CLINICAL STUDY

Ultrasonographic and clinical parameters for early differentiation between precocious puberty and premature thelarche

Liat de Vries^{1,3}, Gadi Horev^{2,3}, Michael Schwartz^{2,3} and Moshe Phillip^{1,3}¹Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes and ²Imaging Department, Schneider Children's Medical Center of Israel, 14 Kaplan Street, Petah Tiqwa 49202, Israel and ³Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

(Correspondence should be addressed to L de Vries; Email: liatd@clalit.org.il)

Abstract

Objective: To determine if uterine and ovarian measurements can significantly distinguish between precocious puberty (PP) and premature thelarche (PT) and whether ultrasound has any advantage over the gonadotropin-releasing hormone (GnRH) stimulation test.

Design: Prospective.

Methods: One hundred and three girls referred consecutively for evaluation of breast budding before age 8 years underwent physical examination, GnRH stimulation test, bone age assessment, and transabdominal pelvic ultrasound. The diagnosis of PP or PT was based on clinical judgment. The clinical, laboratory, and ultrasound data of the PP and PT groups were compared.

Results: Eighty-one girls were diagnosed with PP and 22 with PT. Significant differences in most of the uterine and ovarian measurements were found between the groups. On logistic regression analysis, bone age standard deviation score, uterine transverse diameter, and uterine volume were the most significant variables predicting PP. Comparison of 30 girls with PP and 21 with PT in whom peak luteinizing hormone was < 5 mIU/ml on the GnRH stimulation test, using analysis of variance, yielded significant differences in uterine width ($P < 0.001$), fundus diameter ($P < 0.04$), uterine volume ($P = 0.006$), and ovarian circumference ($P < 0.02$).

Conclusions: Increased uterine and ovarian measurements may be an early and sensitive sign of PP. Pelvic ultrasound, a noninvasive, inexpensive, and reliable tool, may give the clinician a complementary indication to the GnRH test in distinguishing isolated PT from early-stage PP in girls with early breast budding.

European Journal of Endocrinology 154 891–898

Introduction

Precocious puberty (PP) in girls is defined as the appearance of secondary sex characteristics before the age of 8 years. In most cases, it is caused by premature activation of the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator ("central" PP) and is considered to be idiopathic. Central PP (CPP) may cause early epiphyseal maturation with compromised final height (1,2) as well as psychological stress (3,4). Thus, early initiation of treatment is important (2). However, CPP often resembles premature thelarche (PT), characterized by isolated early breast development, which is not associated with acceleration of growth or bone maturation and thus does not require therapy (5). The incidence of PT is highest in the first year of life, with a second peak after the fifth year (6). The latter increase

may represent an "intermediate" entity between isolated PT and CPP (7), also called "thelarche variant", "non-classical PT" and "atypical PT". It is characterized by older age at onset and occasional progression to CPP (8).

The differentiation of CPP from PT is based on physical examination, bone age assessment, growth velocity, and the GnRH stimulation test. It is difficult to distinguish between early stages of CPP and PT. With the significant increase in obesity prevalence in recent years, the distinction between CPP and obesity with or without thelarche poses another diagnostic challenge. Bone age may be advanced in obese girls who present with pseudothelarche due to increased fat tissue (9,10), whereas bone age advancement and growth acceleration might not be observed in the early stages of CPP. The GnRH stimulation test is considered the gold standard for diagnosis. Yet, despite its high specificity,

its sensitivity is low (11–13), and researchers disagree as to which response to GnRH stimulation should be used for diagnosis of CPP.

The aim of the present study was to identify clinical, biochemical and ultrasonographic parameters that can best differentiate CPP from PT, with emphasis on the contribution of pelvic ultrasound. In addition, we sought to determine if uterine and ovarian measurements by ultrasound have significant diagnostic value, especially when findings on the GnRH stimulation test have a prepubertal pattern. Although the clinical diagnosis of CPP was supported by ruling out other pathologies by further laboratory (adrenal androgens, prolactin, liver function, alpha-fetoprotein, beta-human chorionic gonadotropin (beta-HCG)) and imaging work-up, because of the remote possibility that prepubertal response to GnRH stimulation may represent a diagnosis other than CPP, the study group was designated as having precocious puberty (PP), not CPP.

