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The Prevalence and Etiology of Delayed Puberty in Southern Thailand: A 20-Year Experience

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Abstract:

Objective: Delayed puberty (DP) arises from various etiologies. Distinguishing self-limited DP (SLDP) from congenital hypogonadotropic hypogonadism (CHH) proves challenging due to similar clinical and biochemical markers during adolescent presentation. To identify the etiology of DP, the associated clinical characteristics, and the predictive factors differentiating SLDP from CHH.

Material and Methods: A retrospective study was conducted on 75 patients seeking DP evaluation in a tertiary-care hospital between 2002 and 2021. Etiologies were classified based on clinical and biochemical data.

Results: Among the 75 patients (47 boys, 28 girls), the etiologies differed by sex. In boys, SLDP was the most common cause (38.3%), followed by permanent hypogonadotropic hypogonadism (PHH, 29.8%), functional hypogonadotropic hypogonadism (FHH, 25.5%), and hypergonadotropic hypogonadism (HHH, 6.4%). In girls, HHH was the most prevalent diagnosis (57.1%), followed by PHH (17.9%), SLDP (14.3%), and FHH (10.7%). Kallmann syndrome was the leading cause of PHH in boys, while central nervous system (CNS) tumors were the most common cause in girls. Turner syndrome was the predominant etiology among girls with HHH (n=8, 28.5%). In the comparison between SLDP and CHH, micropenis was observed only in CHH boys (p-value=0.01), and cryptorchidism was significantly more frequent in the CHH group (36.4%) than in the SLDP group (5.6%) (p-value=0.05).

Conclusion: The etiology of DP showed distinct sex patterns in the Thai population, with SLDP predominant in boys and HHH predominant in girls. Clinical predictors, such as micropenis and cryptorchidism, can help differentiate CHH from SLDP.

Keywords: constitutional delay of growth and puberty, delayed puberty, gonadal failure, hypogonadotropic hypogonadism, Kallmann syndrome

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Introduction

Delayed puberty (DP) is characterized by the absence of secondary sex characteristics by an age 2–2.5 standard deviations (S.D.) later than the population mean. In girls, it is typically defined as the absence of breast development (Tanner stage II breast) by the age of 13 years, whereas in boys, it is marked by a testicular volume of less than 4 mL by the age of 14 years[1,2]. The etiology of DP can be broadly classified into 3 main categories. The first is self-limited delayed puberty (SLDP), also known as constitutional delay of growth and puberty (CDGP), which is more benign but may have long-term health consequences, as suggested by data from the UK Biobank[3]. It typically resolves spontaneously or with a short course of sex steroid therapy. The second category is hypogonadotropic hypogonadism (HH), which includes permanent hypogonadotropic hypogonadism (PHH), an often irreversible condition, although approximately 15% of patients may experience reversal[4,5] and functional hypogonadotropic hypogonadism (FHH), a reversible state associated with factors such as psychological stress, malnutrition, chronic illness, or excessive exercise. The third cause is hypergonadotropic hypogonadism (HHH), characterized by a primary gonadal defect, and typically identified by elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in conjunction with low sex hormone levels. Although FHH can often be excluded through a thorough medical history and clinical evaluation, distinguishing SLDP from congenital hypogonadotropic hypogonadism (CHH), a subset of PHH, remains a significant clinical challenge. During adolescence, the similar clinical presentations and overlapping hormonal profiles of SLDP and CHH complicate the diagnostic process. Although various clinical and biochemical markers have been proposed to aid in differentiation, uncertainty persists regarding standardized protocols and investigations. Consequently, careful monitoring of pubertal progression until the age of 18 years is often necessary in clinical practice to establish a definitive diagnosis[2].

This study aimed to investigate the etiology of DP and analyze the clinical characteristics associated with its various causes. Specifically, we aimed to identify predictive factors that could help distinguish between SLDP and CHH.

