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Natural history of premature thelarche: review of 60 girls

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ABSTRACT In Indonesia report on the natural history of premature thelarche is very limited. Daily practice requires physicians to have some basic practical knowledge, among others the natural history of premature thelarche, in order to manage these patients properly. We reviewed data of 85 premature thelarche patients who visited our department from January 1989 until December 1998. Only 60 patients met the study criteria. The mean chronological age of the patients at diagnosis was 43.4 months. About half of these patients (31/60) were diagnosed before they were 2 years old. Half of the patients had bilateral breast involvement. The hormonal pattern showed 24/48 follicle stimulating hormone predominant-response. Most patients (33/47) showed normal plasma estradiol level. Bone age analysis was normal in 46/57 patients, and only 9 showed accelerated bone age. Pelvic ultrasonography showed prepubertal reproduction organs in 26/35. Vaginal smears showed signs of estrogenization with various degree of stimulation in 13 patients. At the end of observation the outcome of premature thelarche were: 31 regressed, 19 persisted, 6 had progressive breast development and 4 progressed to central precocious puberty. The initial clinical and laboratory characteristics of those who developed CPP varied. Among 31 premature thelarche patients who regressed, 21 had onset of breast enlargement before age of 2 years. In most of the regressed patients (20/31), regression occurred completely within the first year. Most premature thelarche patients with onset before 2 years will regress within one year after diagnosis. **[Paediatr Indones 2001; 41:279-283]**

***Keywords**: premature thelarche, prognosis, spontaneous regression, precocious puberty*

PREMATURE THELARCHE IS A CONDITION CHARACTERIZED BY isolated breast development without any other clinical signs of sexual maturation in girls before the age of 8 years. The highest prevalence of premature thelarche is during the first 2 years of life. The relationship between premature thelarche and central precocious puberty (CPP) has been discussed in several reports. The current concept is that premature thelarche is a benign, self-limited, condition that only rarely progress to central precocious puberty.[1, 2] The pathophysiology of premature thelarche is still unknown. In Mills[3] report of 46 girls with premature thelarche, the majority had no change in breast development during 3-5 years of follow up (57%), 11% reported progressive breast enlargement without the development of other symptoms, and 32% regressed.

The natural history of premature thelarche contrasts with that of idiopathic CPP, which causes progressive breast and pubic hair development, behavioral changes, accelerated rates of growth and bone maturation, and early epiphyseal fusions. Consequently it is very important to differentiate between these two conditions for both prognostic and therapeutic reasons. Premature thelarche need no treatment while CPP should be treated properly.[1-2] In Indonesia there is still a limited report about both the incidence and the natural history of premature thelarche. During 1987-1991, Assin[4] reported that at the Pediatric Endocrine Clinic Cipto Mangunkusumo Hospital, Jakarta, there were 53 (7.8%) premature thelarche patients out of total 682 new endocrine patients in the same period. The aim of this study was to know the occurrence, clinical features and natural history of premature thelarche patients in our

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department from 1989 to 1998. We hope this study will be useful for practicing physicians taking care of premature thelarche patients.

Methods

This retrospective study was carried out on all premature thelarche patients who visited Pediatric Endocrine Clinic, Child Health Department, Cipto Mangunkusumo Hospital, Jakarta, during the period of January 1989 - December 1998. Patients with incomplete records or unknown addresses, those with neonatal gynecomastia, and patients who died before the end of the observation period, were excluded. Premature thelarche was diagnosed according to the classic criteria, i.e, breast development without other signs of puberty and before the age of 8 years, bone age within 2 standard deviations of normal, normal growth velocity, and basal gonadotropin showed follicle stimulating hormone (FSH)-predominant response.[1,2]

The degree of breast development was assessed according to the stages recommended by Marshall and Tanner.[5] Bone age was determined according to the method of Greulych and Pyle.[6] Vaginal smear examination, stained by Shorr method[7] were interpreted according to Forst and Kasdon. The stage of internal genital development was determined by measuring the mean uterine and ovarian volumes using ultrasound. The initial clinical and laboratory features of the patients and all the follow-up data noted during the period were recorded in a special form. Premature thelarche was considered regressing if the patient showed a decreased breast size or Tanner breast staging. A patient was diagnosed as developing CPP when pubertal staging, growth velocity or bone age were progressing more than expected. A patient was considered having progressive premature thelarche if the breast developed without any other signs of secondary sexual characteristics.