Materials and methods

Patients

Girls referred for evaluation because of the appearance of breast buds between ages 4 and 8 years were recruited consecutively. All patients underwent clinical, biochemical, and bone age evaluation on referral. Assessment of the bone age (BA) and calculation of the bone age standard deviation score (BA-SDS) were performed according to Greulich and Pyle (14). Pubertal stage was determined according to Marshall and Tanner (15). Only patients in Tanner stages 2 or 3 were included. The hormonal evaluation included basal and GnRH-stimulated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) using a solid-phase, two-site chemiluminescent immunometric assay (Immulite 2000, DPC, Los Angeles, CA, USA). Serum basal blood levels of estradiol (Double Antibody Estradiol procedure, DPC), androstenedione (RIA, Diagnostic Systems Laboratories, Webster, TX, USA), and 17-hydroxyprogesterone (RIA, MP Biomedicals, Orangeburg, NY, USA) were determined. GnRH stimulation test was performed with 100 mcg GnRH, given as an i.v. bolus; serum LH and FSH concentrations were measured at 0, 30 and 60 min. Peak LH levels over 5 mIU/ml were considered a "pubertal response", as previously suggested for the immunochemiluminometric assay (16). Height was calculated as height-standard deviation score (Ht-SDS) for all girls and for both their parents, using the Centers for Disease Control growth charts (17). Body weight was expressed as body mass index ($\text{BMI} = \text{weight in kilograms/height in m}^2$), and the BMI-SDS was calculated according to the method of Rosner *et al.* (18).

The diagnosis of PP was based on the appearance of breast buds before 8 years of age accompanied by the presence of one or more of the following findings:

menses, pubic hair, accelerated growth velocity, or bone age greater than 2 SD above the chronological age. The diagnosis of PT was based on the presence of breast buds in the absence of bone or growth acceleration or pubic or axillary hair. Cases that were equivocal on referral were diagnosed after at least 6 months' follow-up on the basis of clinical judgment by an experienced clinician, who was blinded to the ultrasound results. Other forms of precocious puberty were ruled out by performing further laboratory (adrenal androgens, prolactin, liver functions, alpha-fetoprotein, and beta-HCG) and imaging studies (MRI of CNS, abdominal ultrasound) according to clinical judgment. The diagnosis of PP after follow-up was based on progression of breast development accompanied by at least one of the following: growth acceleration, bone age acceleration, and appearance of pubic hair. All diagnoses were confirmed after at least 3 years of clinical and auxiological follow-up. Girls with chronic disease, bone dysplasia, organic brain disease, congenital adrenal hyperplasia, or other endocrinological abnormalities were excluded, as were girls after radiation therapy and/or chemotherapy. None of the patients had clinical features of McCune-Albright syndrome, and none had known exposure to exogenous androgens or estrogens.

The clinical and laboratory data of the PP and PT groups were compared. To determine if uterine and ovarian measurements by ultrasound can significantly distinguish between girls with true PP and nonpubertal girls of the same age group, the findings were compared to findings in 83 otherwise healthy girls who were referred to the emergency department for intercurrent disease or to our institute for growth observation. One pediatric endocrinologist (L.D.) examined all control patients; none presented with PP or PT. The control findings were also analyzed against norms for healthy girls published in the literature (19). The ultrasound parameters were then compared between the girls with PT and PP in whom the GnRH stimulation test revealed a prepubertal pattern.

Written informed consent was obtained from all families. The institutional human research committee approved the study.

Pelvic ultrasound

Transabdominal pelvic ultrasound scans were performed with a conventional full-bladder 5-MHz real-time sector scanner (Sonoline prima, Siemens) by the same investigator (L.D.). The following parameters were analyzed: (1) Uterus: Length, transverse diameter (width), endometrial thickness, fundal anteroposterior diameter, and cervical anteroposterior diameter. The ratio between the fundal and cervical diameters (FCR) was calculated, and the uterine length was multiplied by the fundal anteroposterior diameter to determine the uterine cross-sectional area (CSA). (2) Ovaries: Height,

width, length, number of follicles, and maximal diameter of largest follicle observed. Ovarian circumference was measured in the transverse position. Uterine and ovarian volumes were calculated according to the formula for ellipsoid bodies: $V = \text{longitudinal diameter} \times \text{anteroposterior diameter} \times \text{transverse diameter} \times 0.5233$.

To assess reproducibility, ultrasound examinations were performed twice on the same occasion in 15 girls by two experienced operators who were unaware of the other's results. The correlation coefficients between two observers (Pearson correlation) for the 7 ultrasonographic parameters were 0.93–0.99 ($P < 0.001$ for all).