Material and Methods

In this retrospective study, we reviewed the medical records of 75 patients diagnosed with DP at the Pediatric Endocrine Clinic of Songklanagarind Hospital, a tertiary-care center in southern Thailand, between January 2002 and December 2021. Girls and boys who lacked the development of secondary sex characteristics by 13 and 14 years of age, respectively, were included. The following baseline demographic and clinical information was collected: age at first presentation and diagnosis, parental height, history of spontaneous or induced puberty, medical history, underlying conditions, height, weight, and red flag signs of CHH, such as micropenis, cryptorchidism, anosmia, and synkinesia.

Anthropometric measurements, including height and weight, are expressed as standard deviation scores (SDSs) based on the measurements of sex- and age-matched Thai children. Midparental height (MPH) was calculated using Tanner's method as follows: for boys, (father's height [cm] + mother's height [cm] + 13)/2, and for girls, (father's height [cm] + mother's height [cm] – 13)/2. Pubertal status was determined using Tanner Staging[6]. Prepubertal status was defined as Tanner staging I breast development in girls and a testicular volume of less than 4 mL in boys, as assessed using a Prader orchidometer. The age of pubertal onset was defined as the age at which patients first exhibited any secondary sex characteristics, specifically breast development corresponding to Tanner stage II in girls and a testicular volume ≥4 mL in boys with spontaneous puberty. In boys who underwent puberty induction with testosterone, pubertal onset was defined by

the appearance of penile enlargement and/or pubic hair development consistent with Tanner stage II. The etiology of DP was classified into 4 main groups based on clinical, biochemical, and radiological data. Bone age (BA) was estimated through a left-hand X-ray using the Greulich-Pyle method[7]. SLDP was diagnosed when clinical and biochemical evaluations ruled out pathological causes of DP. PHH included both congenital and acquired causes, characterized by low gonadotropin and sex hormone levels, and could be associated with central nervous system disorders. The distinction between SLDP and normosmic CHH was based on pubertal status by the age of 18 years. SLDP was diagnosed in patients who entered and maintained spontaneous puberty by age 18 without requiring sex hormone replacement therapy. Otherwise, patients were classified as having normosmic CHH. FHH was diagnosed in patients with underlying conditions that transiently suppressed the hypothalamic-pituitary-gonadal axis but did not lead to permanent hypogonadotropic hypogonadism. HHH was identified in patients with gonadal failure, evidenced by low sex hormone levels and elevated gonadotropin levels. Serum estradiol, testosterone, LH, and FSH were measured using Electrochemiluminescence Immunoassay (ECLIA) on the Roche cobas e 601 analyzers (Roche Diagnostics). Limits of detection were 18.4 pmol/L (estradiol), 0.087 nmol/L (testosterone), and 0.100 IU/L (LH, FSH). Inter-assay coefficient of variations (CVs) were <5%. Reference ranges (female, follicular phase) were: estradiol 99–446 pmol/L, testosterone 0.29–1.67 nmol/L, LH 1.9–12.5 mIU/mL, and FSH 3.5–12.5 mIU/mL.

Statistical analysis

Statistical analyses were performed using R version 3.2.2. Continuous variables are expressed as the mean and S.D. for normally distributed data or the median with interquartile range (IQR) for non-normally distributed data. The χ^2 test or Fisher's exact test was used to compare categorical variables between groups of patients. The rank-sum test or t-test was used to compare continuous variables between the 2 groups, and the ANOVA test was used for comparisons involving more than 2 groups. A p-value of less than 0.05 was considered statistically significant.

