Breast Ultrasonographic Assessment of Premature Thelarche: Preliminary study of correlation with Bone Age and Precocious Puberty

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Aims and objectives

Premature thelarche (PT) is defined as isolated early breast development without bone maturation in girls before 8 years of age, and does not require therapy (1, 2). In contrast, precocious puberty (PP) in girls is defined as the development of secondary sex characteristics including growth acceleration or bone maturation before the age of 8 years, and early initiation of treatment is required (1, 2). PT and PP are both characterized by breast budding, and while it is important to distinguish PP and PT early in order to make decisions about treatment, it is very difficult to do so at initial presentation.

Ultrasonography (US) is an easy, valuable modality to evaluate breast condition, but is rarely used in children because pathologic conditions are unusual during this period (3). However, physicians are currently more often using US than they have in the past to diagnose breast development in young girls. If it is possible to use US for the quantitative evaluation of breast parenchyma, including visual assessment and degree, US may be useful to diagnose PT and PP while determining breast development. In turn, if it is possible to distinguish between PP and PT using breast US findings, early initiation of treatment would be feasible in PP patients. However, to our knowledge, there have been only two English publications regarding US findings of normal breast development (4, 5). Another report found that breast US findings were correlated with bone age and hormonal status in PT and PP (5).

The purpose of this study was to evaluate breast US findings such as Tanner stage and breast budding diameter in pediatric subjects with PP and PT while comparing bone age and hormone levels.
Methods and materials

Between March 2011 to February 2013, 107 girls who had undergone breast US for evaluation of PP in our institution were recruited for this study. Seventeen patients were excluded because they had no record of bone age and laboratory data such as luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (E2). Among these 17 patients, one with no record of bone age demonstrated a left subareolar benign cystic mass based on breast US. We included 90 girls (mean age, 7.8 years; range 2 - 12 years) in the final sample. Our institutional review board approved this retrospective study, and informed consent was waived for the review of images and records.

Real-time gray-scale US was performed using a 5-12-MHz linear-array transducer (iU22; Philips Medical Systems, Bothell, WA, USA) and all US scans were retrospectively reviewed by two breast radiologists. We categorized breast US grades into five Tanner stages according to characteristic US findings as summarized in Table 1 using the larger of the bilateral breasts (4). Breast budding diameter (cm) was defined as the longest diameter of fibroglandular echogenic area in the larger of the bilateral breasts on US images including the nipple as determined by two radiologists. Bone age was measured according to the Greulich and Pyle scale (6) and the difference between bone age and chronological age (BA-CA) was also calculated. Hormonal evaluations were obtained via outpatient clinic blood tests. Basal LH levels were assessed using a MiniVIDAS apparatus (VIDAS 12, 1992, Biomerieux Company, France) through an enzyme immunoassay (EIA) technique, and the basal levels of FSH and serum E2 were measured using direct chemiluminescence and the ADVIA Centaur CP Immunoassay System (Siemens Medical Solutions).

Among a total of 90 subjects, 69 girls (mean age, 7.3 years; range 2 - 8 years) less than 8 years of age were re-classified into PP, PT, and normal groups. We diagnosed PP in subjects of Tanner stage 2 or greater by breast US before 8 years of age and advanced bone age compared to chronological age by 1 year or more. PT was diagnosed in girls with accelerated breast development more than Tanner stage 2 before 8 years of age, but who were within the normal range in bone age. The normal group was defined as Tanner stage 1 by breast US and being within the normal range in bone age.