Statistical analysis

Statistical analyses were done with BMDP software (New System version, Statistical Solutions, Cork, Ireland). The results are given as mean $\pm$ s.d. ANOVA was used to compare the ultrasonographic parameters of the study and control groups and the published norms. Three separate analyses were performed to compare the ultrasonographic parameters between the girls with PT and PP who had a prepubertal response to the GnRH stimulation test, each using a different criterion for prepubertal pattern: peak LH ≤ 5 mIU/ml (20), peak LH ≤ 8 mIU/ml (21), and peak LH/peak FSH ratio ≤ 1 (11). The variables found to be significant were entered into a univariate model with a logistic regression to identify those that predict PP. Receiver operating characteristics

(ROC) curves were used to select cutoff points for androstenedione level and ultrasonographic measurements. Sensitivity and specificity were calculated for each variable using the area under the ROC curve (AUC). A P value of ≤ 0.05 was considered significant.

Results

Eighty-one girls were diagnosed with PP and 22 with PT. The disposition of the girls is presented in Fig. 1.

Significant differences were found in uterine volume, length, and anteroposterior diameter and in ovarian volume between the control subjects and the PP group (Fig. 2), but not the PT group. There were no differences in any of these variables between the control group and published data for normal healthy girls (19).

The clinical and auxiological data are shown in Table 1. On referral, the girls with a final diagnosis of PP were slightly older than the girls with PT, but within the same age range (the youngest patient in each group was 5.7 and 4.4 years old respectively). Tanner stage 2 breast development was documented in 49 girls with PP and 20 with PT, and Tanner stage 3 in 32 girls with PP and 2 girls with PT. Pubarche at presentation in the PP group was stage P1 in 19 girls (23.5%), P2 in 43 girls (53%) and P3 in 19 girls (23.4%). None of the girls in the PT group presented with pubarche.

Bone age was more advanced in the PP group than the PT group, as expressed by both the bone

Figure 1 Of 103 girls presenting with breast buds before 8 years, 40 met the clinical criteria of precocious puberty (PP) at referral; 37 of them had a peak LH of > 5 mIU/ml on GnRH stimulation test. The diagnosis of 63 girls was equivocal at referral. After follow-up of 6–18 months, 41 were diagnosed with PP and 22 with premature thelarche (PT). Treatment with GnRH analog was administered in 72 of the 81 girls with PP.

Figure 2 Ultrasound measurements of A: uterine volume, B: mean ovarian volume, C: uterine anteroposterior diameter, and D: uterine length in girls with precocious puberty (PP) and controls by age groups.

age–chronological age difference (1.5 ± 1.1 vs. 0.4 ± 0.5 respectively, $P < 0.001$) and the BA-SDS (1.9 ± 1.5 vs. 0.6 ± 0.7 , $P < 0.001$). However, in the PP group, the difference between the bone and chronological ages was less than 1 year in 27 of the 81 girls, and the BA-SDS was less than 1 in 23 girls.

Table 1 Clinical and auxiological data of girls with precocious puberty (PP) or premature thelarche (PT).

Variable	PP (n=81) (Mean $\pm$ s.d.)	PT (n=22) (Mean $\pm$ s.d.)	P value
Age at first signs (year)	6.9 ± 0.9	6.5 ± 1.2	0.06
Age at referral (year)	7.9 ± 0.9	7.3 ± 1.0	0.039
Bone age-SDS	1.8 ± 1.5	0.5 ± 0.7	< 0.001
Height-SDS	0.5 ± 0.8	0.1 ± 0.6	0.039
BMI-SDS	0.7 ± 0.9	0.3 ± 0.1	0.007
Androstenedione (nmol/l)	1.7 ± 1.2	0.6 ± 0.3	< 0.001
Basal LH (mIU/ml)	0.9 ± 1.1	0.4 ± 0.3	0.04
Basal FSH (mIU/ml)	3.0 ± 3.8	2.0 ± 1.4	0.10
Peak LH (mIU/ml)	12.0 ± 13.2	3.4 ± 1.5	0.007
Peak FSH (mIU/ml)	13.3 ± 6.7	14.9 ± 5.6	0.36
Peak LH/Peak FSH	0.9 ± 0.8	0.2 ± 0.1	< 0.001

SDS = standard deviation score; BMI = body mass index; LH = luteinizing hormone; FSH = follicle-stimulating hormone.

There were no between-group differences in mean serum levels of estradiol, testosterone, dehydroepiandrosterone-sulfate, and basal gonadotropins. Compared to the PT group, the PP group had significantly higher mean levels of androstenedione, peak LH, and peak LH/peak FSH ratio. However, peak LH > 5 , which is considered a pubertal response by many authors, was noted in only 51 girls (62%) in the PP group and 1 girl (4.5%) in the PT group, for a sensitivity of 62% and specificity of 93.7%. Peak LH/peak FSH ratio was greater than 1 in 29 girls (35.8%) with PP and in none of the girls with PT.