Results

Etiology of delayed puberty

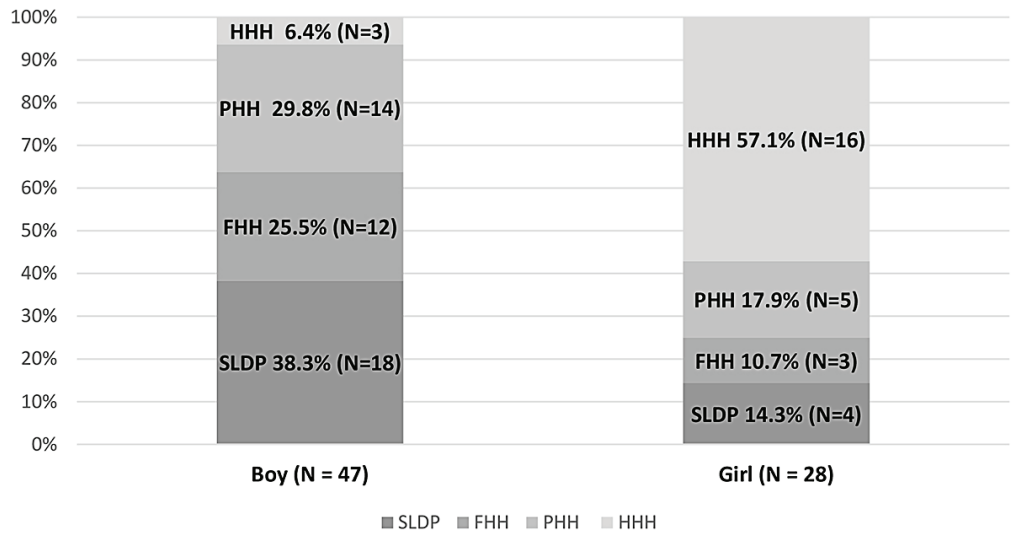
Among the 75 patients with DP included in this study, there was a male predominance with 47 boys (62.7%) and 28 girls (37.3%). The age at first presentation was 14.1 years (IQR 12.1,14.6) for boys and 11.1 years (S.D. 4.9) for girls. SLDP emerged as the most common diagnosis overall, accounting for 29.4% of cases (n=22). The remaining cases were equally distributed between PHH and HHH at 25.3% each (n=19), while FHH comprised 20.0% of cases (n=15) (Table 1). The etiological pattern demonstrated marked gender differences. In boys (n=47), SLDP was the predominant cause (38.3%), followed by PHH (29.8%), FHH (25.5%), and HHH (6.4%). Conversely, in girls (n=28), HHH was the most frequent diagnosis (57.1%), followed by PHH (17.9%), SLDP (14.3%), and FHH (10.7%) (Figure 1).

Within the PHH group (n=19), Kallmann syndrome was the most common cause in boys (6 cases, 12.8%), whereas CNS tumors were predominant in girls (3 cases, 10.7%). Among these, one girl had craniopharyngioma that was surgically removed, while the other 2 had medulloblastomas and underwent tumor resection followed by craniospinal irradiation. Nine patients had isolated CHH, including 6 cases of Kallmann syndrome (all boys) and 3 cases of normosmic CHH (1 boy, 2 girls). Among patients with FHH (n=15), renal disease, including patients with SLE with renal involvement, steroid-resistant nephrotic syndrome, and renal tubular acidosis, was the most common cause (n=7), followed by thalassemia major (n=5). Other conditions included single cases each of chronic lung disease, Noonan syndrome with pulmonary stenosis, and

Table 1 Underlying etiology of delayed puberty in 75 patients

	Total N=75 (%)	Boys N=47 (%)	Girls N=28 (%)
SLDP	**22 (29.4)**	**18 (38.3)**	**4 (14.3)**
PHH	**19 (25.3)**	**14 (29.8)**	**5 (17.9)**
Kallmann syndrome	6 (8.0)	6 (12.8)	0 (0)
CNS tumors	5 (6.7)	2 (4.3)	3 (10.7)
Congenital MPHD		4 (5.3)	4 (8.5)
Normosmic CHH	3 (4.0)	1 (2.1)	2 (7.2)
Other	1 (1.3)	1 (2.1)	0 (0)
FHH	**15 (20)**	**12 (25.5)**	**3 (10.7)**
Renal disease	7 (9.4)	6 (12.8)	1 (3.57)
Thalassemia major	5 (6.7)	4 (8.5)	1 (3.57)
Chronic lung disease	1 (1.3)	1 (2.1)	0 (0)
Noonan syndrome	1 (1.3)	0 (0.0)	1 (3.57)
Cyanotic heart disease	1 (1.3)	1 (2.1)	0 (0)
HHH	**19 (25.3)**	**3 (6.4)**	**16 (57.1)**
Turner syndrome	8 (10.7)	0 (0.0)	8 (28.5)
Post-chemotherapy	4 (5.3)	0 (0.0)	4 (14.3)
Idiopathic	7 (9.3)	3 (6.4)	4 (14.3)

