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REVIEW ARTICLE

Premature Thelarche: An Updated Review

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Abstract: ***Background*:** Premature thelarche is the most common pubertal disorder in girls. The condition should be differentiated from central precocious puberty which may result in early epiphyseal fusion and reduced adult height, necessitating treatment.

***Objectives*:** The purpose of this article is to familiarize physicians with the clinical manifestations of premature thelarche and laboratory tests that may help distinguish premature thelarche from central precocious puberty.

Methods: A search was conducted in September 2022 in PubMed Clinical Queries using the key term "Premature thelarche". The search strategy included all clinical trials, observational studies, and reviews published within the past 10 years. Only papers published in the English literature were included in this review. The information retrieved from the above search was used to compile the present article.

Results: Premature thelarche denotes isolated breast development before the age of 8 years in girls who do not manifest other signs of pubertal development. The condition is especially prevalent during the first two years of life. The majority of cases of premature thelarche are idiopathic. The condition may result from an unsuppressed hypothalamic-pituitary-gonadal axis in the early years of life, an "overactivation" of the hypothalamic-pituitary axis in early childhood secondary to altered sensitivity to steroids of the hypothalamic receptors controlling sexual maturation, increased circulating free estradiol, increased sensitivity of breast tissue to estrogens, and exposure to exogenous estrogens. The cardinal feature of premature thelarche is breast development which occurs without additional signs of pubertal development in girls under 8 years of age. The enlargement may involve only one breast, both breasts asymmetrically, or both breasts symmetrically. The breast size may fluctuate cyclically. The enlarged breast tissue may be transiently tender. There should be no significant changes in the nipples or areolae and no pubic or axillary hair. The vulva, labia majora, labia minora, and vagina remain prepubertal. Affected girls have a childlike body habitus and do not have mature contours. They are of average height and weight. Growth and osseous maturation, the onset of puberty and menarche, and the pattern of adolescent sexual development remain normal. Most cases of premature thelarche can be diagnosed on clinical grounds. Laboratory tests are seldom indicated. No single test can reliably differentiate premature thelarche from precocious puberty.

Conclusion: Premature thelarche is benign, and no therapy is necessary apart from parental reassurance. As enlargement of breasts may be the first sign of central precocious puberty, a prolonged follow-up period every 3 to 6 months with close monitoring of other pubertal events and linear growth is indicated in all instances.

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1. INTRODUCTION

Thelarche is derived from the Greek word thëlë, meaning nipples, and archë, meaning beginning, and can be loosely translated to "beginning of the breasts at puberty". The term "premature thelarche" was coined by Wilkins in 1957 to denote isolated breast development before the age of eight years in girls who do not manifest other signs of pubertal development [1-3]. Although the condition is benign, it may cause considerable parental concern. It is crucial to differentiate premature thelarche from precocious puberty, which

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may affect the menarcheal age and the final adult height and with possible psychological consequences [4]. The purpose of this communication is to familiarize readers with the clinical manifestations of premature thelarche, its natural course, and the need for regular follow-up to monitor other pubertal events and linear growth.

A search was conducted in September 2022 in PubMed Clinical Queries using the key term " Premature thelarche". The search strategy included all clinical trials, observational studies, and reviews published within the past 10 years. Only papers published in the English literature were included in this review. The information retrieved from the above search was used to compile the present article.