On ultrasound, a uterus was identified in all patients, and both ovaries were visualized in all patients but one, in whom only the left ovary was visible.

Most of the uterine and ovarian measurements were significantly different between the girls with PP and PT (Table 2). For the uterus, differences were noted in transverse diameter, length, fundal anteroposterior diameter, and volume. Endometrial echo was observed in 43 girls in the PP group (53%) and in none of the girls in the PT group. For the ovaries, differences were found in length, circumference, and mean (right and left) volume, but not in number of ovarian follicles or size of largest follicle. Continuous data for some of the crucial measures marking individual points as PT versus PP are shown in Fig. 3.

The variables found to be significant on univariate analysis were BA-SDS, peak LH, peak LH/peak FSH ratio, androstenedione, uterine width, volume, cross-section area, and length, FCR, mean (right and left) ovarian volume and ovarian circumference. We applied square root transformation to uterine volume which did not have a normal (Gaussian) distribution. The inclusion of these variables in the logistic regression model yielded uterine transverse diameter, BA-SDS, and uterine volume as the most significant predictors of PP (Table 3). The area under the ROC curve was 0.95. Peak LH was not as good a predictor of PP as the above variables. Cut-off points predictive for PP were as

Table 2 Ultrasound measurements in girls with precocious puberty (PP) or premature thelarche (PT).

Variable	PP (n=81) (Mean $\pm$ s.d.)	PT (n=22) (Mean $\pm$ s.d.)	P value
Uterine transverse diameter (cm)	1.8 $\pm$ 0.4	1.3 $\pm$ 0.2	<0.001
Uterine length (cm)	3.9 $\pm$ 0.7	3.4 $\pm$ 0.6	<0.001
Fundus (cm)	1.2 $\pm$ 0.4	0.8 $\pm$ 0.2	<0.001
Fundus/cervical ratio	1.3 $\pm$ 0.4	1.0 $\pm$ 0.4	0.03
Uterine volume (cm ³)	4.5 $\pm$ 3.4	1.8 $\pm$ 0.8	<0.001
Endometrial thickness (cm)	0.2 $\pm$ 0.2	0.02 $\pm$ 0.0	0.001
Uterine cross-sectional area (cm ²)	4.7 $\pm$ 2.1	2.7 $\pm$ 0.9	<0.001
Ovarian length (cm)	2.3 $\pm$ 0.6	1.8 $\pm$ 0.4	<0.001
Ovarian width (cm)	1.2 $\pm$ 0.3	1.1 $\pm$ 0.3	0.2
Ovarian height (cm)	1.8 $\pm$ 0.5	1.7 $\pm$ 0.6	0.3
Ovarian volume (cm ³)	2.8 $\pm$ 2.1	1.8 $\pm$ 1.3	0.05
Ovarian circumference (cm)	5.0 $\pm$ 1.2	4.0 $\pm$ 0.5	0.003
Number of follicles	4.0 $\pm$ 1.9	3.4 $\pm$ 1.6	0.2

follows: androstenedione > 1.0 nmol/l; uterine antero-posterior diameter > 8 mm; uterine transverse diameter > 1.5 cm; uterine length > 3.4 cm; uterine volume > 1.96 ml; ovarian circumference > 4.5 cm. The sensitivity and specificity of most of the significant variables are shown in Table 4.

Comparison of the 30 girls with PP and 21 with PT in whom peak LH was $\leq$ 5 mIU/ml on GnRH stimulation

test yielded significant differences in uterine transverse diameter ($P < 0.001$), fundal diameter ($P = 0.04$), uterine volume ($P = 0.006$), and left and right ovarian circumference ($P < 0.02$ and $P = 0.03$ respectively). Similar differences were noted on comparison of the 38 girls with PP and 20 with PT in whom peak LH was $\leq$ 8 mIU/ml, and the 48 girls with PP and 22 girls with PT in whom peak LH/peak FSH ratio was $\leq$ 1 (Table 5).

Ultrasound had a good predictive power for PP in unequivocal cases. Specifically, the odds ratio for predicting peak LH > 8 mIU/ml was 1.3 (CI 1.12–1.5; $P < 0.001$) for uterine transverse diameter (AUC = 0.76) and 2.0 (CI 1.4–2.9; $P < 0.001$) for uterine volume (AUC = 0.85). The correlation between peak LH and uterine volume (Pearson correlation) by diagnosis was 0.47 for PP and 0.52 for PT.