CHH=congenital hypogonadotropic hypogonadism, CNS=central nervous system, FHH=functional hypogonadotropic hypogonadism, HHH=hypergonadotropic hypogonadism, MPHD=multiple pituitary hormone deficiency, PHH=permanent hypogonadotropic hypogonadism, SLDP=self-limited delayed puberty



HHH=hypergonadotropic hypogonadism, SLDP=self-limited delayed puberty, FHH=functional hypogonadotropic hypogonadism, PHH=permanent hypogonadotropic hypogonadism

Figure 1 Etiology of delayed puberty in boys and girls

cyanotic heart disease. In the HHH group (n=19), which showed a strong female predominance (84.2%; n=16/19), Turner syndrome was the most common cause among girls (n=8, 28.5%). Among these, 6 patients had a 45,X karyotype; one had a 46,X,r(X)(p11.2,q13) and another was mosaic with 45,X/46,X,idic(X)(p11.2). Post-chemotherapy cases were the next most common cause (n=4): 3 patients had medulloblastoma and one had Ewing sarcoma, all of whom received chemotherapy regimens that included cyclophosphamide. The remaining cases were idiopathic (n=7) (Table 1).

Clinical characteristics by diagnostic categories

Clinical characteristics varied significantly among the diagnostic groups. Overall, the age at first presentation was earliest in the PHH group (median: 11.9 years, IQR: 8.7–14.1); however, the diagnosis was made at a median age of 14.2 years (IQR: 14–15). In contrast, SLDP patients typically presented at a median age of 13.6 years (IQR: 9.7–14.6) and were diagnosed slightly earlier, at a median age of 14 years (IQR: 14–14.5). FHH and HHH patients presented later, with median ages of 14.7 years (IQR: 12.7–15.7) and 14.3 years (IQR: 12.8–15.5), respectively, and were diagnosed a few months after presentation. Notably, patients with PHH and HHH underwent pubertal induction with sex hormones (i.e., oral conjugated estrogen for girls and intramuscular testosterone cypionate for boys), whereas those with SLDP and FHH did not.

Red flag signs for CHH showed significant differences among the groups. None of the SLDP or FHH patients exhibited micropenis, whereas 35.7% (n=5/14) of PHH and 33.3% (n=1/3) of HHH cases did (p-value<0.01). The highest incidence of cryptorchidism was observed in the HHH group (66.7%), followed by the PHH group (28.6%), with both groups having only bilateral cases. There was one unilateral case in the SLDP group (5.6%), and none in the FHH group (p-value<0.01). Additionally, the PHH and HHH groups showed significantly smaller testicular volumes, with a mean of 2 mL, compared to the SLDP and FHH groups, which had mean volumes of 2.5 mL and 3 mL, respectively (p-value<0.01). FSH and LH levels showed significant differences among the groups (p-value<0.01), with the HHH group notably exhibiting elevated levels: FSH 68.3 mIU/mL (IQR 47–119) and LH 23.7 mIU/mL (IQR 20.7–40) (Table 2).

