

EPIDEMIOLOGY

Natural History and Incidence of Premature Thelarche in Puerto Rican Girls Aged 6 Months to 8 Years Diagnosed Between 1990 and 1995

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Objective. To describe the natural history and estimate the incidence of premature thelarche in girls aged 6 months to 8 years living in Puerto Rico and diagnosed between 1990 and 1995.

Background. In the 1970s and 1980s, several pediatric endocrinologists, based on their clinical experience, acknowledged a dramatic increase in the number of cases of precocious sexual development in Puerto Rico. In 1987, the Puerto Rico Health Department developed the Registry of Premature Thelarche and Precocious Sexual Development, which began to operate in 1989. Data regarding the long-term outcomes of girls diagnosed with premature thelarche are insufficient. Knowledge about the natural history of this condition is relevant for predicting the long-term prognosis and therapeutic management of the affected population.

Methods. Of 2,716 cases of precocious sexual development reported to the Premature Thelarche and Precocious Sexual Development Registry, 1,916 (70.5%)

were premature thelarche. The clinical characteristics and evolution during follow-up of premature thelarche cases were described and compared by age group at diagnosis.

Results. Incidences were 6.2 and 1.62 per 1,000 live births for girls aged <2 years and 2 to 8 years, respectively. These estimates were 10 and 15 times higher than those reported in Olmsted, MN. When the average change in mammary tissue diameter during follow-up was evaluated, a slight reduction in girls aged <2 years was observed; however, it remained constant for girls aged 2 to 8 years.

Conclusions. The results of this study underscore the need to continue an active search of premature thelarche cases and to perform analytical investigations of precocious sexual development to expand the understanding of the etiology of this important public health problem.

Key words: Premature thelarche, Precocious sexual development, Natural history, Incidence, Puerto Rico

Precocious sexual development is a condition characterized by the occurrence of puberal changes before the age of eight years in girls and nine years in boys (1-4). Premature thelarche is an incomplete form of precocious sexual development, which is defined as the development of isolated breast tissue in girls between 6 months and 8 years of age. The etiology of this condition remains unknown; however, epidemiologic studies have associated endogenous and

exogenous factors to the development of premature thelarche including the ingestion of exogenous estrogens and frequency of ovarian microcysts (5).

In the 1970s and 1980s, several pediatric endocrinologists, based on their clinical experience, acknowledged a dramatic increase in the number of cases of precocious sexual development in Puerto Rico (5-9). In 1982, approximately 1,000 cases of precocious sexual development had been reported in the island, of which, premature thelarche was the predominant manifestation. The greater frequency was observed in girls aged 6 months to < 2 years of age (8). A hypothesis that linked the high incidence of precocious sexual development to estrogen-contaminated food led to a prompt epidemiologic investigation by CDC officials and the University of Puerto Rico Medical Sciences Campus. The results of this investigation included a positive association with maternal ovarian cysts and consumption of soy-based formula and various meat products; however, no association was

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observed for exposure to other substances with possible estrogenic effect (9). In 1987, the Puerto Rico Health Department developed the Registry of Premature Thelarche and Precocious Sexual Development, which began to operate in 1989. All cases diagnosed prior to this year were retrospectively identified from 1969. From 1969 to March 1997, a total of 6,190 cases had been identified and reported to the Registry (10). Of these, 71% corresponded to cases diagnosed with premature thelarche. The average cumulative incidence of premature thelarche in Puerto Rico between 1982 and 1989 in girls aged 6 months to 2 years was 4.8 per 1000 live births (11).

Studies regarding the natural history of premature thelarche suggest that it may accelerate the timing of puberty in some girls, whereas others have concluded that it is a benign condition with no other sign of pubertal development. There have been insufficient data regarding the long-term outcomes of girls diagnosed with premature thelarche. Knowledge about the natural history of this condition is relevant for predicting the long-term prognosis and therapeutic management of the affected population. Therefore, a descriptive study of premature thelarche was undertaken to understand the behavior of this condition in the Puerto Rican population. The specific aims of the study were to 1) describe the natural course of premature thelarche, 2) estimate the incidence of premature thelarche by birth cohort in girls aged 6 months through 8 years of age, 3) evaluate trends over time, and 4) compare clinical characteristics between girls diagnosed prior to the age of 2 and those diagnosed after 2 years of age.