Results

Eighty-five premature thelarche patients visited the Pediatric Endocrine Clinic, Child Health Department, Cipto Mangunkusumo Hospital, Jakarta, during January 1989 until December 1998, giving an average of 8-9 patients each year. Only 60 patients met the inclusion criteria and could be reviewed. The youngest patient was 5 months and the oldest was 7 years and 11 months old. Patients were first diagnosed at a mean chronological age of 43.4 months. Most patients (29/60) were less than 2 years at the first time of diagnosis, 20 patients were diagnosed between 6-8 years, and the least affected were the 4-6 years old (**Table 1**).

Slightly more than half of these patients had an onset of premature thelarche before 2 years of age (**Table 2**).

Most patients (58/60) came in Tanner's B2 stage of breast development, only 2 showed stage B3. Half of the patients (30/60) had bilateral breast involvement, the other half patients were unilaterally affected, 17 left and 13 right side breast enlargements Compared to the standard of National Center of Health Sciences, the height of 11 patients were < P5 NCHS, and 3 were > P95 NCHS, and the remaining patients were in between.

Hormonal assays, basal gonadotropin and plasma estradiol measurements, were done in 48 and 47 pa-

TABLE 1. AGE DISTRIBUTION OF PREMATURE THELARCHE PATIENTS AT THE FIRST TIME OF DIAGNOSIS

Age (yr)	n	%
<2	4	8
2-4	6	10
4-6	5	9
6-8	20	33
Total	60	100

TABLE 2. AGE AT ONSET OF PREMATURE THELARCHE

Age at onset (yr)	n	%
<2	31	51
2-4	6	10
4-6	7	2
6-8	16	27
Total	60	100

TABLE 3. BASAL GONADOTROPIN PATTERNS OF PREMATURE THELARCHE PATIENTS

Basal gonadotropins pattern	Total
FSH-predominant response	24
Prepubertal gonadotropin level	19
Pubertal-gonadotropin level	4
LH-predominant response	1
Total	48

tients, respectively. Half of the them (24/48) showed FSH-predominant response. The remaining showed various results as shown in **Table 3.**

Plasma estradiol level was normal in 33 of 47 patients, the rest showed an increased plasma estradiol level (>22 pg/ml). Bone age analysis on initial presentation was normal in 46 of 57 patients, advanced in 9, and retarded in the rest 2 patients. Pelvic ultrasound examination was performed in 35 patients, the results showed that 26 patients were in prepubertal stage, while the remaining 9 patients were in pubertal stage. None of these patients showed the presence of ovarian cysts. Vaginal smears were performed in 31 girls, signs of estrogenization with various of stimulation were positive in 13 patients, but there were no signs of estrogenization in the 18 patients.

Of these 60 patients, 31 had a complete regression of thelarche. Of the remaining, 19 patients had persisted enlargement, 9 patients showed progressing thelarche without any other secondary sexual characteristics, and 4 patients subsequently developed CPP. Among the 31 regressed patients, 20 patients showed regression in first year after the diagnosis, 5 patients regressed 1-5 years, and in the remaining 6 patients the age of regression was unknown.

There was a close relation between the age onset of premature thelarche with the occurrence of regression. Among the regressed patients, 21/31 patients had the onset of thelarche before the age of 2 years, which is statistically significant (**Table 4**).

Of those 60 premature thelarche patients, 4 girls subsequently progressed to CPP. The initial clinical and laboratory features of these patients can be seen in **Table 5**.

TABLE 4. RELATION BETWEEN THE AGE AT ONSET THELARCHE WITH THE REGRESSION

Onset (yr)	Regression	No regression	Total
< 2	21	10	31
2	10	19	29
Total	31	29	60

$X^2 = 14,83$, df = 1, p<0,05

Discussion

There are only a few reports about the incidence of premature thelarche. Winter et al[8] in Minnessota USA, 1940-1984 reported 48 premature thelarche patients with a crude incidence 21.2 per 100.000 persons per year. Pasquino et al[9] observed 52 girls with isolated breast enlargement for 10 years. While Rodrigues1[0] reported the occurrence of premature thelarche in Puerto Rico during the period from January 1976 to August 1984, 482 patients were caused by exogenous estrogen contamination in the food ingested by the children and by their mothers. In this study the occurrence of premature thelarche in the Child Health Department, Cipto Mangunkusumo Hospital, Jakarta, during period 1989-1998 was 0.058%. This study showed that most of patients (31/60) had the onset of thelarche before the age of 2 years. This finding is in agreement with Pasquino[9] who reported that of 40 premature thelarche patients, 26 had it before 2 years of age. According to the literature, the highest prevalence of premature thelarche is during the first 2 years of life.[1]