Comparison between SLDP and CHH

A comparison between SLDP and CHH revealed significant differences in clinical parameters (Table 3). Micropenis was observed only in CHH patients (p-value=0.01). Cryptorchidism was more prevalent in the CHH group, with all cases being bilateral, compared to the SLDP group, which had a single unilateral case (36.4% vs. 5.6%; p-value=0.05). Anosmia was reported in 6 patients with CHH but was not observed in any SLDP patients. The hormonal profiles differed between the groups, with FSH and LH levels tending to be lower in the CHH group compared to the SLDP group, although the differences did not reach statistical significance (mean FSH: 1.8 vs. 5.0 mIU/mL; median LH: 0.2 vs. 2.1 mIU/mL; p-value=0.07).

Discussion

This study examined the prevalence and etiology of DP in Southern Thailand over a 20-year period at our institute. The findings revealed that SLDP was the most common overall cause (29.4%), with significant gender differences in presentation and underlying etiologies. While SLDP was predominant in males (38.3%), HHH was the most frequent cause in females (57.1%), primarily due to Turner syndrome. These results align with previous large case series studies that have reported gender-based differences in delayed puberty. However, other studies have found SLDP or CDGP to have the highest prevalence of DP in both sexes, which contrasts with our findings (8–10)

Table 2 Clinical characteristics categorized by the 4 main etiologies of delayed puberty

Characteristics	SLDP n=22	FHH n=15	PHH n=19	HHH n=19	p-value
Sex*, n (%)					<0.01
Male	18.0 (81.8)	12.0 (80.0)	14.0 (73.7)	3.0 (15.8)	
Female	4.0 (18.2)	3.0 (20.0)	5.0 (26.3)	16.0 (84.2)	
Age of first visit* (years), median (IQR)	13.6 (9.7,14.6)	14.7 (12.7,15.7)	11.9 (8.7,14.1)	14.3 (12.8,15.5)	0.04
Age of diagnosis (years), median (IQR)	14.0 (14,14.5)	14.9 (14.2,15.6)	14.2 (14,15)	14.3 (14.2,15.5)	0.05
Age of entering puberty (years), median (IQR)	14.5 (14.1,15)	15.0 (14,16)	15.0 (14,15)[β]	15.0 (14.2,15.5) [β]	0.28
Weight SDS, mean (S.D.)	−1.9 (1.2)	−2.0 (1.4)	−0.8 (1.9)	−1.5 (1.7)	0.10
Height SDS, mean (S.D.)	−3.0 (1.6)	−3.7 (2.3)	−2.8 (2.2)	−3.5 (2.3)	0.63
MPH SDS, mean (S.D.)	−0.6 (0.9)	−0.5 (0.8)	−0.5 (0.5)	−0.9 (0.8)	0.63
Micropenis*, n (%)	0.0 (0)	0.0 (0)	5.0 (35.7)	1.0 (33.3)	<0.01
Cryptorchidism*, n (%)	1 (5.6) [unilateral]	0.0 (0)	4.0 (28.6) [bilateral]	2.0 (66.7) [bilateral]	<0.01
Anosmia/hyposmia, n (%)	0.0 (0)	0.0 (0)	6.0 (31.6)	0.0 (0)	<0.01
Breast tanner I*, n (%)	4.0 (100)	2.0 (66.6)	5.0 (100)	16.0 (100)	0.12
Pubic hair tanner I, n (%)	22.0 (100)	12.0 (80)	19.0 (100)	19.0 (100)	0.39
Testicular volume (mL)*[®], mean (S.D.)	2.5 (2,3)	3.0 (2,5)	2.0 (1,2)	2.0 (1.5,2.5)	<0.01
Bone age (years), mean (S.D.)	10.4 (2.3)	10.8 (2.5)	11.6 (2.2)	10.9 (1.9)	0.37
BA/CA, mean (S.D.)	0.8 (0.1)	0.7 (0.1)	0.8 (0.1)	0.8 (0.1)	0.81
FSH (mIU/mL)*, median (IQR)	5.2 (3.6,6.4)	3.8 (3.4,4.2)	1.1 (0.4,2.6)	68.3 (47,119)	< 0.01
LH (mIU/mL)*, median (IQR)	2.1 (1.4,2.3)	4.3 (2.5,6.1)	0.2 (0.1,0.5)	23.7 (20.7,40)	<0.01

