

## CLINICAL STUDY

**Premature thelarche in Macedonia: a three-year follow-up**

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**Abstract**

**Introduction:** Premature thelarche presents as an appearance of breasts and glandular tissue in girls before the age of 8 years. It is mostly a benign and transitory variation of premature sexual development.

**Aim of the study:** We evaluated a group of girls with premature thelarche for clinical and auxologic characteristics for a period of three years. We investigated the duration of the condition and eventual progression toward true idiopathic central precocious puberty.

**Patients, materials, methods:** At the Department of Endocrinology and Genetics at the Pediatric Clinic in Skopje, 127 girls with premature thelarche, from all over the country, were analyzed and followed-up for a period of 3 years (2000–2003). **Results and conclusions:** Premature thelarche as a partial form of premature sexual development, in our study included 98 girls, and showed to be a benign condition, the girls are with normal height, slightly elevated weight, but with increased bone maturation and height velocity in the first year. A progression toward central precocious puberty was not registered. The duration of the condition was about two years in most of the girls, with a regression of enlarged breasts in smaller patients and with occurrence of normal puberty in older patients (Tab. 1, Fig. 3, Ref. 16). Full Text (Free, PDF) [www.bmj.sk](http://www.bmj.sk).

**Key words:** premature thelarche, premature breast development, precocious puberty.

The classic differential diagnosis in girls with premature breast development, is between central precocious puberty and isolated premature thelarche. In premature thelarche, the breast development is the only clinical sign, whereas in central precocious puberty there is an accelerated growth, advanced bone maturation and a positive GnRH test. There may be an appearance of pubic hair, vaginal discharge or bleeding. The ultrasound examination of children's genitalia serves also as an important diagnostic tool (1).

**Materials and methods**

This prospective study on premature thelarche in the Republic of Macedonia included all girls with the stage 2 of breast development (M2), according to Tanner (2). These girls were forwarded by their regular pediatricians to be evaluated at the Department of Endocrinology and Genetics at the Pediatric Clinic in Skopje. Girls with peripheral precocious puberty or central precocious puberty as a consequence of secondary peripheral puberty were excluded from the study.

During the period 2000–2003, 98 patients were registered with isolated premature thelarche. For all children, we constructed a questionnaire to collect information about relevant parameters such as the city of origin, pregnancy of the mother, delivery, breast-feeding, appearance of first symptoms, and the timing of menarche of the mother.

The height was measured using Harpenden's stadiometer, and calculated as SDS (standard deviation score) according to Tan-

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**Table 1.**

	Diagnosis	After 3 years
Height SDS	0.4	0.3
BMI SDS	1.7	2.0
Unilateral Thelarche		7 girls
Bilateral Thelarche		91 girls
Fluctuation of breast size	M3 → M2	60 girls
	M2 → M3	38 girls

ner et al (3). The weight was measured and expressed as BMI SDS (body mass index), according to the tables of Rolland, Cashera et al (4). Height velocity was calculated at an interval of one year (3). A GnRH test was performed (gonadotropin-releasing hormone); hormonal testing was done to assess the values of follicle stimulating and luteinizing hormones. In order to assess the bone age (BA), radiographs of the left hand and wrist were done and evaluated according to the Greulich and Pyle atlas (5). The ultrasound of genitalia of the girls was performed at the Clinic for Gynecology and Obstetrics, by gynecologists trained to examine small children.

**Results**

At the time of their diagnosis, the mean chronologic age (CA) of 98 girls was 4.5±2.1 years.

Height SDS (HSDS) at diagnosis was 0.4±1.8, and after three years remained similar (0.3±1.5).

The body mass index (BMI SDS) was similar at the diagnosis (1.7±2.3) and after 3 years (2.0±3.4) (Tab. 1).

Bone age (BA) at the diagnosis was slightly advanced (5.4±2.8 years), and after three years increased up to 8.2±3.0 years. There was a significant difference in BA during all three years of the follow-up, between the first and the second (p<0.01), the first and the third (p<0.0001), and the second and third years (p<0.02) (Fig. 1).

