility of misdiagnosis of patients' classification (especially IPA, IPT forms of precocious puberty)(9, 21).We analyzed the difference in pelvic sonography parameters between CPP, IPA, IPT, and control groups and calculated cutoff values to differentiate CPP patients from other groups. To our knowledge, few studies compare all these classified groups with each other (14, 22, 24). It is also original in this study that cut off values were extracted from this study to differentiate GnRH treatment needed group (CPP group) from no treatment needed group (other three groups), and also for

the first time we checked the equality of the ROC area of each parameter against a gold standard ROC curve (uterine volume) as judged by the biggest value of area under the ROC curve with acceptable sensitivity and specificity. Our study found that most of the pelvic sonography parameters were useful to distinguish CPP from other groups. Among all of the parameters, uterine volume as the best diagnostic parameter and three other parameters including; uterine transverse diameter, F/C ratio, and endometrial thickness showed an important role in the optimal diagnosis of CPP patients Table 3 and Table 4 (). The cutoff values for uterine volume, which identified CPP patients from other groups and only from the control group was 1.40 ml with sensitivities of 75.27% and 75.27% and specificities of 75.56% and 74.19%, respectively. Most of the previous studies like ours declared uterine volume as the best parameter for CPP diagnosis but there were differences in uterine volume cut-off values. Wen et al. and Yu J et al. respectively reported 91.66 % and 59.1% sensitivities and 77.60% and 71.0% specificities for the cutoff value of 1.09 mL and 1.07 ml of uterine volume (22, 25). On the other hand higher values with acceptable sensitivity and specificity were reported by Haber et al. (cut off value of 1.8 mL with a 100% sensitivity and specificity for the uterine volume) (16). De Vries et al. (cut off value of 1.96 ml with a sensitivity of 88.8% and specificity of 89.4%)(26), and Battaglia et al (cut off value of 4 ml with a sensitivity of 87% and specificity of 87.5 %)(27). These results show the most powerful sonography parameter and its ‘optimal cutoff value may differ according to ethnicity differences, sample size, and type of different studies. The second and third most efficient parameters in our study were uterine transverse diameter and F/C ratio with a cut off of 13.5mm (72.04% sensitivity and 71.11%specificity) and 0.98 (78.49% sensitivity and 70.00% specificity) respectively, for CPP against other groups and with a cut-off of 13.5mm (72.04% sensitivity and 72.58% specificity) and 1 (77.42% sensitivity and 69.35% specificity) respectively, for CPP against the only control group. These findings are in close similarity with Yu J et al. (25) and De Vries et al. (26) findings in transverse uterine diameter and in close similarity with Badouraki et al. (24), De Vries et al. (26), and Binay et al.(28), findings in F/C ratio parameter. Our study also suggests that endometrial thickness and echogenicity had a high specificity in diagnosing CPP patients, which is reported as the same in most of the studies (26, 27, 29) and in comparison with Wen et al. findings (22). Previous studies in different countries found ovarian volume having a good diagnostic value for identifying the CPP patients (15, 24, 26, 30). In our study despite the significant difference between CPP patients compared to control and IPA groups, there was no significant difference between CPP patients compared to the IPT group. That is why we don’t suggest ovarian volume as a discriminate parameter to differentiate CPP from other groups. This suggestion is in agreement with some other studies (16, 22, 27, 31). At the end, we compared all sonography parameters to the uterine volume ROC curve, as selected by the highest value of area under the ROC curve and had acceptable sensitivity and specificity. This analysis helped us to classified pelvic sonography parameters as in equal diagnostic value to uterine volume (such as uterine fundus AP diameter, F/C ratio, uterine length, uterine volume, endometrial thickness, transverse uterine diameter, and ovarian volume) and not equal diagnostic value to uterine volume (such as uterine body AP diameter, uterine cervix AP diameter and average maximal diameter of the largest follicle of both ovaries) (Table 5).

Conclusion

On-time beginning of GnRH agonist treatment in CPP patients is crucial for preventing early bone maturation, reduced final height, and related physiological stress effects. Also, differentiating CPP patients from IPA and IPT groups is important in the clinical field to avoid unnecessary treatment for CPP-like groups (IPA and IPT). In this study, we evaluate female sonography parameters in correlation with precise clinical and laboratory data. Comparison of all sonography parameters in different groups showed that uterine volume, uterine transverse diameter, F/C ratio, and endometrial thickness are good predictors of central precocious puberty. On the other hand, we found that ovarian volume is only helpful in differentiating CPP patients from normal control cases, and using this parameter as a distinguishing factor between treatment needed (CPP patients) and no treatment needed (IPA, IPT, control groups) classification is not accurate.