Methods

All girls aged 6 months to < 8 years diagnosed with premature thelarche without other manifestation of precocious sexual development at the initial evaluation and reported to the Registry of Premature Thelarche and Precocious Sexual Development of the Puerto Rico Health Department between 1990 and 1995 were included in the study. The Registry gathers information regarding age at diagnosis, age of onset, sex, height, weight, municipality of residence, bone age, age when the first sign of precocious sexual development occurred, description of the physical findings, serum luteinizing hormone (LH) level, serum follicle stimulating hormone (FSH) level, serum estradiol level, mammary tissue diameter, right or left location of breast tissue, presence of pelvic ultrasound abnormalities and Tanner stage. In addition, family history of precocious sexual development, maternal history of ovarian cysts, maternal use of oral contraceptives before and during pregnancy, and maternal age at menarche are collected.

The results of laboratory tests of girls with premature thelarche were compared with normal values established for the pre-pubertal ages. To compare the clinical characteristics by age at diagnosis, Mann-Whitney-Wilcoxon test was used to compare quantitative variables that were not normally distributed whereas the chi-square test was used to compare qualitative variables. Incidence was estimated by birth cohort and age group. Rates were calculated using as denominators the total number of live births to mothers residing in Puerto Rico after excluding all deaths and diagnosed cases that occurred outside the study period. Among girls aged 6 months to < 2 years of age, the birth cohorts between 1988 and 1994 were used, whereas the birth cohorts between 1983 and 1987 were used for calculating the incidence in the 2 to < 8 age group. A Poisson regression model was used to evaluate the trend in the incidence rates of premature thelarche over time in each age group. All analyses were performed using the Statistical Analysis System, version 6.12 (12).

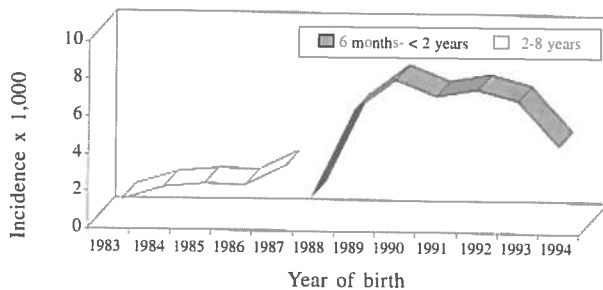
Results

A total of 2,716 cases of precocious sexual development were reported to the Registry between 1990 and 1995. Of these, 1,916 (70.5%) were girls with development of isolated breast tissue or premature thelarche and 190 (7%) of the cases were boys under age 9 presenting breast enlargement or gynecomastia. Cases of premature thelarche were reported in almost all (99%) municipalities of the island, excluding the island of Culebra, having the San Juan metropolitan area the largest number of cases.

During the study period, more than 250 cases were reported annually. The year that accounted for the largest number of cases was 1991 (387), whereas 1995 accounted for the least number of cases (271). The estimated incidence in girls aged 6 months to < 2 years between 1988 and 1994 was 6.2 per 1000 live births, being more pronounced for the 1990 birth cohort, with an incidence of 8.1 per 1000 live births (Figure 1). The estimated incidence in girls aged 2 to < 8 years between 1983 and 1987 was 1.6 per 1000 live births, with the highest incidence observed for the 1987 birth cohort, 2.65 per 1000 live births (Figure 1). A Poisson regression model revealed that the observed increment in the incidence over time in each group was statistically significant ($p < 0.0002$ and $p < 0.0001$, respectively).

The majority of cases (83.6%) had developed mammary tissue before 2 years of age. The age group with the largest percentage of cases was 6 to 12 months (28.5%) followed by newborns at birth (28.2%). The median age at the first observation of mammary tissue was 7 months (minimum, at birth; maximum, 94 months), whereas the

Figure 1. Incidence of Premature Thelarche by Age at Diagnosis, Puerto Rico, 1990-1995*



* Registry of Premature Thelarche and Precocious Sexual Development, Puerto Rico Health Department

median age at diagnosis was 17 months (minimum, 6 months; maximum, 95 months). The vast majority of cases (83.3%) had bilateral breast involvement (data not shown).

Table 1 shows the mean diameter in centimeters of breast tissue at the time of diagnosis. The mean diameter in centimeters ranged from 1.94 (0.92) for left vertical tissue to 2.31 (1.05) for right horizontal tissue. When the mean diameter of breast tissue was compared by age group, no significant differences were observed ($p > 0.05$) (data not shown).

Table 1. Average diameter of mammary tissue at time of diagnosis of premature thelarche, Puerto Rico, 1990-1995*

Mammary tissue	Mean (SD) diameter in cm.	Minimum and maximum diameter in cm.	
Left horizontal (n=1,645)	2.21 (1.03)	0.05, 8.00	
Left vertical (n=952)	1.94 (0.92)	0.50, 7.00	
Right horizontal (n=1,607)	2.31 (1.05)	0.35, 8.00	
Right vertical (n=943)	2.03 (0.94)	0.35, 8.00	

*Registry of Premature Thelarche and Precocious Sexual Development, Puerto Rico Health Department.