The regression analysis showed a tendency toward a decrease in height velocity (HV) during the three years of follow-up (except for the first year). HV in the first year was 7.33 cm, second year 5.88, third year 5.78 (Fig. 2).

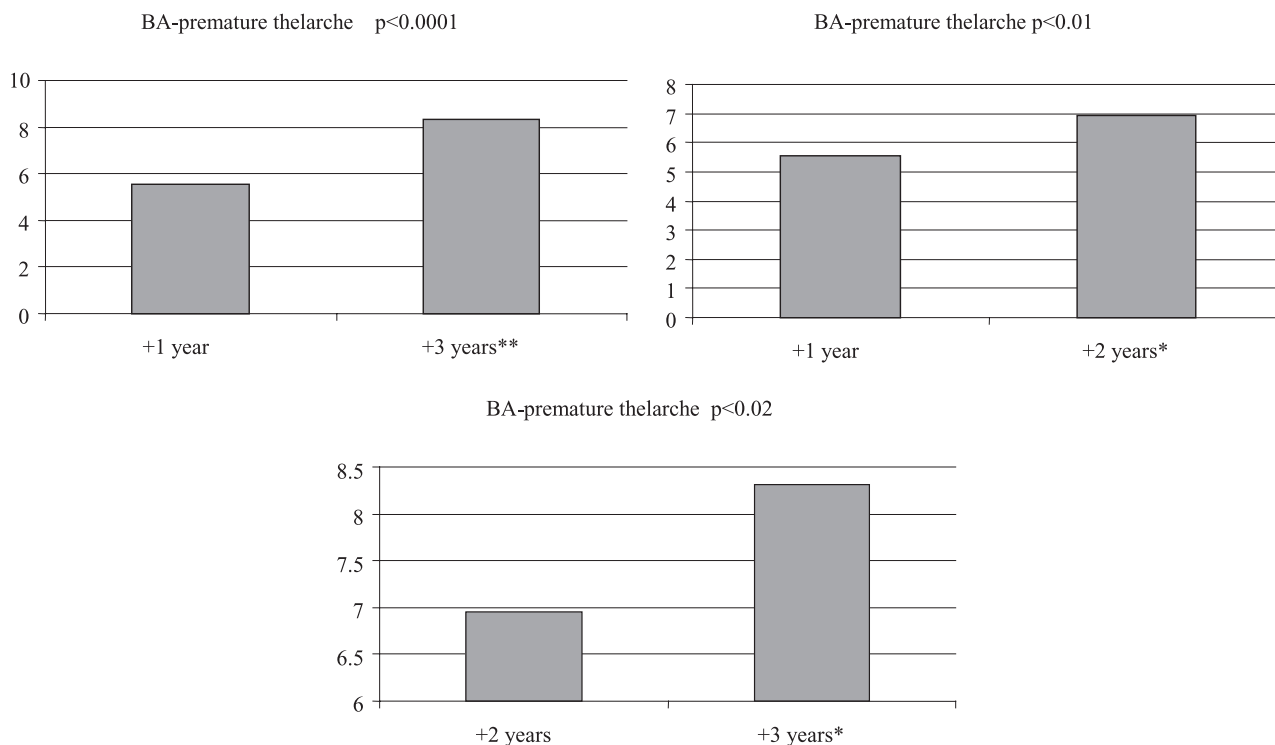
Positive correlations were found between the CA, BA and BMI SDS (p<0.01), as well as HSDS and BA (p<0.01) with BMI SDS (p<0.01) (Fig. 3).

Statistical analysis was performed using the t-test, correlations by Speerman, and multiple regressions by ANOVA.