*=statistical significance (p-value<0.05), [β]=Pubertal induction, [®]=Testicular volume was assessed at the time of diagnosis, BA/CA=ratio of bone age to chronological age, FHH=functional hypogonadotropic hypogonadism, FSH=follicle-stimulating hormone, HHH=hypergonadotropic hypogonadism, IQR=interquartile range, LH=luteinizing hormone, MPH=midparental height, PHH=permanent hypogonadotropic hypogonadism, S.D.=standard deviation, SDS=standard deviation score, SLDP=self-limited delayed puberty

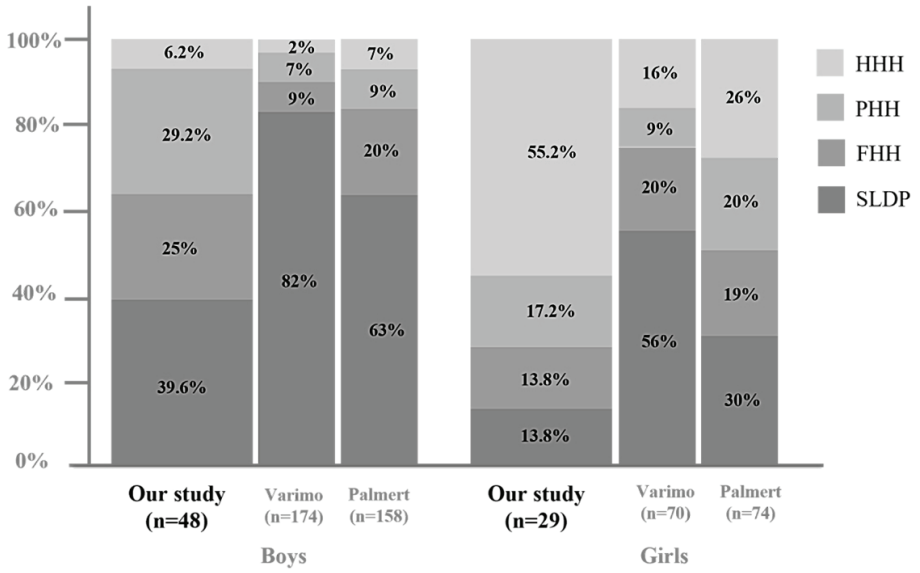
(Figure 2). The male predominance of SLDP in our cohort (38.3% vs. 14.3% in females) is consistent with previous reports showing SLDP as the leading cause of DP in males. This gender disparity may be due to referral bias rather than a true biological difference[9], or it may reflect the smaller sample size in our study compared to others, which could account for the difference in prevalence. Our finding of HHH as the most common cause in females differs from some Western studies where SLDP remains predominant across both genders[11]. The high prevalence of Turner syndrome in the HHH group (50%, n=8/16) is consistent with reported incidence rates[12], highlighting the importance of karyotype screening in this population.

Our findings support the value of certain clinical markers in distinguishing between the causes of DP. The significantly higher prevalence of micropenis (36.4%) and cryptorchidism (36.4%) in CHH compared to SLDP emphasizes the importance of these features in the early identification of pathological causes[11,13]. However, the overlap in hormonal profiles between SLDP and CHH during adolescence remains a diagnostic challenge[14]. Patients with SLDP in our cohort typically entered puberty spontaneously by age 14.5 years (IQR 14.1–15), albeit later than population norms. This relatively favorable natural history supports a watchful waiting approach in selected cases with classic SLDP presentations. Conversely, the permanent nature

Table 3 Comparative clinical characteristics between self-limited delayed puberty and congenital hypogonadotropic hypogonadism