Discussion

In the present study, pelvic ultrasound proved to be an efficient tool in differentiating PP from PT, especially when results of the GnRH stimulation test were equivocal.

Although previous studies have compared the ultrasonographic parameters of girls with PP and PT (22–25), only one examined the efficacy of ultrasound against GnRH stimulation test (11). The PT group in the latter study was significantly younger than the PP

Figure 3 Individual clinical and ultrasound data of girls with precocious puberty (PP) or premature thelarche (PT). The horizontal lines indicate the median for each group.

Table 3 Results of logistic regression to predict precocious puberty.

Variable	Odds ratio*	Lower	Upper	P value
Uterine transverse diameter	1.87	1.1	3.17	<0.001
BA-SDS	2.93	1.0	8.53	0.006
Uterine volume	1.43	1.0	2.13	<0.05

*Odds ratio for increased risk of precocious puberty: for every increase of 1 mm in uterine transverse diameter, of 1 standard deviation score in bone age, and of 0.1 cm³ in uterine volume.

Table 4 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of clinical parameters found to be most significant on ANOVA.

	Sensi- tivity (%)	Speci- ficity (%)	PPV (%)	NPV (%)
Uterine transverse diameter > 1.5 cm	67.9	100	100	39.5
Presence of endometrial echo	57.3	100	100	40.7
Fundus > 0.8 cm	82.5	76.4	94.2	48.1
Uterine length > 3.4 cm	80.2	57.8	89	40.7
Uterine volume > 2.0 ml	88.8	89.4	97.2	65
Ovarian circumference > 4.5 cm	66.6	85.7	95.4	36.3
Androstendione > 1.0 nmol/l	59	76	89	35.5
Peak LH > 5 mIU/ml	62	93.7	98	33.3
Bone-age SDS > 1	73.3	81.8	93.2	47.3

LH = luteinizing hormone; SDS = standard deviation score.

group, as was the case in other studies (12, 24, 26). We focused on girls older than 4 years with premature breast budding because PT in this age group may represent a different entity from "classical" PT and poses a greater diagnostic challenge.

In addition, some of the earlier studies used pubertal response to the GnRH stimulation test as a diagnostic criterion for PP (25,26), creating a possible preselection bias (26). The GnRH test has a low sensitivity (11–13), perhaps because the transition to a LH-predominant response is often a relatively late development in the clinical progression of PP (12). Also, there is no agreement as to the LH cut-off for diagnosis of PP (20, 27, 28). In the present study, as the diagnostic standard, we used clinical judgment based on the assessment of growth velocity and bone age, and findings on dynamic physical examination performed by an objective and experienced clinician. We found that peak LH had a low sensitivity (62%) in predicting PP and was not as good a

predictor of PP as the other variables on logistic regression analysis. Thus, pelvic ultrasound may offer an earlier clinical indication of PP than the GnRH test.

It should be noted that in one girl with a clinical diagnosis of PT, peak LH was > 5 mIU/ml (6.6 mIU/ml). She presented at age 7 years with breast buds but no pubic hair, bone age advancement, or growth acceleration. During the following three years, there was a waxing and waning of the breast buds with no other clinical changes.

The findings for our control girls confirm other studies showing no significant increase in uterine dimensions in healthy girls until age 7 or 8 years (19,22–24).

In agreement with others (29), we found most of the sonographic parameters to be highly specific in differentiating PP from PT, but insufficiently sensitive: Uterine volume > 1.96 ml had a sensitivity of 88.8% and specificity of 89.4%, compared to the 100% sensitivity and specificity reported by Haber *et al.* (11). Corresponding values for uterine transverse diameter > 1.5 cm were 68% and 100%. The mean FCR was significantly different between the PP and PT groups. However, when we narrowed our comparison to patients with a prepubertal response to GnRH stimulation, there was an overlap in values between the groups, and the differences lost their significance (Table 4). Earlier studies (25,30) also reported that after age 7 years, the FCR does not differentiate prepubertal from pubertal girls. Thus, it is a poorer parameter than other uterine findings for distinguishing among forms of sexual precocity. In this study, we also used ovarian circumference, a new parameter that has not been previously applied in this setting. It may reflect ovarian size more accurately than volume, because ovaries, particularly in girls, do not have a symmetrical oval shape. Overall, uterine parameters contributed more than ovarian parameters to the differentiation between PP and PT.

Ultrasound successfully identified both ovaries in all but one patient, in whom only the left ovary was visible.

Table 5 Ultrasound measurements in girls with precocious puberty (PP) or premature thelarche (PT) with a prepubertal response to GnRH stimulation test. Results for three analyses by three criteria of prepubertal response.