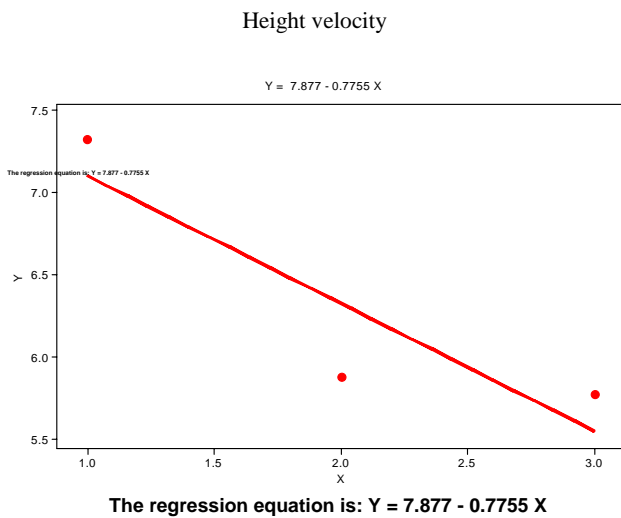
91 girls had bilateral thelarche, while in 7 it was unilateral. The first symptoms in most children appeared 4.6±5.8 months before diagnosis, and in 10 they have been present since birth.

The GnRH test was performed in girls with special indications (increased bone age and advanced breast stage). The test was pre-pubertal; consistent with isolated premature thelarche.

The breast enlargement changed in the girls during the evaluation period. Still, the breast stage in most of the small girls showed a regression.



**Fig. 1. Bone age through the evaluation period.**



**Fig. 2. Multiple regressions for height velocity.**

The duration of premature thelarche was different and showed a variation from a few months to 3 and more years, with the mean value of  $2.0 \pm 2.5$  years.

The ultrasound evaluation of genitalia at the diagnosis was pre-pubertal, and pubertal in the girls who after 3 years had started their normal puberty.

Most of the girls originate from the capital of Macedonia, Skopje (56.1 %), while the rest of them come from other regions in Macedonia with no preponderance.

According to the nationality, 73.4 % were Macedonian, 20.0 % Albanian, and 6.6 % Romany and Turkish.

The menarche of the mothers occurred at the mean age of 12.7 years.

89.7 % of the girls were breast-fed. The pregnancies of their mothers were normal in 97 % of cases, as well as the deliveries (99 %).

The mean values of weight and length of the children were 3250 g and 50 cm, respectively.

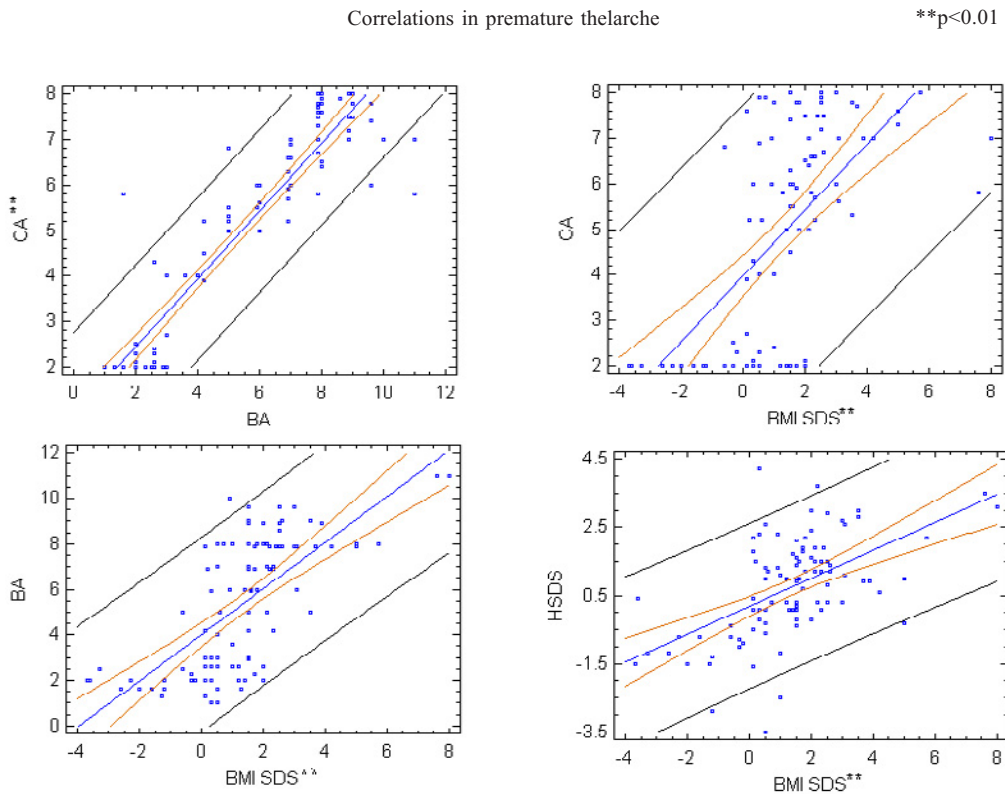
The familial history of premature thelarche was present in two cases.