2. EPIDEMIOLOGY

Premature thelarche is the most common pubertal disorder in girls [5]. The incidence of premature thelarche seems to be increasing [6]. The prevalence has been reported to range from 0.16% to 4.8% among girls in the first four years of life [7-10]. The wide variation in the reported prevalence rates can be accounted for, at least in part, by the age and ethnic background of the studied population, methods used for the diagnosis (history *versus* physical examination), whether the diagnosis was based on observation *versus* palpation of the enlarged breast tissue, the experience of the physician (at times, it is challenging to discriminate fatty tissue from subareolar glandular tissue in an obese girl), and prospective studies *versus* retrospective reviews of medical records. A prospective population-based cohort study of 3,140 girls in Sweden showed a prevalence of premature thelarche of 0.16% in girls at 18 months of age [8]. In one study of 695 healthy girls under four years of age sampled by a stratified cluster random sampling method from eight provinces in China, premature thelarche was found in 15 (2.2%) girls [9]. In another study of 318 girls between 12 and 48 months of age seen in a large Midwestern city in the United States, the overall prevalence of premature thelarche was 4.7% [7]. The peak prevalence by race and ethnicity was 4.2% among white non-Hispanics, 4.6% among Blacks, and 6.5% among white Hispanics [7]. In a cross-sectional study of 2,978 girls aged 2 to 7 years across 9 cities in Zhejiang province in China, 143 girls were diagnosed with premature thelarche with a prevalence rate of 4.8% [10]. Of the 143 girls, 100 (70%) were diagnosed with premature thelarche before the age of 2 years [10]. There is a bimodal age distribution with one peak during the first two years of life (most common) and another peak between six and eight years of age [5, 11]. A higher frequency of premature thelarche is observed in the African American and Mexican populations than in the white population [2, 12, 13]. In a cross-sectional study of 17,077 girls aged three years conducted by 225 paediatricians belonging to Pediatric Research in Office Settings, a practice-based research network in the United States, 2.1% of African American girls and 0.7% of white girls were found to have premature thelarche [12]. Some investigators advocate using a lower age limit of seven years as a diagnostic criterion for African American and Mexican girls [14].

3. ETIOPATHOGENESIS

On average, thelarche occurs between the ages of 8 and 13 years. The exact etiopathogenesis of premature thelarche is still not completely understood, although different pathogenetic mechanisms have been suggested. An unsuppressed hypothalamic-pituitary-gonadal axis in the early years of life may account for premature thelarche in very young girls [2, 15, 16]. Premature thelarche may also be the result of transient partial activation of the hypothalamic-pituitary-gonadal axis in early childhood secondary to altered sensitivity to steroids of the hypothalamic receptors controlling sexual maturation with resultant excessive secretion of follicle-stimulating hormone (FSH) [17]. The excessive FSH causes transient estrogen secretion by the follicular cysts of the ovaries and increased production of adrenal androgens (*e.g.*, dehydroepiandrosterone [DHEA], DHEA sulphate) from the zona reticularis [2, 15, 18]. The increased adrenal androgens may serve as precursors for the peripheral conversion to estrogens [2]. Patients with premature thelarche have a predominance of FSH over luteinizing hormone (LH) secretion [2].

It has been postulated that premature thelarche is associated with enhanced follicular development in the ovary, possibly under the influence of FSH [19]. Under the influence of FSH, inhibin B is produced by granulosa cells of the ovulatory follicles. The inhibin B produced has a paracrine role in estrogen production [19].

Increased circulating free estradiol has been proposed as an etiologic factor [20]. The mechanism (s) for the increased free estradiol levels is not known but could include decreased sex hormone binding globulin or increased estradiol secretion as a result of increased ovarian response to FSH [2, 15, 21]. Increased sensitivity of breast tissue to the low levels of estrogens secreted during early childhood has also been postulated as a cause of premature breast development [15, 22, 23]. Some investigators suggest that premature thelarche may be due to the precocious secretion of adrenal androgens which are converted to estrogens by the breast tissue [24].

The majority of cases of premature thelarche are idiopathic [25, 26]. Premature thelarche may result from exposure to exogenous estrogens, either indirectly through the nursing mother or directly through consumption of phytoestrogen or estrogen-containing or -contaminated foods [27-30]. Beef from cattle fattened with subcutaneous estrogen pellets is a source of exogenous estrogen [28, 30]. Also, premature thelarche may result from prolonged use of estrogen-containing lotion or cream [31].