Our study is limited due to the retrospective and cross-sectional nature of the study design, in which we do not have control over confounding factors such as sample drop in case files. Also due to the small number of under six year's old patients, we don't evaluate cases in age ranged subgroups.

Abbreviations

CPP: Central precocious puberty

IPT: Isolated premature thelarche

IPA: Isolated premature adrenarche

GDPP: Gonadotropin dependent precocious puberty

GIPP: Gonadotropin independent precocious puberty

GnRH: Gonadotropin releasing hormone

E2: Estradiol

LH: Luteinizing hormone

FSH: Follicle stimulating hormone

US: Ultrasonography

HPG: Hypothalamic-pituitary-gonadal

AUC: Area under the curve

ROC: Receiver operating characteristic

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Declarations

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Ethics approval and consent to participate

All participants were informed about the study and confidentiality protocols. Written Informed consent was obtained from all the participants. The Ethics committee of Iran University of Medical Sciences confirmed all procedures of this study. (IR.IUMS.FMD.REC.1399.246)

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

EZ and MV (study conception & design and Critical revision), NR and MK (Acquisition of data, Analysis and interpretation of data & Drafting of manuscript), NR, AA and KM (Critical revision & Analysis and interpretation of data)

Tables

Table 1. Demographic characteristics and hormonal laboratory values between groups

Variables	Controls(n=62) (mean ±SD)	**CPP(n=93) (mean ±SD)	IPT(n=16) (mean ±SD)	IPA(n=12) (mean ±SD)	Total(n=183) (mean ±SD)	P value
Chronological age (m)	86.69±9.79	88.96±13.40	88.50±18.75	85.00±12.350	87.89±12.75	0.605
Bone age (m)	85.51±14.40^{a*}	107.76±19.81^{b}	91.43±20.92^{a}	94.16±9.04^{a}	97.90±20.38	<0.001
Height (cm)	124.15±8.70^{*a}	129.53±8.97^{b}	126.53±11.58^{a}	123.75±8.59^{a}	127.07±9.43^{a}	0.003
BMI	18.66±3.80	19.44±3.74	20.25±4.09	18.69±3.94	19.20±3.80	0.385
Baseline LH (mIU/ml)	0.26±0.34^{a}	1.35±2.13^{b}	0.42±0.43^{ab}	0.22±0.07^{ab}	0.82±1.63	<0.001
Baseline FSH (mIU/ml)	2.36±1.58^{a}	3.43±2.60^{b}	2.85±2.43 ^{ab}	2.30±1.27 ^{ab}	2.94±2.26	0.024
Estradiol (pg/ml)	8.65±7.58^{a}	22.33±7.58^{b}	10.63±6.74 ^{ab}	5.23±1.74^{a}	15.55±20.94	<0.001
Vitamin D (ng/mL)	27.68±16.72	27.86±20.15	34.12±16.60	24.65±11.56	28.16±18.40	0.664

*One-Way ANOVA was used for data analyzing; Dissimilar values (a, b) in each rows are significantly different based on the Tukey's Test in post-hoc analysis.
**CPP: central precocious puberty; IPT: idiopathic premature thelarche; IPA: idiopathic premature adrenarche, Baseline LH: baseline luteinizing hormone baseline FSH: baseline follicle-stimulating hormone BMI: body mass index.