All statistical analyses were performed using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). Categorical data were summarized as frequencies and percentages. Spearman's correlation or Pearson's correlation analysis was used to evaluate the relationships between breast US grade, breast budding diameter, BA-CA, and laboratory results for FSH, LH, and E2 levels. Mann-Whitney U tests were used to analyze PP and PT group differences in variables after excluding patients in the normal
group among enrolled cases. Statistical significance was established as a two-sided P value less than 0.05.
<table>
<thead>
<tr>
<th>Tanner stage</th>
<th>US grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Elevation of papilla only.</td>
<td>Prepubertal stage; Ill-defined hyperechoic retroareolar tissue.</td>
</tr>
<tr>
<td>II Elevation of breast and papilla as a small mound, enlargement of areola diameter.</td>
<td>Palpable subareolar bud before elevation; A hyperechoic retroareolar nodule with central star-shaped/linear hypoechoic area.</td>
</tr>
<tr>
<td>III Further enlargement of breast and areola, with no separation of their contours.</td>
<td>Obvious enlargement and elevation; Extending hyperechoic glandular tissue away from the retroareolar areas with central spider-shaped hypoechoic region.</td>
</tr>
<tr>
<td>IV Projection of areola and papilla to form a secondary mound above the level of the breast.</td>
<td>Transient areolar mounding; Hyperechoic periareolar fibroglandular tissue with prominent central hypoechoic nodule and sometimes subcutaneous adipose tissue.</td>
</tr>
<tr>
<td>V Projection of papilla only, due to recession of the areola to the general contour of the breast.</td>
<td>Mature breast contour; Hyperechoic glandular tissue with increased subcutaneous fat tissue and without hypoechoic central nodule.</td>
</tr>
</tbody>
</table>

**Table 1:** Breast sonographic (US) grades with detailed characteristic findings compared to clinical Tanner stages.

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Results

The clinical data for each US grade are summarized in Table 2. Among the total sample of 90 girls, the distribution of breast US grade was as follows: grade I, 18 (20.0%); grade II, 30 (33.3%); grade III, 26 (28.9%); grade IV, 15 (16.7%) and grade V, 1 (1.1%). The mean breast budding diameters of each group are presented in Table 2, and the median values were 0 cm in grade I, 1.9 cm in grade II, 2.4 cm in grade III, 2.5 cm in grade IV and 10 cm in grade V. Breast US grade was positively correlated with age ($P = 0.020, r_s = 0.244$), breast budding diameter ($P < 0.001, r_s = 0.854$, Fig. 1), LH ($P < 0.001, r_s = 0.469$), FSH ($P < 0.001, r_s = 0.531$) and E2 ($P = 0.012, r_s = 0.265$). Breast budding diameter was also positively correlated with age ($P = 0.020, r_s = 0.244$), LH ($P < 0.001, r_s = 0.363$) and FSH ($P = 0.004, r_s = 0.300$) but there were no significant differences in US grade with BA-CA ($P = 0.410$), breast budding diameter with BA-CA ($P = 0.718$) and E2 ($P = 0.243$).

Among 69 subjects less than 8 years of age, we excluded 16 normal girls (23.2%) among the enrolled cases and 40 (58.0%; mean age, 7.3 ± 1.0 years; range, 4-8 years) were diagnosed with PP, whereas 13 (18.8%; mean age, 7.1 ± 1.7 years; range, 2-8 years) were diagnosed with PT retrospectively. The differences in the values of BA-CA ($P < 0.001$) and the levels of LH ($P = 0.048$) were statistically significant, but there were no significant difference in other variables between PP and PT groups (Table 3).
### Table 2: Clinical and hormonal characteristics of subjects in each grade according to sonography.

Continuous variables are expressed as mean ± SD. Spearman's correlation was used to evaluate associations of breast US grade with variables. US, ultrasonography; BA-CA, difference between bone age and chronological age; LH, luteinizing hormone; FSH, follicle stimulating hormone; E2, estradiol

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Grade I (n = 18)</th>
<th>Grade II (n = 30)</th>
<th>Grade III (n = 26)</th>
<th>Grade IV (n = 15)</th>
<th>Grade V (n = 1)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>7.7 ± 1.2</td>
<td>7.5 ± 1.1</td>
<td>7.8 ± 2.0</td>
<td>8.7 ± 1.1</td>
<td>8</td>
<td>0.020</td>
</tr>
<tr>
<td>Breast budding diameter (cm)</td>
<td>0.5 ± 0.1</td>
<td>1.9 ± 0.5</td>
<td>3.1 ± 0.7</td>
<td>3.7 ± 0.9</td>
<td>10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BA-CA (yr)</td>
<td>0.6 ± 1.1</td>
<td>1.3 ± 0.9</td>
<td>1.0 ± 1.0</td>
<td>0.9 ± 1.1</td>
<td>2.2</td>
<td>0.410</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>0.1 ± 0.2</td>
<td>0.2 ± 0.2</td>
<td>0.3 ± 0.5</td>
<td>0.7 ± 0.7</td>
<td>2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>1.6 ± 0.6</td>
<td>3.1 ± 3.0</td>
<td>3.6 ± 2.2</td>
<td>3.9 ± 1.2</td>
<td>6.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E2 (pg/mL)</td>
<td>16.1 ± 10.3</td>
<td>18.4 ± 10.9</td>
<td>24.3 ± 21.7</td>
<td>25.7 ± 16.0</td>
<td>94.0</td>
<td>0.012</td>
</tr>
</tbody>
</table>
Fig. 1: Correlations between sonographic (US) grade and breast budding diameter (cm).