Exposure to estrogenic environmental pollutants is a potential cause of premature thelarche [32, 33]. Estrogenic environmental pollutants are universally present in the form of substances naturally present in cereals and plants, hormones used in stockbreeding, and chemicals (bisphenol A [BPA] - used to harden plastics and phthalates - used to make plastics soft and durable; polybrominated diphenyl ethers [PBDEs] and polybrominated biphenyls [PBBs] - used as flame

retardants; chlorophenol thane [DDT], polychlorinated ketone, dioxin, imidacloprid, glyphosate, methoxychlor, and chlorpyrifos - contained in some pesticides or herbicides) employed in agriculture and industry [32-43]. However, there is a lack of conclusive data and more research is needed in these areas.

Non-estrogen-containing drugs associated with premature thelarche include spironolactone, digitalis, cimetidine, risperidone, marijuana, and phenothiazines [44, 45]. The underlying mechanism is not known. Also, there is a lack of definitive evidence of these associations.

Premature thelarche has been reported following chronic consumption of herbal medicine, *Foeniculum vulgare* (sweet cumin, fennel, Fenchel) [21, 46]. *Foeniculum vulgare* is a plant known for its calming and gas-eliminating effects and is widely used in many countries such as Turkey, China, India, and Egypt to regulate bowel movements and eliminate gas pain in children [21]. The plant is available in pharmacies in granulated form as an organic tea, and it can also be directly consumed after it has been boiled [21]. Thus far, evidence of *Foeniculum vulgare* as a cause of premature thelarche has been limited to case reports.

In vitro, studies showed that lavender essential oil extracted from *Lavandula* spp. and tea tree essential oil extracted from *Melaleuca alternifolia* have weak estrogenic or anti-androgenic activities due to the phytochemicals that they contain [47]. The phytochemicals implicated include linalool, α-terpineol, and 4-terpinenol [48]. However, reports that chronic exposure to these oils resulting in premature thelarche are conflicting [49-52]. A systematic review of eleven case reports showed that lavender essential oil has no estrogenic effect and that chronic exposure to lavender essential oil or tea tree essential oil would not lead to premature thelarche [53]. Because of the scarcity of available data, the lack of evidence of harm cannot be interpreted as evidence of safety [53]. Epidemiological studies are necessary to confirm or refute the association between chronic exposure to lavender essential oil or tea tree essential oil and premature thelarche.

Studies have shown that girls with excessive body mass index (BMI) have a higher prevalence of premature thelarche [13, 54]. It has been suggested that a subset of girls is sensitive to an earlier onset of thelarche due to increased adipose tissue [13]. The situation can be compounded by the fact that adipomastia may be mistaken as glandular breast tissue. Early onset of menarche in the mother is another risk factor [54].

Xu *et al*. analyzed the nutrient intake, insulin resistance and lipid profiles of 262 Chinese girls with premature thelarche and 222 healthy girls (recruited as the control group) [55]. The authors found that premature thelarche is correlated with high intakes of fat and protein, high BMI, altered lipid profiles (elevated serum triacylglycerol, total cholesterol, and low-density lipoprotein levels) and elevated potential to develop insulin resistance [55]. These preliminary findings need to be confirmed or refuted by well-designed, large-scale studies in future.

Although the occurrence of premature thelarche is usually sporadic, several familial cases have also been reported [3, 20]. Some girls with premature thelarche may have an activating mutation in the guanine nucleotide-binding protein, alpha stimulating 1 (*GNAS1*) gene, which codes for a subunit of G stimulating protein, without other classical signs of McCune-Albright syndrome [2, 34, 56].

4. CLINICAL MANIFESTATIONS

The cardinal feature of premature thelarche is breast development which occurs without additional signs of pubertal development in girls under 8 years of age. Signs of pubertal development include a growth spurt, pubic and/or axillary hair development, and menarche [55].

The enlargement may involve only one breast, both breasts asymmetrically or symmetrically (Figs. **1** and **2**) [2, 3, 20, 55]. Typically, breast enlargement does not proceed beyond Tanner stage III if the breast enlargement is bilateral [5, 23, 55]. On the other hand, breast enlargement typically does not proceed beyond Tanner stage II if the enlargement is unilateral [5, 23, 55]. The breast size may fluctuate cyclically [54, 56]. The enlarged breast tissue may be tender, but this is usually transient. No significant changes in the nipples or areolae develop [3, 20].