Table 2. Pelvic ultrasonography parameters between groups

Variables	Controls(n=62) (mean ±SD)	**CPP(n=93) (mean ±SD)	IPT(n=16) (mean ±SD)	IPA(n=12) (mean ±SD)	Total(n=183) (mean ±SD)	P value
Uterine fundus AP diameter(mm)	5.33±1.92^{a}	8.60±3.95^{b}	5.00±1.44^{a}	4.55±1.25^{a}	6.91±3.52	<0.001
Uterine body AP diameter(mm)	5.90±2.01 ^{a}	8.26±3.49^{b}	5.82±1.39 ^{a}	4.85±1.40 ^{a}	7.02±3.07	<0.001
Uterine cervix AP diameter(mm)	6.00±1.51^{a}	7.34±2.51^{b}	6.21±0.836^{ab}	5.54±1.01^{a}	6.67±2.14	<0.001
F/C ratio	0.90±0.28 ^{a}	1.16±0.323^{b}	0.79±0.17 ^{a}	0.84±0.32 ^{a}	1.02±0.33	<0.001
Uterine length	28.96±4.81 ^{a}	38.04±8.33^{b}	31.03±5.27 ^{a}	32.16±3.51 ^{a}	33.96±7.48	<0.001
Uterine volume	1.13±0.95 ^{a}	3.13±2.64^{b}	1.16±0.38 ^{a}	0.96±0.51 ^{a}	2.34±3.03	<0.001
Endometrial thickness	0.37±0.30 ^{a}	1.09±0.69^{b}	0.45±0.16 ^{a}	0.35±0.13 ^{a}	0.80±0.83	<0.001
L-Ovarian volume (mm)	1.08±0.64 ^{a}	1.94±1.47^{b}	1.45±0.92 ^{ab}	1.08±0.77 ^{a}	1.55±1.23	<0.001
R-Ovarian volume (mm)	1.10±0.73 ^{a}	2.01±1.14^{b}	1.51±0.83 ^{ab}	1.14±0.74 ^{a}	1.60±1.05	<0.001
Transverse uterine diameter (mm)	11.66±4.12 ^{a}	17.02±6.49^{b}	11.90±3.17 ^{a}	10.87±3.51 ^{a}	14.35±6.00	<0.001
AMD of largest follicle(mm)	2.60±2.46 ^{a}	5.00±6.08^{b}	3.90±2.19 ^{ab}	4.25±1.81 ^{ab}	4.04±4.74	0.022

*One-Way ANOVA was used for data analyzing; Dissimilar values (a, b) in each rows are significantly different based on the Tukey's Test in post-hoc analysis.
**CPP: central precocious puberty; IPT: idiopathic premature thelarche; IPA: idiopathic premature adrenarche AMD of largest follicle: average maximal diameter of largest follicle.

Table 3. Receiver–operating characteristics (ROC) curve parameters of study variables for identifying patients with central precocious puberty (CPP) from other groups.

Parameter	Area under ROC curve	SE	Cut-off point	Sensitivity (%)	Specificity (%)	*LR+	*LR-
Uterine fundus AP diameter	0.802	0.032	5.50	80.65	62.22	2.134	0.311
Uterine body AP diameter	0.733	0.037	6.30	66.67	64.44	1.875	0.517
Uterine cervix AP diameter	0.678	0.039	6.20	63.44	66.67	1.903	0.548
F/C ratio	0.788	0.034	0.98	78.49	70.00	2.616	0.307
Uterine length	0.842	0.028	35.00	70.97	82.22	3.991	0.353
Uterine volume	0.826	0.030	1.40	75.27	75.56	3.079	0.327
Endometrial thickness	0.675	0.026	1.00	37.63	96.67	11.290	0.645
L-Ovarian volume	0.722	0.037	1.30	66.30	63.33	1.808	0.532
R-Ovarian volume	0.748	0.036	1.10	78.49	61.11	2.018	0.351
Transverse uterine diameter	0.780	0.034	13.5	72.04	71.11	2.493	0.393
AMD of largest follicle	0.611	0.041	4.00	61.29	52.22	1.282	0.741

*LR+: positive likelihood ratio; LR-: negative likelihood ratio

Table 4. Receiver–operating characteristics (ROC) curve parameters of study variables for identifying patients with central precocious puberty (CPP) from control group.

Parameter	Area under ROC curve	SE	Cut-off point	Sensitivity (%)	Specificity (%)	*LR+	*LR-
Uterine fundus AP diameter	0.785	0.036	6.50	68.82	75.81	2.844	0.411
Uterine body AP diameter	0.718	0.040	6.30	66.67	61.29	1.722	0.543
Uterine cervix AP diameter	0.676	0.043	6.50	61.29	70.97	2.111	0.545
F/C ratio	0.769	0.039	1.00	77.42	69.35	2.526	0.325
Uterine length	0.871	0.027	33.00	79.57	72.58	2.902	0.281
Uterine volume	0.826	0.032	1.40	75.27	74.19	2.916	0.333
Endometrial thickness	0.893	0.028	1.00	37.63	95.16	7.777	0.655
L-Ovarian volume	0.744	0.039	1.2	69.57	61.29	1.797	0.496
R-Ovarian volume	0.776	0.038	1.2	76.34	69.35	2.491	0.341
Transverse uterine diameter	0.778	0.037	13.5	72.04	72.58	2.627	0.385
AMD of largest follicle	0.650	0.042	4.00	61.29	61.29	1.583	0.631

*LR+: positive likelihood ratio; LR-: negative likelihood ratio

Table 5. ROC area of each parameter against uterine volume ROC curve as gold standard ROC curve

