Original Article

The Ovarian Volume in Girls Presented as Precocious Puberty

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Abstract

Background: Isosexual precocious puberty (PP) is defined as the appearance of secondary sexual characteristics before the age of 8 years in girls and before the age of 9 years in boys. The aim of this study was to evaluate the association of ovarian volume and bone age measurements with the number of symptoms in female patients diagnosed with PP. **Methods:** The dataset includes pelvic ultrasound and bone age tests from 96 girls diagnosed with PP who presented to a tertiary hospital's pediatric outpatient clinic with signs and symptoms of early puberty between January 1, 2020, and January 1, 2021. The study included 96 healthy ladies of the same age as a control group. **Results:** A total volume >2.75 was shown to predict the existence of pubertal pre with 79.2% sensitivity and 90.6% specificity (area under the curve [AUC]: 0.903; $P = 0.001$). A total volume of >3.25 predicted the existence of 2 or more symptoms in patients with PP, with a sensitivity of 72.1% and a specificity of 98.1% (AUC: 0.917; $P = 0.001$). **Conclusion:** To the best of our knowledge, no study has been published that investigates the relationship between the number of symptoms at the time of presentation and ovarian volume and bone age in girls with PP. Our investigation, which involved 192 female participants (96 patients and 96 controls), revealed a statistically significant correlation between the frequency of symptoms indicating early puberty and a rise in both ovarian capacity and bone age.

Keywords: Bone age, ovarian volume, precocious puberty, ultrasound

Introduction

Isosexual precocious puberty (PP) is described as the development of secondary sexual features in girls before the age of 8 years and in boys before the age of 9 years. As it is well known, there are three forms of early puberty: gonadotropin dependent (central), gonadotropin independent (peripheral), and incomplete (premature thelarche or adrenarche). This etiological classification suggests several techniques for follow-up and treatment. Early puberty symptoms manifest in females. These include higher weight gain, a growth spurt in comparison to peers, breast budding, menstruation, pubic hair growth, and new psychosocial changes.[1,2]

The first stage of evaluating early pubertal development comprises a clinical history, complete physical examination, and bone age assessment. Every discovery acquired during the physical examination, particularly the endocrine and genital systems, should be documented. Left hand–wrist radiography and evaluation using Greulich–Pyle or Tanner–Whitehouse atlases is the most often utilized approach for determining bone age.[3,4]

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The etiology of early puberty in children is predominantly explored by the Gonadotropin-releasing hormone (GnRH) test, which distinguishes between central PP (CPP), peripheral PP, and incomplete PP.[5,6] The GnRH stimulation test is widely regarded as the most reliable method for diagnosing CPP. A rise in blood luteinizing hormone (LH) levels of more than approximately 8 mIU/mL and more than approximately 5 IU/L after the administration of GnRH or GnRH analogs, respectively, validates the diagnosis of CPP. In other words, an elevation of LH after GnRH stimulation rather than an elevation of GnRH *per se* is indicative of CPP.[7] To improve diagnostic power, repeat measures should be taken. As a result, various ways of diagnosing have come to the fore in the literature. The importance of ultrasonography, which is noninvasive and simple to use and is frequently utilized to diagnose diseases of pelvic organs such as the uterus and ovaries, cannot be overstated. We know from the literature that pelvic sonography

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is particularly useful in the diagnostic and follow-up stages of pubertal internal genital organ development.[8,9]

Furthermore, in the literature, ovarian circumference, volume, and morphology are used to evaluate pubertal development; the relationships between many parameters such as uterine volume, fundal/cervical diameter ratio, endometrial thickness and chronological age, bone age, and the development of secondary sexual characters according to the Tanner scale were investigated.[8-11]

In light of these discoveries, the previous publications' threshold values with high sensitivity and/or specificity consistent with puberty are 1.5–2 ml for uterine volume, 3–4.09 cm for uterine length, and 1.2–1.3 ml for ovarian volume.[11-14]

PP patients have bones that are at least 2 years older. Although rare, earlier research has indicated that bone age may be within the normal range in some people who develop secondary sexual characteristics.[9-11]

Girls who reach puberty early may first grow faster and be taller than their contemporaries. However, because these children's bones mature faster than the typical growth process, their growth is stunted. As a result, when girls reach maturity, they are shorter than their typical target height.[10,11,14-16]

Eksioglu *et al*. published a study on the associations between ovarian volume and bone age in symptomatic PP patients. In this study, ovarian volume and bone age measurements were shown to be considerably higher in PP female cases compared to cases diagnosed with isolated premature pubarche and isolated early thelarche.[14]

As it is well known, the nature and amount of symptoms for which people seek medical attention may change in PP cases. These symptoms might manifest as a single or multisystem finding. However, we have found no scientific study that examines the association between the frequency of symptoms for which patients are admitted to the hospital and ovarian volume or bone age in prepuberty patients.