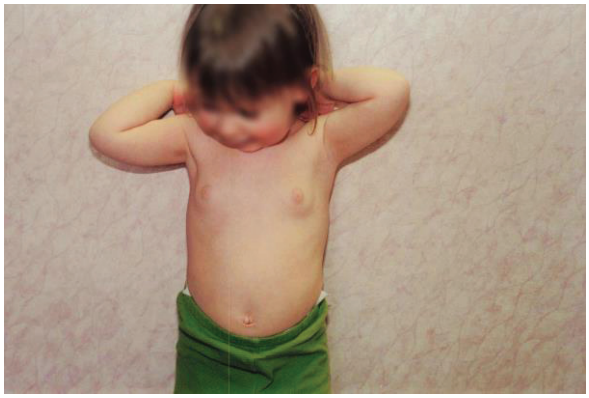

Fig. (1). Premature thelarche presenting as bilateral breast enlargement in a 16-month-old Caucasian girl. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

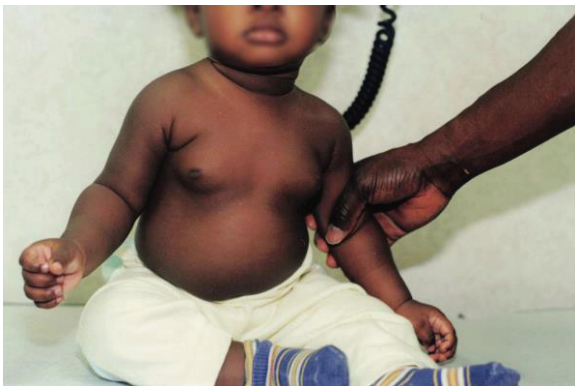

Fig. (2). Premature thelarche presenting as bilateral breast enlargement in a 12-month-old African American girl. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In girls with premature thelarche, the vulva, labia majora, labia minora, and vagina remain prepubertal [3, 20]. There is no pubic or axillary hair. The size of the uterus remains consistent with the child's chronological age [3, 20]. The body habitus is childlike and does not show mature contours. The onset of puberty and menarche and the pattern of adolescent sexual development remain normal [10, 57].

The majority of affected girls are of normal height and weight. Growth and osseous maturation are usually normal [58]. A subset of obese children with premature thelarche have advanced bone age [59]. In this regard, obesity is a possible cause of premature thelarche [54]. Obesity per se may account for the advanced bone age [60].

In most cases, premature thelarche is an isolated finding. However, premature thelarche can be an infrequent manifestation of Kabuki syndrome (short and depressed nose, long palpebral fissures with eversion of the lateral third of the lower eyelid, broad eyebrows, large and prominent or cupped ears, thinning of the upper lip and thickening of the lower lip, poor physical growth, scoliosis, hypotonia, developmental delay, and hypertrichosis) [61-68], Rubinstein-Taybi syndrome (low hanging columella, down slanting palpebral fissures, broad thumbs and great toes, short stature, intellectual deficit) [69-71], Coffin-Siris syndrome (coarse face with busy eyebrows, wide mouth, thick lips, sparse scalp hair, hypertrichosis, absent fifth fingernails and toenails, absent terminal phalanges of the fifth finger, growth retardation, prominent expressive language delays, intellectual deficit) [72, 73], Möbius syndrome (congenital facial nerve palsy, abducens nerve palsy, craniofacial malformation) [74, 75], Mayer-Rokitansky-Kuster-Hauser syndrome also known as Müllerian agenesis or aplasia (combined agenesis of the uterus, cervix and upper-two thirds of the vagina in a genotypic and phenotypic female, may have unilateral renal agenesis and cervicothoracic somite anomalies) [76], Torg-Winchester syndrome (nodular arthropathy, progressive osteolysis mainly affecting the carpal, tarsal, and interphalangeal joints) [77, 78], purine-rich element-binding protein A (PURA) syndrome (neonatal hypotonia, feeding difficulties, hypothermia, hypersomnolence, respiratory compromise, severe intellectual disability) [79-82], and duplication of the pituitary gland (DPG)-plus syndrome (duplication of the pituitary gland, agenesis or hypoplasia of the corpus callosum, hypothalamic mass, broad or duplicated sella turcica, hypertelorism, cleft palate, bifid tongue, oropharyngeal tumors [usually teratomas], and vertebral malformations) [83, 84].

