

# REVIEWS

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## Precocious Thelarche – Current Opinions

### Przedwczesne izolowane powiększenie gruczołów piersiowych – obecny stan wiedzy

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#### Abstract

Isolated premature mammary gland enlargement, or precocious thelarche (thelarche praecox, t.p.), is a glandular tissue development which occurs in girls below eight years of age without any other symptoms of systemic estrogen activity. T.p. is usually observed during the first two to three years of life. Ethnic and nutritional factors influence the frequency of t.p. incidence. T.p. is connected with endogenous and exogenous factors. Early stages in the activation of the hypothalamic-pituitary-ovarian axis, activating *GNAS1* gene mutation, and FSH receptor polymorphism are the most frequently mentioned endogenous factors. It has been suggested that exposure to estrogenic disrupters, such as dioxins, furans, organic halogens, and phthalates, can cause t.p. epidemics in some geographical areas. FSH levels, both basal and GnRH $\alpha$  stimulated, are significantly higher in t.p. girls than in their peers. The concentrations of inhibin B, leptin, and IGF1 in t.p. patients are in between those of the prepubertal and pubertal periods. Visual examinations, such as pituitary gland MR and breast and pelvic ultrasound, are also useful in the differential diagnose of t.p. and other disorders of puberty. Spontaneous regression of t.p. occurs from six months to six years after establishing diagnosis in most girls. However, in 14% of cases, GnRH-dependent precocious puberty develops. Continued control of the clinical state and use of available diagnostic methods in each suspicious case is essential in the care of t.p. patients (**Adv Clin Exp Med 2007, 16, 2, 329–334**).

**Key words:** precocious thelarche, precocious puberty.

#### Streszczenie

Przedwczesnym izolowanym powiększeniem gruczołów piersiowych (*thelarche praecox*, t.p.) określa się rozwój tkanki gruczołowej u dziewcząt poniżej 8. roku życia, któremu nie towarzyszą objawy układowego działania estrogenów. T.p. jest obserwowane najczęściej w pierwszych 2.–3. latach życia. Czynniki etniczne i żywieniowe mają wpływ na częstość występowania t.p. Pojawienie się t.p. jest związane z oddziaływaniem czynników endo- i egzogennych. Wczesne stadium aktywacji osi podwzgórzowo-przysadkowo-gonadalnej, aktywujące mutacje genu *GNAS1*, polimorfizm receptora FSH to najczęściej wymieniane wewnątrzpochodne przyczyny t.p. Estrogenopodobne działanie dioksyn, furanów, organohalogenów, ftalatów jest uważane za powód występowania i okresowego nasilenia częstości t.p. w niektórych rejonach geograficznych. Pacjentki z t.p. mają istotnie większe od rówieśniczek stężenie FSH zarówno w warunkach podstawowych, jak i po stymulacji analogiem GnRH. Stężenia inhibiny, leptyny i IGF1 u dziewcząt z t.p. zajmują pozycję pośrednią między okresem przedpokwitaniowym i pokwitaniowym. Pomocne w różnicowaniu t.p. z innymi zaburzeniami dojrzewania są badania obrazowe: MR przysadki mózgowej, USG piersi i miednicy małej. Samoistna regresja t.p. u większości dziewcząt następuje w okresie od 6 miesięcy do 6 lat od rozpoznania, ale w 14% przypadków dochodzi do rozwoju GnRH-zależnego przedwczesnego dojrzewania płciowego. Okresowa ocena stanu klinicznego z wykorzystaniem dostępnych metod diagnostycznych w każdym niepokojącym przypadku jest niezbędna w opiece nad pacjentkami z t.p. (**Adv Clin Exp Med 2007, 16, 2, 329–334**).