The objective of this study was to assess the potential correlation between the quantity of symptoms and measurements of ovarian volume and bone age at the initial consultation in female patients diagnosed with PP.

Materials and Methods

The Erzincan Binali Yıldırım University Ethics Committee accepted this unique study (Decision no: 13/12 Date: December 06, 2021), and it was carried out in conformity with the Helsinki Declaration. Due to the study's retrospective nature, informed consent was waived. The dataset consisted of pelvic ultrasound (US) and bone age assessments from 96 girls who visited the pediatric outpatient clinic of a tertiary care hospital. These girls exhibited signs or symptoms of PP and had already undergone other laboratory tests, such as the GnRH stimulation test, and imaging procedures, such as pituitary magnetic resonance imaging, conducted by the relevant clinical unit. Ultimately, they were diagnosed with PP. For the control group, 96 female patients within the same age range (under 9 years old) who did not have isolated premature thelarche/adrenarche/pubarche or any symptoms of early puberty were selected randomly to be part of the study. An experienced radiologist with 8 years of knowledge in the field conducted a retrospective examination of the patients' data from the digital patient record repository.

The principal exclusion criteria for bone age are genetic and acquired dysplastic bone illnesses, growth hormone disorders, thyroid hormone disorders, chronic renal diseases, primary/secondary phosphorus, and calcium metabolism problems. Instances with polycystic ovary syndrome, instances with ovarian neoplasm (teratoma, etc.), and cases diagnosed with pelvic inflammatory disease were chosen as exclusion criteria in the group impacting ovarian volume. In the study, only cases of isosexual PP were included in the study.

The following information was gathered as part of the study's scope: gender, bone age, calendar age, ovarian volume, and the number of symptoms at the time of admission were all considered. The Greulich–Pyle atlas was used to compare the left hand–wrist radiographs of the patients with the control group to determine bone age. Patients were asked to undergo the examination with a full bladder to create an optimal pelvic

Table 1: Clinical characteristics

Variables	Normal (*n*=96)	Precocious puberty (*n*=96)	*P*
Chronological age (months)	81.7±20.7	82.9±23.4	0.718
Bone age (months)	80.8±20.6	81.8±24.7	0.747
Total volume (cm^3)	2.6 (1.2–3.0)	3.0 (2.4–10.7)	<0.001*
Right ovary volume (cm^3)	1.4 (0.6–1.8)	1.6 (1.1–5.4)	<0.001*
Left ovary volume (cm^3)	1.3 (0.6–1.5)	1.5 (1.1–5.4)	<0.001*
Count of symptoms			
1	0	53 (55.2)	-
2	0	37 (38.5)	
3	0	6 (6.3)	

*P<0.05 indicates statistical significance. Numerical variables are shown as mean±SD or median (minimum–maximum). Categorical variables are shown as *n* (%). SD: Standard deviation

Table 2: Distribution of clinical features in precocious puberty patients based on the number of symptoms

Variables	Count of symptoms		*P*
	1 (*n*=53)	≥2 (*n*=43)	
Chronological age (months)	74.8±28.1	92.8±8.8	<0.001*
Bone age (months)	73.0±29.6	92.7±9.2	<0.001*
Total volume (cm^3)	2.8 (2.4–3.9)	3.8 (2.7–10.7)	<0.001*
Right ovary volume (cm^3)	1.4 (1.1–2.1)	1.8 (1.3–5.4)	0.001*
Left ovary volüme (cm^3)	1.4 (1.1–1.8)	2.1 (1.3–5.4)	<0.001*

*P<0.05 indicates statistical significance. Numerical variables are shown as mean±SD or median (minimum–maximum). SD: Standard deviation