5. CLINICAL EVALUATION

A detailed history and a complete physical examination are essential in evaluating girls with precocious breast development. A careful history should be taken for accidental estrogen administration, any recent growth spurt, a history of a previous central nervous system disorder, and a family history of early puberty.

The girl's weight and height should be taken and plotted on a growth chart. General body habitus should be noted, and the breasts should be examined to evaluate their development and the presence of increased pigmentation. Increased pigmentation of the external genitalia and development of the labia minora may indicate an early estrogenic effect. An abdominal examination should be performed to rule out an abdominal mass, and a neurologic and fundoscopic examination should be performed to rule out central nervous system pathology.

6. LABORATORY FINDINGS

With few exceptions, total serum estrone and estradiol concentrations in girls with premature thelarche are within the normal range for prepubertal girls [57, 85]. Laboratory tests are seldom indicated.

The mean basal serum FSH levels have been reported as normal or slightly elevated in girls with premature thelarche and are not significantly different from girls with central precocious puberty [3, 23]. On the other hand, girls with central precocious puberty have higher basal serum LH levels than premature thelarche [23]. Because of different cut-off values being used for basal FSH and LH levels, a luteinizing hormone-releasing hormone (LHRH) stimulation (100 μg as an intravenous bolus) should be performed if there is uncertainty about the diagnosis [86, 87]. Peak LH levels and LH/FSH ratio are significantly and constantly elevated in precocious puberty compared to premature thelarche after LHRH stimulation [2, 88]. With LHRH stimulation, a high LH value (> 4.29 IU/L) or a LH/FSH ratio of > 0.66 suggests precocious puberty [88, 89]. However, in girls under three years, a stimulated LH value of even 10 IU/L does not exclude premature thelarche, whereas a peak LH/FSH ratio < 0.43 suggests premature thelarche in girls of this age group [90]. A recent study showed that in addition to an elevated LH level, LHRH stimulation could lead to an elevation of the serum insulin-like growth factor-1 (IGF-1) and IgF binding protein-3 (IGFBP-3) levels [91]. The combined analysis of these data will improve the diagnostic accuracy of precocious puberty.

New markers for diagnosing premature thelarche and precocious puberty have been investigated. A recent study on 44 girls with premature thelarche and 33 age-matched healthy girls showed that serum leptin ($p < 0.001$), orexin-A ($p < 0.001$), and nesfatin-1 ($p < 0.001$) levels were significantly elevated in girls with premature thelarche as compared to healthy girls [92]. The elevated serum leptin and nesfatin-1 levels in girls (including non-obese girls) with premature thelarche have been substantiated in other studies [93, 94]. These studies suggest a permissive role of leptin, orexin-A, and nesfatin-1 in initiating premature thelarche. Anti-Müllerian hormone (AMH) is produced by the granulosa cells of primary, prenatal, and early antral follicles and may play a role in suppressing puberty [95, 96]. It has been shown that the mean AMH levels of girls with precocious puberty are significantly lower than those in girls with premature thelarche and healthy age-matched girls [97, 98]. Also, girls with premature thelarche have lower mean AMH levels compared to healthy age-matched girls [96]. These data need to be validated by future, well-designed, large-scale studies before they can be used to differentiate premature thelarche

from precocious puberty. Other markers under investigation for the diagnosis of premature thelarche and precocious puberty include serum neurokinin B [99, 100], irisin [101], and kisspeptin [102, 103]. Thus far, none of these markers can reliably differentiate girls with premature thelarche from central precocious puberty.