**Słowa kluczowe:** przedwczesne powiększenie gruczołów piersiowych, przedwczesne dojrzewanie.

The development of glandular tissue observed in girls younger than eight years of age which is not accompanied by accelerated growth, advanced skeletal age, or other sexual maturation character-

istics is described as precocious thelarche (*thelarche praecox*, t.p.). The size of the mammary glands in t.p. rarely exceeds stage 3 of development according to Tanner. In some reports, the age

limit for t.p. is set at below 3 years, while t.p. variants are mentioned in cases of older girls [1, 2]. Such classification results from a tendency towards self-limitation of the symptoms in younger girls and less frequent t.p. progression to precocious puberty [3]. In the case of older children before puberty, periodic enlargement of the mammary glands is observed more frequently as well as a tendency towards precocious or accelerated sexual maturation [4]. In 85% of t.p. cases, symptoms occur during the first two to three years of life, while in 30% of girls they are observed from birth [5].

Isolated mammary gland enlargement accompanied by symptoms of systemic estrogen effects, such as growth or skeletal age acceleration, however without a tendency to earlier puberty, is described by the term “exaggerated thelarche” in English-language scientific literature in contrast to the classical form of t.p. [6]. Stanhope et al. described a variant of precocious thelarche in which the symptoms occur in cycles, while clinical condition, hormonal test results, and ultrasound imaging of the ovaries constitute a staging post between t.p. and precocious puberty [7]. Therapy with GnRH analog is completely ineffective in this variant.

The incidence of t.p. differs significantly depending on the ethnic origin of the examined patients. This is difficult to determine because epidemiological studies are conducted on various age groups. Among Lithuanian girls over seven years of age, only 0.4% were diagnosed with t.p. [8], while analysis of the first puberty symptoms in a group of Chilean girls confirmed the presence of t.p. in 16% of the same age group [9]. However, obesity was observed much more frequently among the Chileans, which could have influenced the frequency of t.p. cases.

Girls with t.p. constitute 18–20% of all children referred to endocrinological clinics because of precocious puberty [10, 11]. However, Kaplovitz defines t.p. as a symptom occurring in children younger than three years of age, while in older girls, 9% in total, he suggests using the term “early non-defined mammary gland development” [11]. The Lawson Wilkins Pediatric Endocrine Society recommends reduction of the t.p. age to seven years for the population of Caucasian girls and to six years for Afro-American girls [11]. The recommendation was based on an analysis of examinations of 17,077 girls 3 to 12 years of age living in the USA who were evaluated with regard to the moment of the occurrence of secondary sexual characteristics [12]. These recommendations, however, aroused controversy since an age reduction of the examined girls could delay the diagno-

sis of many serious diseases in which t.p. might be the first symptom [13]. The more frequent t.p. incidence in the American population is related not only to greater ethnic differentiation, but also the quality of nutrition.

A coincidence with primary hypothyroidism is the best known of the disease entities in which t.p. might occur. A high TSH concentration exerts an FSH-like receptor effect, inducing the development of the mammary glands [14]. Sharma diagnosed t.p. in 50% of girls with hypothyroidism, while ovarian cysts were present in 100% of the same group and genital hemorrhages in 90% [15]. Compensation of thyroid gland function usually leads to the withdrawal of puberty symptoms. T.p. has also been described in cases of chromosome 12 trisomy with cellular mosaicism, where growth hormone deficiency, precocious mammary gland enlargement, and hypertrophy of the right ovary have also been found [16]. T.p. coincidence with type I [17] neurofibromatosis, Coffin-Siris syndrome [18], Angelman syndrome [19], Rubinstein-Taybi syndrome [20], family hyperestrogenism related to CYP19 anomalies and increased aromatization [21], as well as gonadic dysgenesis [22] is also known.

Early development of mammary glands might be the first signal of pseudo-puberty, for example a tumor originating from ovarian granule cells [23]. This occurs when the tumor manifests before physiological puberty, while menstruation disorders, virilization, and abdominal pains dominate during the later period. The low malignancy of the tumor, with lesions limited to an ovary, means that surgical treatment is usually efficient. In more advanced disease stages, prognosis is uncertain, despite chemotherapy [23].

Both endogenous and exogenous factors are responsible for t.p. incidence. T.p. might constitute the earliest stage of hypothalamic-pituitary-ovarian axis activation and lead to precocious puberty development [5, 24]. Increased FSH secretion, especially during the night, has been observed; however, it was impossible to find increased activity of the hypothalamus with regard to LH secretion [5, 6, 24]. It is thought that t.p. might be a symptom of an increased sensitivity of mammary gland tissue to normal estrogen concentrations [6]. This opinion is contradicted, however, by higher estradiol and inhibin concentrations, which suggest increased hormonal function of the ovaries in t.p. [25, 26].