	Peak LH ≤ 5 mIU/ml			Peak LH ≤ 8 mIU/ml			Peak LH/Peak FSH ≤ 1 mIU/ml		
	PP (n=30)	PT (n=21)	P value	PP (n=38)	PT (n=20)	P value	PP (n=48)	PT (n=22)	P value
Uterine transverse diameter (cm)	1.6 ± 0.4	1.3 ± 0.2	<0.001	1.6 ± 0.4	1.3 ± 0.2	<0.001	1.7 ± 0.4	1.3 ± 0.2	<0.001
Uterine length (cm)	3.7 ± 0.5	3.4 ± 0.6	0.03	3.8 ± 0.5	3.4 ± 0.6	0.005	3.8 ± 0.6	3.4 ± 0.6	0.01
Fundus (cm)	1.0 ± 0.3	0.8 ± 0.2	0.04	1.0 ± 0.3	0.8 ± 0.2	0.01	1.0 ± 0.3	0.8 ± 0.2	0.003
Fundus/cervical ratio	1.2 ± 0.3	1.1 ± 0.3	0.19	1.2 ± 0.3	1.1 ± 0.4	0.31	1.2 ± 0.3	1.1 ± 0.4	0.20
Uterine volume (cm ³)	3.1 ± 1.9	1.8 ± 0.7	0.006	3.2 ± 1.7	1.8 ± 0.8	0.001	3.5 ± 1.8	1.8 ± 0.8	<0.001
Uterine cross-section area (cm ²)	3.7 ± 1.6	2.7 ± 0.8	0.01	3.8 ± 1.4	2.7 ± 0.9	<0.001	3.9 ± 1.6	2.8 ± 1.4	0.009
Ovarian length (cm)	2.1 ± 0.5	1.8 ± 0.4	0.04	2.2 ± 0.6	1.8 ± 0.4	0.007	2.2 ± 0.6	1.8 ± 0.4	0.005
Ovarian circumference (cm)	4.8 ± 1.2	4.0 ± 0.4	0.02	4.9 ± 1.2	4.0 ± 0.5	0.01	4.9 ± 1.2	4.0 ± 0.5	0.003
Ovarian volume (cm ³)	2.3 ± 1.4	1.7 ± 1.2	0.14	2.4 ± 1.5	1.8 ± 1.2	0.10	2.5 ± 1.6	1.8 ± 1.2	0.06

LH = luteinizing hormone; FSH = follicle-stimulating hormone.

Previous studies report that at least one ovary is identified in about 90% of pediatric patients over 5 years of age, and both ovaries in up to 80% (31,32). Our high yield was probably attributable to our long-term experience.

Performing pelvic ultrasound in pediatric endocrinology institutes saves time and money, and provides the clinician with a broader clinical view, because the ultrasound data are obtained at the same time as the physical examination data. Furthermore, as the environment is already familiar to the patients, the test is less stressful.

At present, most of the girls have not yet reached final height, and some are still being treated. Therefore data on height outcome and age at menarche are sparse.

We found no increase in BMI-SDS in either group, thereby excluding obesity as a cause of PP or PT or "pseudo-precocious puberty".

Overall, the girls with PT comprised 21% of our cohort, and the girls with PP, 79%. These rates are in accordance with the study of Battaglia *et al.* (33) wherein 33% of the girls had PT and 67% had CPP. Pescovitz *et al.* (12) reported rates of 26% PT, 38% CPP, and the rest intermediate forms of PP; the average chronological age of the girls with PT was 2.5 years. In another study, PT accounted for 18.5% of all cases of early breast budding (34). The relatively low ratio between the sizes of the PT and PP groups in the present study can be explained by our exclusion of girls younger than 4 years. The increased incidence of PT after age 4 years, following the progressive decrease up to age 4 years, may reflect "intermediate" or "atypical" forms of premature sexual maturation (6, 8, 35). Unfortunately there is no one parameter that is accurate and sensitive enough to distinguish among the different presentations of premature sexual development.

Interestingly, mean androstenedione level was significantly higher in the PP than the PT group. This most probably indicates true activation of the gonadotroph-ovarian axis. However, the androstenedione level by itself was not a sensitive parameter for differentiation of PP from PT. A similar observation was reported in one study comparing 3 girls with PT to 3 girls with CPP (23), but not in another study, which failed to find any such difference (33). No significant difference was found in mean estradiol level between the groups. Nevertheless, it should be noted that the sensitivity of the assay in our laboratory changed over the period of the study, from a lower limit of 20 pmol/l at onset to 2.3 pmol/l later.