Table 3: Relationship between age and volume

Group	Variables	Right ovary volume		Left ovary volume		Total volume	
		r	*P*	*r*	*P*	*r*	*P*
Normal	Chronological age	0.371	<0.001*	0.368	<0.001*	0.360	<0.001*
	Bone age	0.326	0.001*	0.352	<0.001*	0.324	0.001
	Right ovary volume	-	-	0.711	<0.001*	0.921	<0.001*
Precocious puberty	Chronological age	0.377	<0.001*	0.322	<0.001*	0.352	<0.001*
	Bone age	0.362	<0.001*	0.437	<0.001*	0.369	<0.001*
	Right ovary volume	-	-	0.746	<0.001*	0.923	<0.001*
	Count of symptoms	0.586	<0.001*	0.583	<0.001*	0.637	<0.001*

*P<0.05 indicates statistical significance

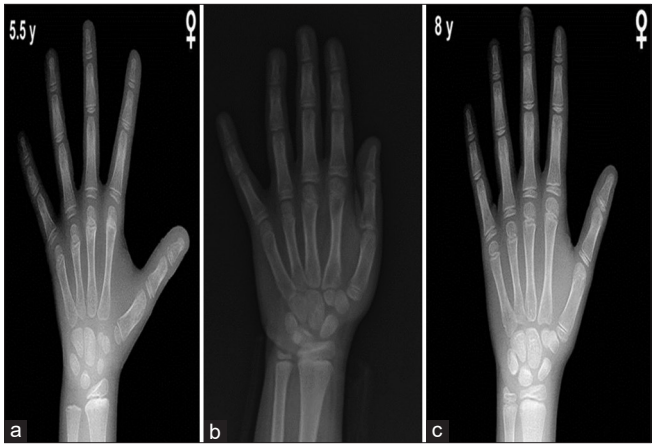


Figure 1: (a) Calendar and bone age; left wrist radiograph image of a healthy girl aged 5 years/6 months (Tanner–Whitehouse atlas). (b) When the left wrist radiograph of our PP patient, whose calendar age is 5 years/6 months, was compared to the Tanner–Whitehouse atlas, the bone age was judged to be 8 years. (c) Calendar and bone age; left wrist radiograph of an 8-year-old healthy girl (Tanner–Whitehouse atlas)

window before ovarian volume measurements. A radiologist performed a pelvic US examination utilizing a 3.5- or 5-MHz real-time US instrument (Samsung RS85 Prestige, South Korea). Ovarian volumes (V) were determined using the ellipsoidal formula: V = longitudinal diameter × anterior–posterior diameter × transverse diameter, multiplying the value obtained by the formula "0.523," and the average values of the right and left ovaries were recorded.

The patients' symptom numbers were acquired from the information on their digital electronic patient cards.

The Statistical Package for the Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL, USA) application was used for statistical analysis. The Kolmogorov–Smirnov test was used to determine whether the data had a normal distribution. Numerical variables with normal distributions were represented as mean standard deviation, whereas numerical variables with nonnormal distributions were represented as median (minimum–maximum). Numbers and percentages were used to express categorical variables. To compare numerical variables between two groups, the Student's *t*-test or Mann–Whitney *U*-test was utilized. Spearman correlation

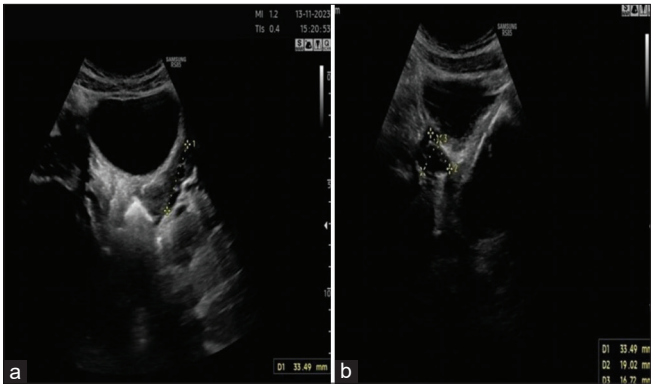


Figure 2: The left ovary volume was assessed as 5.5 ml in the transverse (a) and sagittal (b) greyscale ultrasound images of a 6-year-old precocious puberty patient (normal value is 1.2–1.3 ml)