History of precocious sexual development in siblings, family history of ovarian cysts, and maternal use of oral contraceptives prior or during pregnancy were similar in cases diagnosed prior to age 2 and those diagnosed at a later age ($p > 0.05$) (data not shown).

Analysis of FSH levels performed during the initial evaluation by age at diagnosis (< 2 years versus ≥ 2 years) revealed that 98.8% and 72.8% of girls, respectively, presented normal levels (Table 2). When LH levels were compared by age group (< 1 year versus ≥ 1 year), it was observed that only 22.5% of girls < 1 year and 87.9% of girls ≥ 1 year presented normal values. Analysis of estradiol levels showed similar results, 3% of girls aged < 1 year

Table 2. Hormonal levels by age at diagnosis of premature thelarche, Puerto Rico, 1990-1995*

Hormone	Normal levels	Abnormal levels
FSH		
6 months to <2 years	98.8%	1.2%
2 years to <8 years	72.8%	27.2%
LH		
<1 year	22.5%	77.5%
≥ 1 year	87.9%	12.1%
Estradiol		
<1 year	3.0%	97.0%
≥ 1 year	3.3%	96.7%

*Registry of Premature Thelarche and Precocious Sexual Development, Puerto Rico Health Department.

and 3.3% of those aged ≥ 1 year presented normal values. Of 24 girls aged 6 months to < 8 years who had measurement of estrone levels, 4.2% presented normal values whereas all girls had abnormal values of total estrogen.

When pelvic ultra-sonographic findings were evaluated by age at diagnosis, no significant differences ($p > 0.05$) were observed in uteri and cervix sizes.

Table 3. Pelvic ultrasonographic findings by age at diagnosis of premature thelarche, Puerto Rico, 1990-1995*

Organ	Normal size		Above normal size		P value
	<2 years	≥ 2 years	<2 years	≥ 2 years	
Uteri	292(94.2%)	151(92.1%)	18(5.8%)	13(7.9%)	0.38
Cervix	181(93.8%)	91(91.9%)	12(6.2%)	8(8.1%)	0.55
Right ovary	231(91.7%)	117(80.7%)	21(8.3%)	28(19.3%)	0.001
Left ovary	237(94.8%)	127(85.8%)	13(5.2%)	21(14.2%)	0.002

*Registry of Premature Thelarche and Precocious Sexual Development, Puerto Rico Health Department.

The sizes of most uteri and cervix in both age groups were within the normal range (94.2% and 92.1% for uteri; 93.8% and 91.9% for cervix, respectively) (Table 3). When the right and left ovaries were compared by age group, it was observed a higher percentage of patients aged 2 to < 8 years had relatively larger ovaries compared to those younger than 2 years ($p < 0.001$).

The finding of ovarian cysts was present in 44.1% of girls (data not shown). Almost 40% of girls diagnosed prior to age 2 and 52% of girls aged 2 to < 8 years had a family history of ovarian cysts, and this difference reached statistical significance ($p=0.009$). On the other hand, the bone age was appropriate for the chronological age in 78.8% of girls, and it did not differ by age at diagnosis (78.2% and 79.7%, respectively) ($p > 0.05$).

Nearly 71% (1,357) of the study subjects had at least two follow-up visits during the entire study period. After

a median follow-up time of 7.2 months (minimum, 4 days; maximum, 85 months), in only 6.9% of the girls the premature thelarche resolved. The median duration time of follow-up in this subgroup was 11 months (1-72 months). The median duration time in girls diagnosed prior to age 2 was 10 months (1-71 months); among those diagnosed after age 2, this was slightly longer (14 months). However, no significant differences were observed between the two groups ($p=0.05$). No significant correlation was observed between the age at diagnosis and duration of premature thelarche ($p>0.05$).

To describe the evolution of the mammary tissue enlargement in the girls, all measurements registered between the first and ninth month follow-up visits were included in the analysis. Differences in mammary tissue diameter in centimeters between the first and subsequent visits were calculated. Due to variations in the number of follow-up visits and the time elapsed between two visits for each patient, the average time in months was calculated. The change in diameter of the right and left, and horizontal and vertical mammary tissue through the average follow-up period was computed. After a mean follow-up ranging from 6 to 39 months, a slight reduction in mammary tissue diameter in girls diagnosed prior to age 2 was observed. However, the mammary tissue persisted in girls diagnosed after 2 years of age throughout the whole period. Among girls who had two or more follow-up visits, 8.5% reported the presence of at least one new finding of precocious sexual development. Apocrine secretion was the most commonly reported sign (4.1%) followed by pubic hair (3.2%) during follow-up. The present data showed that the percentage of girls who developed one or more new findings was significantly higher ($p<0.001$) when thelarche occurred after age 2 compared to a younger age (23.2% versus 7.2%, respectively) (data not shown).