Breast ultrasound may be useful in evaluating sexual development with respect to breast bud diameter and breast masses in girls [104, 105]. However, its ability to distinguish premature thelarche from precocious puberty is very limited [104, 105].

Girls with premature thelarche usually have a bone age consistent with chronological age [23, 57]. In contrast, girls with precocious puberty usually have an advanced bone age [23].

Pelvic ultrasound is not indicated in the majority of cases but, if performed, may show ovarian and uterine volumes in the prepubertal range in girls with premature thelarche [23]. A 2021 meta-analysis of 13 studies (n = 1,977) showed that the standardized mean differences (95% confidence interval [CI]) in ovarian volume, fundal-cervical ratio, uterine length, uterine cross-sectional area, and uterine volume between girls with precocious puberty and girls with premature thelarche were 1.12 (0.78 to 1.45; p <0.01), 0.90 (0.07 to 1.73; p = 0.03), 1.38 (0.99 to 1.78; p < 0.01), 1.06 (0.61 to 1.50; p < 0.01), and 1.21 (0.84 to 1.58; p < 0.01), respectively [106]. A uterine length of 3.2 cm yielded a pooled sensitivity of 81.8% (95% CI 78.3 to 84.9%), specificity of 82% (95% CI 61 to 93%), positive likelihood ratio of 4.56 (95% CI 2.15 to 9.69), negative likelihood ratio of 0.26 (95% CI 0.17 to 0.39), and diagnostic odds ratio of 19.62 (95% CI 6.45 to 59.68) [106]. Thus, pelvic ultrasound may serve as a complementary tool to aid in differentiating premature thelarche from central precocious puberty [106-108].

7. DIAGNOSIS

Most cases of premature thelarche can be diagnosed on clinical grounds, based on the age of onset (less than two years of age for the majority of cases), stage of breast development (typically does not proceed beyond Tanner stage 3 if the breast enlargement is bilateral and does not proceed beyond Tanner stage 2 if the breast enlargement is unilateral), absence of signs of puberty (*e.g.*, pubic or axillary hair development, menarche, growth spurt), and childlike body habitus. Laboratory testing is usually unnecessary unless there are red flags based on the growth rate and findings on physical examination (*e.g.*, growth spurt, pubertal progression) [109]. Thus far, no single test can reliably differentiate premature thelarche from precocious puberty, nor can tests accurately predict which girls with premature thelarche are at risk of developing precocious puberty [23]. This is because there is considerable overlap in the expected values of the laboratory tests in these two conditions [23].

8. DIFFERENTIAL DIAGNOSIS

Premature thelarche must be differentiated from neonatal hyperplasia of the breast, which can occur in either sex and generally subsides spontaneously within a few weeks or months. In some cases, the hyperplasia of the breast may persist. Premature thelarche must also be differentiated from precocious puberty. In girls, precocious puberty is traditionally defined as the onset of secondary sexual characteristics before the age of eight years. Typical findings in girls with precocious puberty include rapid linear growth, feminine body contours, progressive breast, pubic hair, axillary hair development, and advanced bone age [4]. Based upon the underlying pathologic process, precocious puberty can be classified as central precocious puberty (also known as gonadotropin-dependent precocious puberty or true precocious puberty), peripheral precocious puberty (also known as gonadotropin-independent precocious puberty or peripheral precocity), and nonprogressive or intermittent progressive precocious puberty. Central precocious puberty is caused by early maturation of the hypothalamic-pituitary-gonadal axis. Peripheral precocious puberty is sexual precocity secondary to autonomous gonadal or adrenal sex hormone secretion, iatrogenic administration of sex hormones, or ectopic gonadotropin production [4, 110]. Nonprogressive or intermittent progressive precocious puberty is caused by early hypothalamic-pituitary-adrenal axis activation. Girls with nonprogressive or intermittent progressive precocious puberty have clinical features of both gonadarche (breast development) and pubarche (pubic and/or axillary hair) but have either no progression or intermittent slow progression in these pubertal signs [25, 111].