Characteristics	SLDP (N=22)	CHH (N=13)	p-value
Sex, n (%)			1.00
Male	18.0 (81.8)	11.0 (84.6)	
Age of first visit (years), median (IQR)	13.6 (9.7,14.6)	13.1 (8.2,14.1)	0.48
Age of entering puberty (years), median (IQR)	14.5 (14.1,15)	15.0 (13.6,15)[β]	0.74
Weight SDS, mean (S.D.)	−1.9 (1.2)	−1.2 (2.1)	0.95
Height SDS, mean (S.D.)	−3.0 (1.6)	−3.1 (2.5)	0.95
MPH SDS, mean (S.D.)	−0.6 (0.9)	−0.6 (0.5)	0.98
Micropenis*, mean (S.D.)	0.0 (0)	4.0 (36.4)	0.01
Cryptorchidism*, n (%)	1.0 (5.6) [unilateral]	4.0 (36.4) [bilateral]	0.05
Anosmia/hyposmia, n (%)	0.0 (0)	6.0 (46.2)	<0.01
Breast Tanner stage I, n (%)	4.0 (100)	2.0 (100)	1.00
Testicular volume (mL), median (IQR)	2.5 (2,3)	1.5 (1,2)	0.07
Bone age (years), mean (S.D.)	10.4 (2.3)	12.0 (1.8)	0.10
BA/CA, mean (S.D.)	0.8 (0.1)	0.9 (0.1)	0.15
FSH (mIU/mL), mean (S.D.)	5.0 (2.8)	1.8 (2.1)	0.06
LH (mIU/mL), median (IQR)	2.1 (1.4,2.3)	0.2 (0.1,0.5)	0.07

*=statistical significance (p-value<0.05), [β]=pubertal induction, BA/CA=ratio of bone age to chronological age, CHH=congenital hypogonadotropic hypogonadism, FSH=follicle-stimulating hormone, IQR=Interquartile range, LH=luteinizing hormone, MPH=midparental height, S.D.=standard deviation; SDS=standard deviation score; SLDP=self-limited delayed puberty



HHH=hypergonadotropic hypogonadism, PHH=permanent hypogonadotropic hypogonadism, FHH=functional hypogonadotropic hypogonadism, SLDP=self-limited delayed puberty

Figure 2 Comparison of etiologies of delayed puberty in each study, data adapted from Varimo et al.[9] and Palmert et al.[10]

of CHH and HHH underscores the importance of timely hormone replacement therapy to promote normal secondary sexual development, optimize bone health, and mitigate potential psychosocial consequences. However, this study shows that treatment for CHH and HHH is often delayed, with pubertal induction occurring at a median age of around 15 years.

A major strength of our study is that it utilizes data from a referral center where hormonal evaluations are routinely performed and all patients undergo chromosomal analysis, resulting in a high detection rate of Turner syndrome. However, being a referral center also presents a limitation, as it may introduce selection bias affecting the distribution of etiologies, particularly regarding chromosomal abnormalities. Furthermore, a gender bias is evident, as girls with delayed puberty are less frequently referred—likely because their height is not as much of a concern—resulting in a lower incidence of SLDP and FHH compared to other studies[15]. Additionally, although inhibin B and AMH have been reported as useful markers for distinguishing SLDP from CHH[16], these tests are not available at our center and therefore were not included in this study.

In conclusion, this 20-year experience demonstrates distinct patterns of DP in Southern Thailand, with notable gender differences in both presentation and etiology. The high prevalence of Turner syndrome among females with DP emphasizes the importance of early genetic evaluation in this group. Recognition of clinical markers such as micropenis and cryptorchidism can help identify patients requiring more extensive evaluation.

Author contributions

T.S. made substantial contributions to the conception and design of the study, analysis, and interpretation of data, as well as drafting the article. M.U. contributed to the acquisition of data and analysis, participated in drafting the article. S.J. contributed to revising the article critically for important intellectual content and gave final approval of the version to be published.

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