Parameter	Area under ROC curve	SE	Chi2	df	PR>chi2	Bonferroni PR>chi2
Uterine volume (standard)	0.826	0.030				
Uterine fundus AP diameter	0.802	0.032	0.901	1	0.342	1
Uterine body AP diameter	0.733	0.037	13.455	1	0.000	0.002
Uterine cervix AP diameter	0.678	0.039	21.707	1	0.000	0.000
F/C ratio	0.788	0.034	1.180	1	0.277	1
Uterine length	0.842	0.028	0.232	1	0.629	1
Endometrial thickness	0.892	0.024	4.049	1	0.044	0.441
L-Ovarian volume	0.722	0.037	7.468	1	0.006	0.062
R-Ovarian volume	0.748	0.036	4.677	1	0.030	0.305
Transverse uterine diameter	0.780	0.034	4.630	1	0.031	0.314
AMD of largest follicle	0.611	0.041	18.994	1	0.000	0.000

Figures

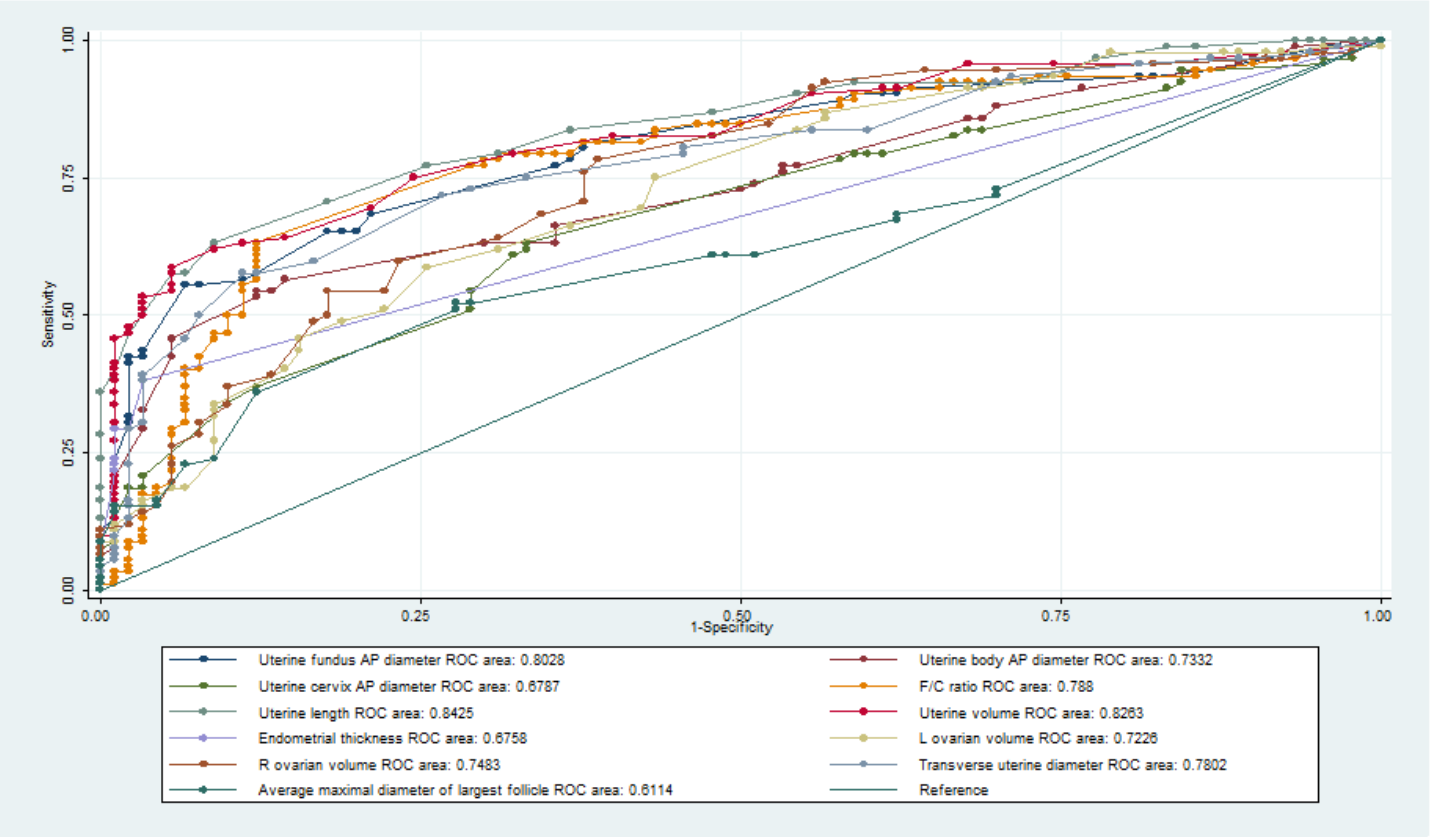

Figure 1

RECEIVER–OPERATING CHARACTERISTICS (ROC) CURVE PARAMETERS OF STUDY VARIABLES FOR IDENTIFYING PATIENTS WITH CENTRAL PRECOCIOUS PUBERTY (CPP) FROM OTHER GROUPS.