Other differential diagnoses include adipose breast tissue in obese children, fibroadenoma, fibrocystic disease of the breast, and neurofibroma of the chest wall [104, 112].

9. MANAGEMENT

As the condition is benign and self-limited, no therapy is necessary apart from parental reassurance. As enlargement of breasts may be the first sign of central precocious puberty, a prolonged follow-up period every 3 to 6 months with close monitoring for other pubertal events and linear growth is indicated in these patients [20, 23, 113]. Although increased growth velocity increases the risk of central precocious puberty, the clinical use of increased growth velocity to differentiate premature thelarche from central precocious puberty is still an open-ended question [114]. Radiologic and laboratory testing should be reserved for selected patients.

10. PROGNOSIS

The prognosis is good. Puberty and menarche usually occur at a normal age [115, 116]. Most cases regress spontaneously [25]. Some cases persist unchanged in size, show a cyclic pattern, or have progressive development of breast tissue [117-120]. In one study of 124 girls with premature thelarche who had follow-ups (mean duration 6.5 ± 3.5 years, range 1 to 13.7 years), 63 (50.9%) girls had regression of the breast tissue, 45 (36.3%) girls had persistent breast tissue, 12 (9.7%) girls had a cyclic pattern, and 4 (3.2%) girls had a progressive pattern [5]. A cyclic or progressive course was more prevalent in girls with premature thelarche

presenting after two years of age compared to those girls with premature thelarche presenting before two years of age [5]. Other authors have found that the age of onset does not predict whether breast tissue will regress, persist, or progress [115, 121]. A retrospective review of medical charts of 158 girls with premature thelarche followed up in a pediatric endocrinology clinic showed that girls with a higher BMI and BMI-standard deviation score (BMI-SDS) were more likely to develop rapidly progressive puberty [122]. The authors of the study suggested that an increase in body weight could stimulate rapidly progressive puberty in girls with premature thelarche.

CONCLUSION

Premature thelarche is a benign condition characterized by isolated breast development before the age of eight years in girls, unaccompanied by accelerated growth velocity, bone age advancement or other signs of pubertal development. Treatment is not necessary apart from reassurance which may help alleviate parental anxiety. It is not always easy to distinguish premature thelarche from precocious puberty. Thus far, no single test can reliably differentiate premature thelarche from precocious puberty. As well, none of these tests can accurately predict which girls with premature thelarche are at risk of developing precocious puberty. As such, laboratory findings should be evaluated together with clinical findings. As enlargement of breasts may be the first sign of central precocious puberty and the fact that some girls with premature thelarche may later progress to central precocious puberty, a prolonged period of follow-up with close monitoring of other pubertal events and linear growth is indicated in all instances.

AUTHORS' CONTRIBUTIONS

Professor Alexander K.C. Leung is the principal author. Dr. Joseph M. Lam and Professor Kam Lun Hon are coauthors. All the authors contributed to drafting and revising the manuscript and approved the final version submitted for publication.

LIST OF ABBREVIATIONS

AMH = Anti-Müllerian Hormone

BMI = Excessive Body Mass Index

BMI-SDS = BMI-Standard Deviation Score

BPA = Bisphenol A

CI = Confidence Interval

DDT = Chlorophenothane

DHEA = Dehydroepiandrosterone

DPG = Duplication of the Pituitary Gland

FSH = Follicle-Stimulating Hormone

GNAS1 = Guanine Nucleotide Binding Protein, Alpha Stimulating 1

IGF-1 = Insulin-like Growth Factor-1

IGFBP-3 = IgF Binding Protein-3

LH = Luteinizing Hormone

LHRH = Luteinizing Hormone-releasing Hormone

PBBs = Polybrominated Biphenyls

PBDEs = Polybrominated Diphenyl Ethers

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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