Most of the previous illnesses of the children were upper respiratory infections (90 %).

Two girls experienced a hemorrhagic secretion from the breasts. The condition was evaluated and showed to be transitory.

**Discussion**

In our previous study (6), we concluded that it was necessary to continue in the follow-up of the evaluated group of 35 girls and to include new patients in order to have an insight whether this condition has a tendency to progress toward central precocious puberty. Our preliminary results in 1999 showed a



**Fig. 3. Compared parameters in the evaluation group.**

high proportion of isolated premature thelarche in Macedonian girls, differences in the levels of body mass, bone maturation and hormonal levels.

In girls with isolated premature thelarche, the growth and epiphyseal maturation are normal; pubic or axillary hair is not present. Neither disturbances in behavior and learning, nor advanced sexual psychological maturation (7) are present. In our patients, the bone maturation significantly increased in each further year of follow-up, possibly due to low age and faster growth. HV also significantly increased during the first year and then decreased in the following years. In one study its authors describe a condition referred to as exaggerated thelarche, in condition of which the thelarche is associated with advanced bone maturation and increased HV (8), hence their results are similar to ours. We found a significant positive correlation between the CA, BA and BMI SDS in the girls, which is an expected finding. Regarding the disturbed sexual behavior, one girl (2 %) manifested masturbation, while in the rest of patients this was not noticed.

Regarding the timing of occurrence, premature thelarche has been described to occur mostly between 2 and 4 years in girls (9). In our study the common age group was between 2 and 8 years of age. A study in USA showed that premature thelarche occurred with an incidence of 21.2 in 100.000 patients, 60 % of the girls were between the age of 6 months to 2 years, and the regression of the condition was between 6 months and 6 years, some having thelarche until puberty. 25 children were followed-up for 10 to 35 years and they did not show any negative consequences for their health, growth or fertility (10).

In our present study, none of the children progressed toward central precocious puberty, although this condition has been described by others. In a series of 100 girls with premature thelarche, in 14 girls, central precocious puberty occurred (11). We did not register such a progression in our group. The strict line that distinguishes the true central precocious puberty from isolated thelarche was questioned by Pescovitz et al and Fontoura et al who described the intermediate clinical conditions as an incomplete or partial sexual development (12), or slow progression toward puberty (13). In our series, we had one patient (2 %) with an intermediate clinical condition and partial sexual development; however this girl did not progress toward central precocious puberty. Other studies also report that even girls who show regression of thelarche, later in their life 4–18 % of them develop precocious puberty (14). Still, it is considered that the golden standard for the diagnosis of central precocious puberty is the GnRH test with elevated levels of luteinizing hormone (LH). The diagnosis may be also confirmed with an ultra sensitive recombinant bioassay where it is seen that these patients with premature thelarche have a significant higher level of estradiol than normal pre-pubertal girls (16). In our study the estradiol was measured by a standard bioassay and showed to be in the pre-pubertal range.

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