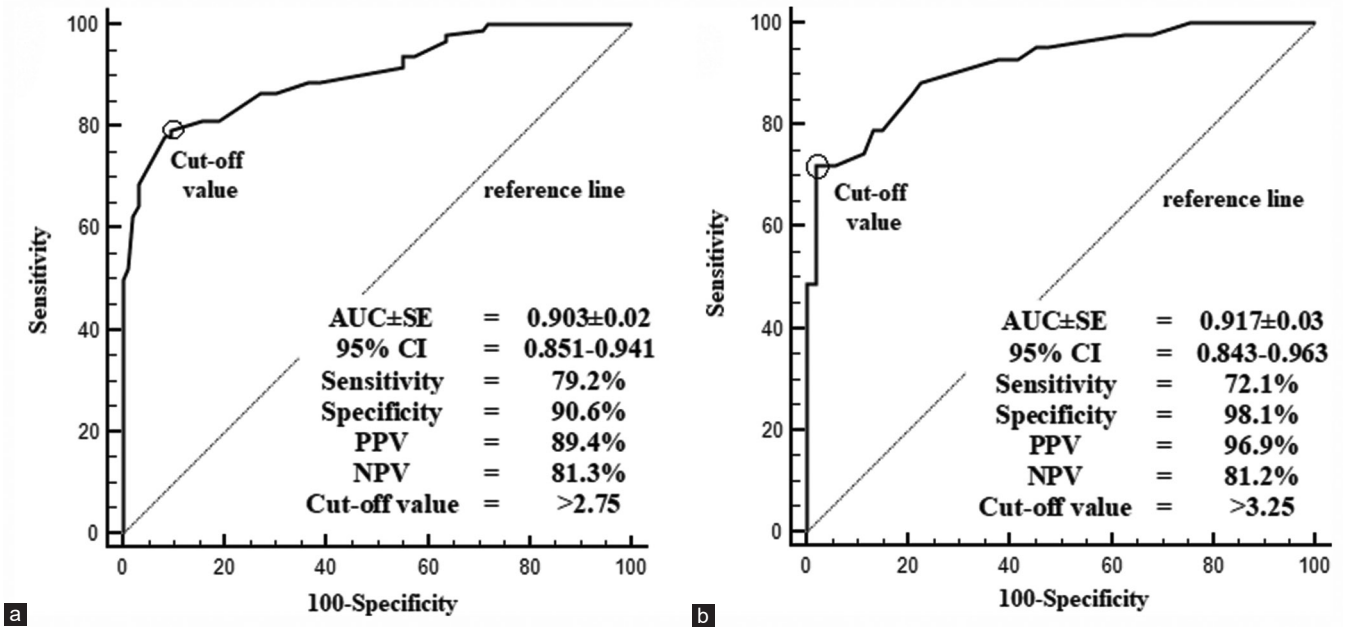
analysis was used to assess the relationship between numerical variables. Diagnostic performance evaluation of total volume was examined by receiver operating characteristic curve analysis, and the predictive value was determined according to the Youden index method. In statistical analysis, $P < 0.05$* value was considered statistically significant.

Results

The study population included 96 healthy people and 96 female patients with premature puberty. The study revealed that the average age of chronological and the average age of bone development were comparable in both the normal and PP groups. The PP group had higher median right ovarian volume (1.6 vs. 1.4; $P = 0.001$), median left ovarian volume (1.5 vs. 1.3; $P = 0.001$), and total volume (3.0 vs. 2) than the normal group. In the PP group, the number of symptoms was found to be 1 in 55.2% ($n = 53$) of the patients, the number of symptoms was 2 in 38.5% ($n = 37$), and the number of symptoms was 3 in 6.3% ($n = 6$) [Table 1].

In cases with PP with 2 or more symptoms, the mean chronological age (92.8 ± 8.8 vs. 74.8 ± 28.1; $P < 0.001$), mean bone age (92.7 ± 9.2 vs. 73.0 ± 29.6; $P < 0.001$), median right ovarian volume (3.8 vs. 2.8; $P = 0.001$), median left ovary volume (1.8 vs. 1.4; $P < 0.001$), and total volume (3.8 vs. 2.8; $P < 0.001$) were found to be higher [Table 2].