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<table>
<thead>
<tr>
<th></th>
<th>Precocious puberty (n = 40)</th>
<th>Premature thelarche (n = 13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>7.3 ± 1.0</td>
<td>7.1 ± 1.7</td>
<td>.843</td>
</tr>
<tr>
<td>US grade</td>
<td>2.7 ± 0.8</td>
<td>2.7 ± 0.6</td>
<td>.866</td>
</tr>
<tr>
<td>Breast budding diameter (cm)</td>
<td>2.4 ± 0.9</td>
<td>2.8 ± 0.7</td>
<td>.163</td>
</tr>
<tr>
<td>BA-CA (yr)</td>
<td>1.7 ± 0.7</td>
<td>0.0 ± 0.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>0.3 ± 0.4</td>
<td>0.2 ± 0.2</td>
<td>.048</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>2.9 ± 1.6</td>
<td>3.3 ± 2.8</td>
<td>.975</td>
</tr>
<tr>
<td>E2 (pg/mL)</td>
<td>24.2 ± 22.7</td>
<td>19.4 ± 11.2</td>
<td>.818</td>
</tr>
</tbody>
</table>
Table 3: Clinical, hormonal and US data in girls diagnosed with precocious puberty and premature thelarche. Continuous variables are expressed as mean ± SD. Mann-Whitney U tests were used to evaluate associations of breast US grade with variables. US, ultrasonography; BA-CA, difference between bone age and chronological age; LH, luteinizing hormone; FSH, follicle stimulating hormone; E2, estradiol

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Conclusion

In women, breast buds enlarge and glandular formation presents during sexual maturation under the influence of hormones. Physiological changes include increased volume of subcutaneous fat and connective tissues, ductal proliferation/elongation, and development of terminal duct lobular units. Puberty is defined as the transition from child to adult, which is a very dynamic, complex period in development with somatic growth and sexual maturation as described above in girls under the influence of multiple genetic and endocrine controls such as increased gonadal hormone levels (7).

Disorders of premature secondary sexual maturation show a wide spectrum ranging from PT to PP, and distinguishing between these conditions is very important for both prognostic and therapeutic reasons (8, 9). PP is caused by the early activation of the hypothalamus, pituitary, gonad (HPG) axis, like normal physiologic puberty, and results in the early progression of secondary sexual maturation, rapid somatic growth including bone maturation, reduced adult height, abnormal body shape and psychological behavioral changes (2, 8, 9). Although the main causes of PP are idiopathic, childhood obesity and environmental changes may be associated with PP, and therefore accurately diagnosing PP is more important than before (9, 10). However, PT is not associated with the HPG axis and does not result in true sexual maturation, advanced bone maturation, or reduced adult height.