Conclusions

An increase in uterine and ovarian measurements represents an early and sensitive sign of PP. Thus, pelvic ultrasound, a noninvasive, inexpensive, and reliable tool, may give the clinician a complementary indication to the GnRH test for the distinction between isolated PT

and early-stage PP in girls with early breast budding. Therefore, we suggest that ultrasound scan should be included in the routine work-up of girls with PP.

Acknowledgements

The authors thank Pnina Lilos for the statistical analysis and Gloria Ginzach and Hanni Penn for their editorial and secretarial assistance.

References

- 1 Kauli R, Galatzer A, Kornreich L, Lazar L, Pertzalan A & Laron Z. Final height of girls with central precocious puberty, untreated versus treated with cyproterone acetate or GnRH analogue. A comparative study with reevaluation of predictions by the Bayley-Pinneau method. *Hormone Research* 1997 **47** 54–61.
- 2 Brauner R, Adan L, Malandry A & Zantleifer D. Adult height in girls with idiopathic true precocious puberty. *Journal of Clinical Endocrinology and Metabolism* 1994 **79** 415–420.
- 3 Ehrhardt AA & Meyer-Bahlburg HFL. Idiopathic precocious puberty in girls: long-term effects on adolescent behavior. *Acta Endocrinologica (Copenhagen)* 1986 **279** (Suppl) 247–253.
- 4 Kletter GM & Klech RP. Clinical review 60: effects of gonadotrophin-releasing hormone analogue therapy on adult stature in precocious puberty. *Journal of Clinical Endocrinology and Metabolism* 1994 **79** 331–334.
- 5 Salardi S, Cacciari E, Mainetti B, Mazzanti L & Pirazzoli P. Outcome of premature thelarche: relation to puberty and final height. *Archives of Disease in Childhood* 1998 **79** 173–174.
- 6 Van Winter JT, Noller KL, Zimmerman D & Melton LJ. Natural history of premature thelarche in Olmsted County, Minnesota, 1940 to 1984. *Journal of Pediatrics* 1990 **116** 278–290.
- 7 Stanhope R & Brook CGD. Thelarche variant: A new syndrome of precocious sexual maturation? *Acta Endocrinologica (Copenhagen)* 1990 **123** 481–486.
- 8 Stanhope R. Premature thelarche: clinical follow-up and indication for treatment. *Journal of Clinical Endocrinology and Metabolism* 2000 **13** (Suppl 1) 827–830.
- 9 Klein KO, Larmore KA, de Lancey E, Brown JM, Considine RV & Hassink SG. Effect of obesity on estradiol level, and its relationship to leptin, bone maturation, and bone mineral density in children. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 3469–3475.
- 10 De Simone M, Farello G, Palumbo M, Gentile T, Ciuffreda M, Oliosio P, Cinque M & De Matteis F. Growth charts, growth velocity and bone development in childhood obesity. *International Journal of Obesity and Related Metabolic Disorders* 1995 **19** 851–857.
- 11 Haber HP, Wollmann HA & Ranke MB. Pelvic ultrasonography: early differentiation between isolated premature thelarche and central precocious puberty. *European Journal of Pediatrics* 1995 **154** 182–186.
- 12 Pescovitz OH, Hench KD, Barnes KM, Loriaux DL & Cutler Jr. Premature thelarche and central precocious puberty: the relationship between clinical presentation and the gonadotropin response to luteinizing hormone-releasing hormone. *Journal of Clinical Endocrinology and Metabolism* 1988 **67** 474–479.
- 13 Aritaki S, Takagi A, Someya H & Jun L. A comparison of patients with premature thelarche and idiopathic true precocious puberty in the initial stage of illness. *Acta Paediatrica (Japan)* 1997 **39** 21–27.
- 14 Greulich WW & Pyle SI. *Radiographic Atlas of the Skeletal Development of the Hand and Wrist*, 2nd edn. Stanford, California: Stanford University Press, 1959.