*GNAS1* gene-activating mutations, present in McCune-Albright syndrome and pituitary or thyroid gland tumors, might also be responsible for t.p. symptoms. While examining 23 patients with periodically occurring or strongly manifested t.p., Roman et al. found arginine substitution by histi-

dine (Arg201His) in 201 codon in 6 cases [27]. Other authors did not confirm the presence of this mutation or activating mutations of FSH receptor in a t.p. group [28]. All patients of the group examined by Hannon et al. had diagnosed FSH receptor Ser680Asn and Ala307Thr polymorphism [28].

T.p. could also be induced by chemical substances, including estrogens and estrogen-like products contained in animal fodder, chemicals used in industry and agriculture, and as natural phytoestrogens present in plants [29, 30, 31]. Dioxins, furans, and organic halogens are among the compounds most frequently mentioned as those disrupting the functions of the hypothalamic-pituitary-ovarian axis. Until around 1990 their main source were incinerating plants of communal waste and chlorine-organic plant protection chemicals. Changes in environmental protection regulations eliminated their use. It is thought that these compounds currently penetrate our environment through uncontrolled waste incineration in household furnaces, while meadow burning promotes their accumulation in the soil. Most of these substances are stored by fat tissue of animals and humans. Local t.p. "epidemics" are undoubtedly related to the organism's exposure to these exogenous substances, which are called "endocrine disrupters" in the English-language literature [30]. During the 1970s and 80s, a dramatic increase in precocious puberty and t.p. was noted in Puerto Rico which was attributed to the use of chemicals in the agricultural industry. T.p. constituted 70.5% of 2716 cases of precocious puberty noted thanks to the introduction of a national register in 1989. Puerto Rico has thus the highest t.p. incidence index ever observed in the world [31]. Another threat are vinyl packaging materials and foils containing phthalates used for packaging food. A higher concentration of phthalates, and especially diethylhexylphthalates (DEHP), in the blood plasma of 41 girls with t.p. than in 35 of their peers (450 ppb (ng/ml) vs. 70 ppb) was confirmed by Colon et al. [31]. However, the probability of such high blood concentrations of these compounds is being questioned by other authors [32].

T.p. symptoms are limited exclusively to mammary glands. Their development usually does not exceed stage 3 of Tanner. Glandular tissue is located concentrically around the nipple and its consistency is more or less compact, without palpable nodules. The areola is not hyperchromatic. Asymmetrical gland development or only one-sided enlargement are found quite frequently. The presence of pubic hair or change in sweat odor are not observed. The girls are usually characterized by normal height and body mass, but there are reports of growth acceleration to be found in literature [5].

Measuring gonadotrophin concentrations is important in t.p. diagnostics. Basic FSH concentrations are significantly higher than those found before puberty and are closer to the values observed in girls during puberty. The LH level remains low, significantly lower than that found after the beginning of puberty [5]. It is commonly known that gonadotrophins are secreted by the pituitary gland in a pulsating manner and a single assay of blood plasma does not always reflect their maximal secretion.

It is often necessary to conduct a test with GnRH analog administered intravenously at a dose of 2.5 µg/kg of body mass, but not exceeding 100 µg. An LH level of over 5 mIU/ml, after stimulation, is regarded as puberty response [33, 34]. An increased release of FSH is observed in t.p. patients in this test [5, 6, 24]. One must remember, however, that gonadotrophin release in infants and children younger than two years of age is higher after stimulation, and thus the LH/FSH ratio, which should not exceed 1 in the case of t.p., is decisive. Zevenhuizen proposed application of a test with a low GnRH dose of 10 µg for differentiating puberty disorders. This test also gave a lower maximal value of the LH/FSH ratio in the case of t.p. than for GnRH-dependant precocious puberty [35].