Defining the etiologic causes of premature secondary sexual maturation is important when a girl under 8 years of age presents with breast enlargement. Careful history and pubertal staging according to the Tanner method should be performed. Anthropometric investigations should also be performed, including body weight, height, and growth velocity per year, which should be calculated and compared with previous data for the same patient. Bone age should be evaluated by left hand and wrist X-rays. The difference between bone age and chronological age also should be calculated, and if bone age is advanced more than 2SD for chronological age or this difference is greater than one year or more, it is more likely that the patient will be diagnosed with PP rather than PT (9, 11). The gonadotropins (FSH, LH) and related sex steroids should be evaluated with or without GnRH stimulation tests. The GnRH stimulation test is still the most important diagnostic test, and LH is the dominant gonadotropin in PP while FSH is the dominant gonadotropin in PT (12). However, Neely et al. reported that spontaneous FSH and LH levels are also useful screening tools for PP (10), while Houk et al. reported that a single basal LH measurement is adequate to evaluate the HPG axis in most cases (13). We evaluated basal gonadotropin levels including FSH and LH without GnRH stimulation tests because these data were not available for all patients, but this omission is acceptable in the study context as noted above. The sizes of ovaries and uterus were compared with reference levels of pelvic US, and increased ratios are detected.
in PP. If clinically needed, cranial magnetic resonance imaging should be performed to differentiate organic PP.

The system designed by Tanner et al. is widely used to grade normal breast development into five stages in pubertal girls (7, 14). However, this classification is based on physical descriptions without considerations of other factors such as US findings. Also in the classification, a higher ratio for fat deposition is used to distinguish between true breast budding and higher fat content, which is a current trend brought about by dietary changes in modern children that may lead to suspected breast enlargement. Therefore, the accuracy of Tanner staging in some cases is doubtful. Breast US is a simple, objective method that may be used to assess the presence, absence, and extent of fibroglandular tissue. Recently the frequency of breast US has increased, although breast US are not used in diagnostic tests for PP because such pathological conditions are unusual in childhood. Moreover, breast US has added benefits in that it is able to diagnose masses that are mistaken for breast budding due to developmental changes. Distinguishing PP from PT and visualizing developing stages by breast US is a more accurate and quantitative method than traditional Tanner staging that is also more practical in daily contexts. Garcia et al. reported the US characteristics of each Tanner stage in normal developing breasts (4), but theirs was only a descriptive report without statistical analysis. Recently, Calcaterra et al. reported that breast volume increases with progressive breast US stage, and presented the first quantified data using US in developing breasts (5). In their study, breast volume \# 0.85 cm3 measured by US was helpful for the diagnosis of PP, but US staging showed only a weak ability to distinguish PP from PT in girls. The use of parameters describing advanced bone age > 2 SD and E2 level \# 50pmol/L may help to diagnose PP.

In our study, we used previously reported breast US grades and found that these were positively correlated with breast budding diameter and age. According to these results, breast US may be useful for determining pubertal grade as well as an ancillary diagnostic tool for premature sexual maturation including PP and PT. Measuring the longest US diameter of the fibroglandular echogenic area is an easier method than others because it is not necessary to understand morphological changes, and it could therefore be used as a parameter describing breast development to replace Tanner staging or breast US grading. The results would be more reliable, because hormonal levels were also positively correlated with US grade and breast budding diameter. Our results are meaningful because there are few studies of breast development demonstrating correlations between US quantification and hormonal status (5). Regarding the parameter of BA-CA, US grade and breast budding diameter were not correlated, but the BA-CA values were significantly different between PP and PT groups. This result suggests that our overall study results are reliable. The values of baseline LH were significantly different between PP and PT groups, and this result agrees with the results of previous studies (2, 9, 12, 15). Longitudinal studies monitoring the progression of BA, including anthropometric investigations and assessments of breast development, would be helpful
to distinguish PP and PT easily as accelerated somatic growth and sexual development are characteristic of PP.

This study has several limitations. First, it was a retrospective study and included only patients who had received US, left hand and wrist X-rays for bone age, and blood hormone level measurements, leaving open the possibility of selection bias. Second, the number of patients included was small, as breast US was performed selectively depending on clinician preference and not routinely to diagnose PP or PT. In the future, larger-scale clinical studies should be performed. Third, we used only baseline gonadal hormone measurements without GnRH stimulation tests, but have already explained why this caveat is acceptable. Fourth, this study included only Korean patients, and our results may not be generalizable to other populations. Finally, three radiologists performed US examinations and therefore interobserver variability may be an issue in clinical practice and in this study.

In conclusion, breast US may be useful for evaluating sexual development in pediatric patients, but its ability to distinguish PP from PT is limited. A better understanding of relationships between objective hormonal values and US findings may allow clinicians to predict hormonal status according to breast US grade.
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