Discussion

This investigation is the first epidemiologic study that examined the natural history of premature thelarche using a significantly large number of cases. A Medline search of this topic disclosed that previous studies have included less than 100 cases of premature thelarche. This analysis confirmed that enlargement of breast tissue is the predominant manifestation of precocious sexual development in Puerto Rico. Likewise, the majority of the cases were girls, with only 7% of the cases being boys under age 9 presenting with breast enlargement or gynecomastia.

There is limited information reported in the medical literature regarding the incidence of premature thelarche worldwide. Van-Winter and colleagues estimated the

incidence rate of thelarche for girls aged 6 months to 7 years for the period from 1940 to 1984 in Olmsted County, Minnesota (13). The incidence for girls under 2 years of age was 0.000602 per 1000 person-years, and in girls aged 2 to < 8 years was 0.000106 per 1000 person-years. When the rates calculated in this study are compared with those found in Minnesota, the incidence of premature thelarche for Puerto Rican girls aged 6 months to < 2 years (6.2 per 1,000 live births) is 10 times greater ($RR=10.3$) whereas for girls aged 2 to < 8 years the incidence observed (1.6 per 1000 live births) in Puerto Rico is 15 times greater ($RR=15.3$). This analysis evidenced that Puerto Rico has an incidence of premature thelarche higher than reported elsewhere. Furthermore, the Poisson regression model showed a statistically significant upward trend in the incidence of premature thelarche in the island throughout the study period. The incidence calculated in this study was 1.3 times greater ($RR=1.29$) than the estimate obtained in Puerto Rico between 1982 and 1989 among girls aged 6 months to 2 years (11).

However, most likely the magnitude of premature thelarche in Puerto Rico is higher than the incidence estimated in this study. The following arguments suggest this possibility: 1) not all physicians, including pediatric endocrinologists, report their cases to the Registry despite the mandatory reporting by law; 2) Puerto Rico's health system is undergoing a transformation towards a managed care system, which may limit referral of premature thelarche cases by primary care physicians to sub-specialists from which the Registry collects its data; 3) the Puerto Rico Department of Health or any other health agency in the island has not instituted any program aimed at educating the general population or the medical and allied professions about early detection of premature sexual development in the island youth. For this reason, a significant number of cases have not sought medical care, or if they have, the diagnosis has not been adequately established (14). Future studies should address these hypotheses in order to clarify further the real incidence of premature sexual development in Puerto Rico.

Thirty percent of the cases of premature thelarche reported a sign of sexual development at the time of birth. Our study found that according to their parents or custodians, 28.2% of girls diagnosed with premature thelarche presented mammary tissue growth from birth. These findings are comparable with those reported by Mills et al. (15) and Ilicki et al. (16) in which 37% and 33.8% of the cases, respectively, presented the condition since birth.

The levels of pubertal hormones measured in subjects with premature thelarche showed a pattern different from others published studies. Various investigators have

reported that levels of hormones are slightly higher in girls with premature thelarche compared with prepubertal girls without the condition, especially FSH levels (16-18). During the 1990s, the term "exaggerated thelarche" was used to refer to cases of premature thelarche with hormonal estrogen and gonadotropin levels above the normal levels. In addition, signs of estrogenization like accelerated growth and intermediate characteristics between premature thelarche and complete central precocious sexual development were present. A possible explanation was the activation of the hypothalamic-pituitary-ovarian axis causing a predominant increase in the secretion of FSH that stimulates the ovaries to produce significant amounts of estradiol (19-20). Although the cause of idiopathic premature thelarche in Puerto Rico and other geographic areas of the world is not entirely clear, some authors have indicated that many of these cases are caused by a slight secretion of estrogen by the ovaries. Moreover, intermittent or persistent signs of estrogenization in lesser degree in the urogenital mucosa and a slight increase in the seric levels of estradiol have been observed (21).

The finding of elevated hormonal level in the subjects of this study suggests that early activation of the pituitary-ovarian axis occurs. If other endogenous evidence or exogenous environmental mechanisms participate in the etiology of premature thelarche in Puerto Rican girls, it is presently unknown and warrants further research. Colón and collaborators (1999) studied the presence of endocrine disrupting chemicals in serum samples of girls diagnosed with premature thelarche in Puerto Rico (22). They found that a significant higher proportion of girls with premature thelarche (28/41) had notable concentrations levels of phthalate esters (ranging from tens of ppb to units of ppm) in serum compared with a group of girls without signs of premature sexual development (5/35) ($p < 0.05$). Further studies to clarify the endogenous and exogenous components of the etiology of premature thelarche in Puerto Rico are necessary.