Estradiol assayed with commercial methods is not useful for the differential diagnostics of t.p. Only the use of ultrasensitive technology revealed significantly higher concentrations of this hormone in blood plasma of girls with t.p. compared with a control group of prepubertal patient [36]. On the other hand, an assay of inhibin B might be a helpful test. This glycoprotein is produced under the influence of FSH by granular cells in small antral follicles. It plays a paracrine role in stimulating androgen synthesis by thecal cells, thus indirectly influencing estradiol production. Higher inhibin B concentration is found during the first three months of life, which indicates an early activation of the hypothalamic-pituitary-ovarian axis. In contrast to estradiol, it is usually found in blood plasma during pre-puberty, correlating positively with FSH level [37]. It is regarded as a marker of follicle growth and granular cell proliferation marker as well as of their production of estradiol. In a study by Crofton et al., inhibin B level was higher in girls with t.p. than in their peers with no puberty characteristics and reached similar values to those during the second stage of physiological puberty or precocious sexual maturation, correlating with FSH concentration [37].

Leptin and IGF-I constitute two peripheral signals connecting metabolic body condition with the hypothalamic pulse generator. They play an important role in sexual development and meta-

bolic disorders. A sudden increase in free leptin index and free IGF-I between the first and the second puberty stage according to Tanner might influence the beginning of puberty, including mammary gland development [38]. IGF-I level and IGF-I/IGFBP-3 ratio in girls with t.p. reaches an intermediate value between that of the prepubertal period and that found in precocious puberty of central origin [39].

Skeletal age evaluation is useful in the differential diagnosis between t.p. and precocious puberty, when acceleration of epiphyses ossification takes place [10]. Some authors have also found acceleration of skeleton development in obese girls without activation of the hypothalamic-pituitary axis [40]. In contrast to precocious puberty, where an increased length of the pituitary gland has been found in MR imaging, no change in its size has been observed in t.p. [41]. Ultrasound evaluation of the small pelvis includes uterine length, its cross-wise dimension, endometrium thickness, length of its body and cervix, and their ratio. Measurement of length, width and height, number of follicles, as well as the maximal diameter of the largest follicle is conducted with regard to the ovaries. Uterine and ovarian growth during puberty correlated with age and the degree of maturation [42]. In t.p., no uterine enlargement or endometrium echo, which are found in central precocious puberty, are detected. Herter et al. determined ultrasound value limits suggesting the beginning of puberty: uterine length above 4 cm, volume 3 cm<sup>3</sup>, and ovarian volume of 1 cm<sup>3</sup> [42]. Ovarian volume in girls with t.p. is similar to that of their peers with no puberty characteristics; however, the structure of gonads is not homogenous, with developing follicles present [26, 43]. The number of ovarian follicles as well as the size of the dominant follicle was similar in the

groups of girls with t.p. and precocious puberty examined by Vries et al. [34].

While differentiating t.p., one should bear in mind other changes in the mammary glands which might take place even at a very young age, such as extra-areolar cysts, adenofibromas, leukemic metastases, as well as metastatic lesions of other neoplastic diseases, especially sarcoma, lymphoma, and neuroblastoma. The clinical picture might be similar to that described in t.p., but one-sided enlargement of a mammary gland is more frequent. Ultrasound examination of the breasts is helpful in evaluating changes in glandular changes and its vascularization [44].

The most frequently recommended action in girls with t.p. is long-term observation. In most cases, spontaneous regression of mammary gland development takes place, occurring within a period from 6 months to 6 years from diagnosis. The glands remain enlarged until puberty in about 10% of patients. So far, studies have not confirmed a negative influence of t.p. on general health and the development of patients or their subsequent fertility. Girls with t.p. menstruate earlier than others, but the first menstruation age is consistent with their mothers' age at menarche [2]. Their final height does not differ from that of other girls and frequently exceeds that of their parents [2]. However, one must remember that t.p. is not always a benign condition not requiring therapeutic intervention, since in some 14% of the girls a progression towards GnRH-dependant precocious puberty occurs [4]. T.p. might also be a symptom of other serious diseases and for this reason a periodic evaluation of clinical condition using available diagnostic methods in each suspicious case is very important with regard to the medical care of the t.p. patient.

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