- 15 Marshall WA & Tanner JM. Variations in the pattern of pubertal changes in girls. *Archives of Disease in Childhood* 1969 **44** 291–303.
- 16 Neely EK, Hintz RL, Wilson DM, Lee PA, Gautier T, Argente J & Stene M. Normal ranges for immunochemiluminometric gonadotropin assays. *Journal of Pediatrics* 1995 **127** 40–46.
- 17 Kuczmarski RJ, Ogden CL & Grummer-Strawn LM. CDC Growth Charts: United States Advanced Data from Vital and Health Statistics NCHS Advance Data Report No. 314, pp 1–27 Hyattsville, MD: US Department of Health and Human Services, 2000.
- 18 Rosner B, Prineas R, Loggie J & Daniels SR. Percentiles for body mass index in US children 5 to 17 years of age. *Journal of Pediatrics* 1998 **132** 211–222.
- 19 Orsini LF, Salardi S, Pilu G, Bovicelli L & Cacciari E. Pelvic organs in premenarcheal girls: real-time ultrasonography. *Radiology* 1984 **153** 113–116.
- 20 Neely EK, Wilson DM, Lee PA, Stene M & Hintz RL. Spontaneous serum gonadotropin concentrations in the evaluation of precocious puberty. *Journal of Pediatrics* 1995 **127** 47–52.
- 21 Eckert KL, Wilson DM, Bachrach LK, Anhalt H, Habiby RL, Olney RC, Hintz RL & Neely EK. A single-sample, subcutaneous gonadotropin-releasing hormone test for central precocious puberty. *Pediatrics* 1996 **97** 517–519.
- 22 Stanhope R, Adams J, Jacobs HS & Brook CGD. Ovarian ultrasound assessment in normal children, idiopathic precocious puberty, and during low-dose pulsatile gonadotrophin releasing hormone treatment of hypogonadotrophic hypogonadism. *Archives of Disease in Childhood* 1985 **60** 116–119.
- 23 Stanhope R, Abdulwahid A, Adams J & Brook CGD. Studies of gonadotrophin pulsatility and pelvic ultrasound examinations distinguish between isolated premature thelarche and central precocious puberty. *European Journal of Pediatrics* 1986 **145** 190–194.
- 24 Salardi S, Orsini LF, Cacciari E, Partesotti S, Brondelli L, Cicognani A, Frejaville E, Pluchinotta V, Tonioli S & Bovicelli L. Pelvic ultrasonography in girls with precocious puberty, congenital adrenal hyperplasia, obesity, or hirsutism. *Journal of Pediatrics* 1988 **112** 880–887.
- 25 Griffin IJ, Cole TJ, Duncan KA, Hollman AS & Donaldson MDC. Pelvic ultrasound findings in different forms of sexual precocity. *Acta Paediatrica* 1995 **84** 544–549.
- 26 Herter LD, Golendziner E, Flores JA, Moretto M, Di Domenico K, Becker E, Jr & Spritzer PM. Ovarian and uterine findings in pelvic sonography. Comparison between prepubertal girls, girls with isolated thelarche, and girls with central precocious puberty. *Journal of Ultrasound in Medicine* 2002 **21** 1237–1246.
- 27 Palmert MR, Malin HV & Boepple PA. Unsustained or slowly progressive puberty in young girls: initial presentation and long-term follow-up of 20 untreated patients. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 415–423.
- 28 Oreter-Klein K, Uriarte MM, Rose SR, Barnes KM & Cutler GB. Gonadotropin secretory dynamics during puberty in normal girls and boys. *Journal of Clinical Endocrinology and Metabolism* 1990 **71** 1251–1258.
- 29 Buzzi F, Pilotta A, Dordoni D, Lombardi A, Zaglio S & Adlard P. Pelvic ultrasonography in normal girls and in girls with pubertal precocity. *Acta Paediatrica* 1998 **87** 1138–1145.
- 30 Herter LD, Golendziner E, Flores JA, Becker E, Jr & Spritzer PM. Ovarian and uterine sonography in healthy girls between 1 and 13 years old: correlation of findings with age and pubertal status. *American Journal of Roentgenology* 2002 **178** 1531–1536.
- 31 Griffin IJ, Cole TJ, Duncan KA, Hollman AS & Donaldson MDC. Pelvic ultrasound measurements in normal girls. *Acta Paediatrica* 1995 **84** 536–543.
- 32 Siegel MJ. Pediatric gynecologic sonography. *Radiology* 1991 **179** 593–600.
- 33 Battaglia C, Mancini F, Regnani G, Persico N, Lughetti L & De Aloysio D. Pelvic ultrasound and color Doppler findings in different isosexual precocities. *Ultrasound in Obstetrics and Gynecology* 2003 **22** 277–283.
- 34 Bridges NA, Cooke A, Healy MJR, Hindmarsh PC & Brook CGD. Ovaries in sexual precocity. *Clinical Endocrinology* 1995 **42** 135–140.
- 35 Ilicki A, Prager Lewin R, Kauli R, Kaufman H, Schachter A & Laron Z. Premature thelarche - natural history and sex hormone secretion in 68 girls. *Acta Paediatrica Scandinavica* 1984 **73** 756–762.

Received 14 June 2005

Accepted 1 March 2006