Table 4: Diagnostic performance evaluation of total volume in predicting the presence of precocious puberty (a) and the number of symptoms 2 or more (b)



AUC: Area under the curve, SE: Standard error, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

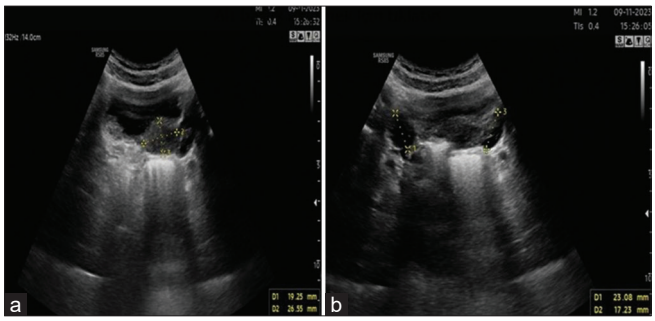


Figure 3: (a and b) Grayscale ultrasound scans of a 7-year-old girl with premature puberty showing an enlarged uterus and bilateral ovaries

A positive correlation was detected between right ovarian volume, left ovary volume, total ovarian volume, and chronological age and bone age in both the control and PP case groups. A positive correlation was found between the number of symptoms and right ovarian volume, left ovary volume, and total volume in PP patients [Table 3].

A total volume >2.75 was shown to predict the existence of PP with 79.2% sensitivity and 90.6% specificity (area under the curve [AUC]: 0.903; $P = 0.001$) [Table 4a]. A total volume of >3.25 predicted the existence of 2 or more symptoms in patients with PP, with a sensitivity of 72.1% and a specificity of 98.1% (AUC: 0.917; $P = 0.001$) [Table 4b].

As stated in our study, bone age in patients of premature puberty is frequently older than calendar age. According to the Tanner–Whitehouse atlas, the bone age of our 5 years and 6 months old cases, which we included in the study, was assessed as 8 years [Figure 1].

In our study's sample of 6- and 7-year-old prepubescent girls, gray-scale ultrasonography imaging revealed that ovarian and uterine volumes had risen [Figures 2 and 3].

Discussion

The goal of this original investigation was to see if there was a link between the number of symptoms at the time of admission and the ovarian volume and bone age of females with isosexual PP. It was also to compare these cases with a control group in a similar age group. The PP group had a greater median right ovarian volume (1.6 vs. 1.4; $P = 0.001$), median left ovarian volume (1.5 vs. 1.3; $P = 0.001$), and total volume (3.0 vs. 2) than the normal group. In PP patients, there was a positive association between the number of symptoms and right ovarian volume, left ovarian volume, and total volume [Table 3]. A link was discovered between the amount of symptoms and bone age.

Some physical and psychological changes occur in prepuberty situations. When compared to their normal contemporaries, PP patients have an increase in height and weight, as well as acne. They may exhibit dermatological issues, external genital organ prominence, axillary and pubic hair growth, the onset of menarche, anxiety, and a heightened feeling of self.

Depending on the underlying etiological etiology of premature puberty, there are some laboratory results. The essential sex hormones (estrogen and testosterone), as well as basal LH and follicle-stimulating hormone (FSH) values, should be sought initially. To confirm the diagnosis, stimulated FSH and LH levels should be tested with a GnRH test. To rule out

secondary causes that will cause puberty, thyroid function tests should be checked, and for those with puberty, 17-OH progesterone level should be measured early in the morning to rule out congenital adrenal hyperplasia. An attentive parent and a symptom recognized by a competent pediatrician can lead to an early diagnosis.[14,17-19]

In a multicenter study conducted by Carel *et al.* in 1999 on 58 PP girls, it was shown that there was a significant increase in the target height of the cases who received early diagnosis and treatment.[9] In a 2012 study on female instances with PP, Eksioglu *et al*. discovered that the bone age of the cases with PP was considerably advanced compared to patients in the isolated pubarche and isolated thelarche groups of the same age group.[14]

In a study conducted by Lee *et al*. in 2016, a difference of 1.96 ± 0.88 years was observed between the bone age and chronological age of girls with PP, and this was significantly higher than the 1.61 ± 1.00 year value of girls with PP ($P = 0.01$).[6]

Girls who undergo early puberty develop quicker than their peers because of increased bone turnover, yet they are unable to reach their usual target height.[19,20]