Half of these premature thelarche patients (30/60) had bilateral breast involvement. This is in agreement with Van Winter's[8] finding who reported that of 48 premature thelarche patients, 23 showed bilateral enlargement. It seems that the side of breast enlargement at time of diagnosis could not be used as a predictive factor to indicate patients at risk of developing CPP. The pathophysiological mechanism of premature thelarche is still unknown. It has been postulated to be a result of increased breast sensitivity to estrogen, transient estrogen secretion by follicular ovarian cysts, increased estrogens production from precursors of adrenal origin, increased dietary estrogen as a results of exogenous contamination of food.[1]

TABLE 5. CLINICAL AND LABORATORY FEATURES OF PREMATURE THELARCHE WHO PROGRESSED TO CPP

No	Age (yr)	Age of onset (yr)	Stage of puberty	Bone age	Basal Gonadotropin	Plasma Estradiol	Pelvic US	Degree of estrogenation
1	3 9/12	1	A1PH1M2	Advanved	FSH-predom	Normal	-	-
2	7 4/12	7	A1PH1M2	Normal	FSH-predom	Increased	Pubertal	Slight
3	6 6/12	6	A1PH1M2	Normal	Pubertal	Normal	Prepubertal	-
4	4 9/12	3	A1PH1M3	Advanced	Pubertal	Normal	Prepubertal	Strong

Our data show that 24 of 48 patients who underwent basal gonadotropin examination revealed an FSH-predominant response. It seems that this condition is caused by transient partial activation of the hypothalamus pituitary gonad (HPG). But this finding does not reflect the real condition, due to no one of these patients underwent LHRH testing. Plasma estradiol levels in this study were normal in most of the patients (33/47). Unfortunately because of the inadequate sensitivity of the available estradiol assays, its level in girls with premature thelarche is not well defined. Klein[11] reported that girls with premature thelarche had significantly higher estradiol level than normal prepubertal girls. This is consistent with the hypothesis that the mechanism of premature thelarche involves increased estradiol level rather than increased sensitivity of breast tissue to normal estradiol levels.

Not all patients in this study showed sign of estrogenization of the vaginal epithelium. This finding is not in agreement with Pasquino's report. In this study bone age analysis at initial examination were normal in 48/57 patients. The various results of bone age examination is in accordance with spectrum of premature thelarche mentioned by Pescovitz.[12] Pelvic ultrasound examinations in this study showed that in most of these patients (26/35), the internal genital organ were in prepubertal stage. None of these patients showed ovarian cysts. Freedman[13] reported that there was an increased prevalence of detectable ovarian microcyst in girls with premature thelarche, but the presence or absence of cysts did not correlate with basal gonadotropin or estradiol level.

There are few studies of the natural history of premature thelarche, and their conclusion remains controversial. Mills et al[3] reported that none of the patients had any other problem of sexual development or function during a period of 7 years, and concluded that premature thelarche is a benign condition and that referral to an endocrinologist is not necessary. A more recent retrospective study[3] showed that in the majority of premature thelarche patients, there were regression of breast volume during the period of 6 months to 6 years after diagnosis; in about 10%, breast development persisted until puberty, with no untoward effect on later health, growth, or fertility. This study shows that most of premature thelarche patients will regress within one year after diagnosis especially those who had the onset before 2 years of age.

The initial clinical features of premature thelarche patients who developed CPP varied. Unfortunately only a few data during the period of follow up can be documented. Many reports indicate that currently there are no predictive clinical or laboratory tests that can identify at time of diagnosis, which patients are at risk of developing CPP.

Based on the results of our study we conclude that premature thelarche is generally a mild clinical condition, and patients with onset before age 2 years represent a transient and isolated phenomenon.

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