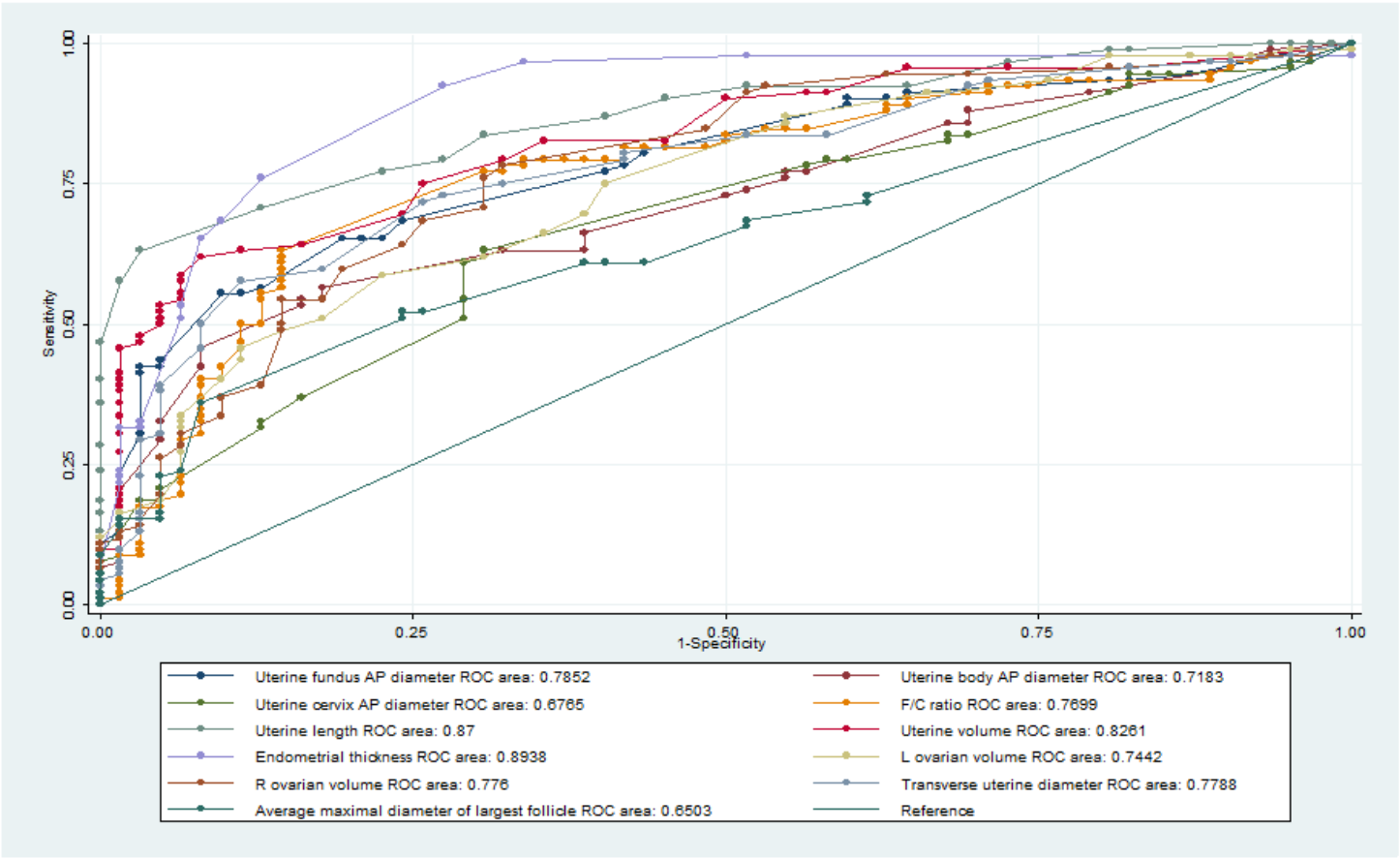

Figure 2

RECEIVER–OPERATING CHARACTERISTICS (ROC) CURVE PARAMETERS OF STUDY VARIABLES FOR IDENTIFYING PATIENTS WITH CENTRAL PRECOCIOUS PUBERTY