In 2004, Sample *et al*. reported that the size of the uterus in prepubertal girls should not exceed 3 cm.[20] In 2002, Herter *et al*. employed the ellipsoid formula to calculate ovarian and uterine volume in PP cases. In the same study, they suggested that utilizing follicle categorization to calculate ovarian volume might not be accurate enough.[9] In a comprehensive study on cases of premature puberty conducted by Ekşiolu *et al.* in 2013, they reported that the ovarian volume was larger than in isolated pubarche and isolated thelarche cases.[14] In the same study and Baduoraki's study in 2008, they suggested that in the detailed statistical analysis made by creating subclasses of ovarian morphology (polycystic, paurocystic, etc.), morphology did not have any significant value in determining PP.[16]

Again, in a 2008 study, Badouraki *et al*. showed percentages of average ovarian and uterine volumes to identify PP cases in normal females aged 1–12 years.[14,16]

In their study on healthy girls in 2019, Gilligan *et al*. created nomograms of ovarian and uterine volumes with pelvic US. In the same study, they claimed that transvaginal US and pelvic US techniques did not create a positive difference in the measurements.[12]

The cutoff value for the long axis of the uterus in pubertal development was 3.0 cm (93% sensitivity and 86% specificity) in a 2014 study by Binay *et al.*, and the cutoff value for ovarian volume was 1.3 ml (72% sensitivity and 90% specificity).[21] With similar measurements, in the study conducted by Lee *et al*. in 2016, the cutoff value of the uterine long axis was 4.09 cm (33% sensitivity and 79% specificity), and the cutoff value of ovarian volume was 3.5 ml (85.00% sensitivity and 26.09% specificity).[6]

Despite the fact that the bone age of the subjects at diagnosis exceeds the calendar age, adult target heights are lower in comparison to their contemporaries. This is due to the early closure of the rapidly developing epiphyseal plates during the pubertal stage. Some studies have found that PP patients who receive early diagnosis and therapy before the growth plates close have a considerable rise in target bone ages.[5,10,15]

In our study, we obtained similar results to some articles in the literature. In cases of PP, both bone age and ovarian volumes were considerably higher compared to the control group. Furthermore, when we considered the cutoff values given in several research for the ovarian volume of PP cases, we discovered that our analysis validates these quantitative values as well. We discovered that the median values of the right ovary were higher than those of the left ovary, confirming earlier research. Although the scientific cause for this is not yet known, numerous possibilities have been proposed. The sigmoid colon in the left pelvic region is in an S configuration, restricting the left adnexal space, and the difference in embryological venous drainage are his two most fundamental theories.[22,23]

Uterine data were not included in the study due to the lack of evidence in the literature supporting the superiority of uterine volumetric studies over ovarian measurements in cases of premature puberty, as well as the heterogeneity in uterine morphological development. While the interpretation may be up to debate, we are glad to inform you that there is evidence to support it.[6,9-12,21]

To the best of our knowledge, no study has been undertaken in the literature to investigate the link between the number of symptoms at the time of presentation and ovarian volume and bone age in females with premature puberty. We believe that our study of 192 female cases (96 patients and 96 controls) has demonstrated that an increased frequency of symptoms is statistically significant and positively connected with bone age and ovarian volumes. We see that cases presenting with more than one symptom are diagnosed with PP at a higher rate. The major goal in cases discovered early with proper imaging following a complete patient history and physical examination is to stop or regress the development of secondary sex characteristics, postpone the closure of the epiphyses, and maintain the final height in future. This circumstance necessitates a comprehensive and multidisciplinary approach to the agenda.

Our study had some limitations. First of all, the main limitations were the small number of patients included in the study and the fact that the study was retrospective. We feel that extracting anamnesis data from an electronic file may be insufficient to establish the number of symptoms. Data on which symptoms are more common in girls with puberty precocity or which is the least accompanying symptom would have made the study more reliable. Other limitations include the study's inclusion of only female cases and the absence of uterine measures in the available measurements due to their retrospective nature. However, because there are no comparable studies based on

the number of symptoms in the literature, we anticipate that addressing these limitations with some new research can bring more relevant information to the literature.

Conclusion

To conclude, as far as we know this is the first study in English literature to evaluate the relationship between the number of symptoms and ovarian volume and bone age. The number of symptoms in girls with PP is positively correlated with bone age and ovarian volume. Our results may emphasize the importance of the number of PP-related symptoms in patient management and prognosis prediction.

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Conflicts of interest

There are no conflicts of interest.

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