The analysis of the evolution of premature thelarche during the follow-up period evidenced that the mammary tissue persisted throughout the whole period. It was observed that ovary size, presence of ovarian cysts, presence of other signs of sexual development during follow-up and persistence of breast tissue differed by age at diagnosis. Girls with observation of breast tissue at birth were not statistically different to girls in which breast tissue was observed after birth with regards to the natural course of premature thelarche.

From a public health perspective, the consideration that a proportion of the pediatric population in Puerto Rico is experiencing precocious development of a secondary sexual characteristic becomes relevant since the long-term

consequences of the hormonal changes that occur in premature thelarche are presently unknown. In addition, the distinction of premature thelarche from idiopathic central precocious puberty may be less evident to the non-specialist caretaker (23). Thus, patients with idiopathic central precocious puberty may not be receiving adequate treatment because of difficulty in distinction of these conditions or may be missed by the island's primary care physicians. This may lead to the development of more serious complications during the course of the condition. Also, parents must be well informed regarding the importance of seeking prompt medical attention at the first observation of mammary tissue development in their daughters. Similarly, affected patients must be educated about the condition in order to minimize emotional or psychological distress.

Moreover, recent data suggest that the mean age of onset of pubertal characteristics in young girls is lower than that established by current norms (24). The mean age (SD) of mammary tissue development was 8.87 (1.93) years for African-American and 9.96 (1.82) years for white girls seen in pediatric practices in the United States ($p < 0.001$) (24). If the age of onset of puberty is decreasing, then clinicians must re-examine the criteria used in the evaluation of cases of precocious sexual development (25) and re-evaluate existing programs geared towards sexual education in these age groups.

The Puerto Rico Premature Thelarche and Precocious Sexual Development Registry has an extensive cover in data compilation. However, the Registry must enforce rigorously the Law 137 that establishes the mandatory reporting of all premature thelarche and precocious sexual development cases diagnosed by all physicians in the island. The continuing high occurrence of precocious sexual development with emphasis on premature thelarche among Puerto Rican children underscores the need to conduct further investigations aimed at elucidating its etiology. In addition, active surveillance of cases with premature thelarche and other manifestations of precocious puberty by health department officials as mandated by the law that created the Registry is strongly recommended in order to gain a full understanding of the real magnitude of this important public health problem in our island.

Resumen

Durante las décadas del 1970 y 1980, endocrinólogos pediátricos, basados en su experiencia clínica, reconocieron un aumento dramático en el número de casos de desarrollo sexual precoz en Puerto Rico. En 1987, el Departamento de Salud de Puerto Rico desarrolló el

Registro de Telarquia Prematura y Desarrollo Sexual Precoz, el cual comenzó a operar en 1989. Sin embargo, datos sobre los efectos a largo plazo en niñas diagnosticadas con telarquia prematura no son suficientes. El conocimiento sobre la historia natural de la condición es relevante para predecir el pronóstico a largo plazo y el manejo terapéutico de la población afectada. Este estudio describió la historia natural y estimó la incidencia de telarquia prematura en niñas entre las edades de 6 meses y 8 años de edad residentes de Puerto Rico y diagnosticadas entre 1990 y 1995. De 2,716 casos de desarrollo sexual precoz reportados al Registro de Telarquia Prematura y Desarrollo Sexual Precoz, 1,916 (70.5%) tenían telarquia prematura. Las características clínicas y la evolución durante el seguimiento de los casos de telarquia prematura fueron descritas y comparadas por grupos de edad al diagnóstico. Las incidencias de telarquia prematura fueron 6.2 y 1.62 por cada 1,000 nacimientos vivos para niñas < 2 años y 2 a 8 años de edad, respectivamente. Estos estimados fueron 10 y 15 veces mayor que los reportados en Olmsted, MN. Al evaluar el cambio promedio en el diámetro del tejido mamario durante el seguimiento, se observó una pequeña reducción en niñas < 2 años; sin embargo, el diámetro promedio permaneció constante para niñas de 2 a 8 años de edad. Los resultados de este estudio enfatizan la necesidad de continuar una búsqueda activa de casos de telarquia prematura además de conducir investigaciones analíticas de desarrollo sexual precoz para así aumentar el conocimiento de la etiología de este problema importante de salud pública en Puerto Rico.

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