Recent pubertal timing trends in Northern Taiwanese children: Comparison with skeletal maturity

Jeffrey C. Chow[a], Ting Ywan Chou[b,c], Tao-Hsin Tung[d], Yeong-Seng Yuh[a,e,*]

[a]Department of Pediatrics, Cheng Hsin General Hospital, Taipei, Taiwan, ROC; [b]Department of Radiology, Cardinal Tien Hospital, Taipei, Taiwan, ROC; [c]Department of Medical Education, College of Medicine, Fu Jen Catholic University, Taipei, Taiwan, ROC; [d]Department of Medical Education and Research, Cheng Hsin General Hospital, Taipei, Taiwan, ROC; [e]Department of Pediatrics, National Defense Medical Center, Taipei, Taiwan, ROC

Abstract

Background: International studies have reported an early age of onset of puberty in girls and boys. However, the current situation of puberty onset in Taiwanese children is unknown. In this study, the timing of menarche and pubertal change in testicular volume (TV) in Taiwanese children was examined, and bone age (BA) was used as an internal somatic maturity scale and compared with the chronological age (CA) at pubertal timing.

Methods: Clinical data from October 1, 2010, to March 31, 2018, were retrospectively collected from a general hospital in Taipei. The data of patients who were diagnosed with endocrine/genetic disorders were excluded. Clinical data included CA, timing of menarche, and X-ray images of TV and BA. BA was determined by a senior pediatrician and a senior pediatric radiologist. The reliability and validity of BA readings were tested. Collected data were analyzed statistically.

Results: Overall, TV records of 241 boys and the menarche timing data of 98 girls were collected from 1823 children. CA for menarche was 11.35 ± 1.06 years (mean ± SD), and BA for menarche was 12.95 ± 0.80 years. CA and BA at TV = 15 mL in male puberty was 12.32 ± 1.22 and 13.46 ± 0.68 years, respectively. A stronger correlation was observed between TV and BA than between TV and CA during the pubertal period.

Conclusion: The secular trend of earlier puberty timing continues. The decline rate of menarche timing was approximately 0.43 years per decade in the past 30 years. Among boys, an advance of more than 1 year in pubertal timing age was observed over the past 20 years. BA and TV showed high correlation during puberty.

Keywords: Bone age; Chronological age; Female; Male; Menarche; Pubertal timing; Testicular volume

1. INTRODUCTION

Puberty is the process by which and the period during which sexual maturation occurs and reproductive capacity is attained. The normal timing of onset of puberty exhibits wide physiological variations. Early onset of puberty may be associated with risks of accelerated bone maturity, short adult height, behavioral problems, and diseases such as obesity, diabetes, heart diseases, and endocrine-related cancers in adulthood.[1–4]

Since the late 1800s, a secular trend toward the early onset of puberty in girls has been reported in multiple countries.[5–7] It is unclear whether the trend has continued since the mid-1900s to the current time or has leveled off in recent years. The secular trend toward the early onset of menarche can be documented because individual health records recording the first menstruation can be compared over time. However, no equivalent biomarker of puberty onset in boys is currently available. In boys and adolescents, secular evidence remains insufficient, and additional studies on this topic are needed.[8]

In 2008, a cross-sectional questionnaire investigation was conducted in postadolescent girls from Central Taiwan, their biological mothers, and their grandmothers.[9] The mean ages at menarche were 15.2, 14.5, and 13.0 years in grandmothers, mothers, and daughters, respectively. The age at menarche was significantly younger (early onset) over the three generations. However, retrospective assessment through the recall method has some limitations because a longer recall period may result in the loss of accuracy. In the same year, another study on female orthodontic patients in Northern Taiwan showed that the mean age of menarche was 11.97 years.[10] The mean menarche data were different in these two studies. In addition to these two articles, three cross-sectional population-based studies have shown that the age of menarche was declining compared with the previously reported age.[11–13] Since 2008, no updated data are available. According to our knowledge, until now, we lack data to determine whether male children in Taiwan in recent years have shown an early onset of puberty. In Eastern countries, such as Korea, Japan, and China, studies have shown secular trends

*Address correspondence. Dr. Yeong-Seng Yuh, Department of Pediatrics, Cheng Hsin General Hospital, 45, Zhenxing Street, Taipei 112, Taiwan, ROC. E-mail address: pubertaltiming@gmail.com (Y.-S. Yuh).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2020) 83: 870-875.

Received January 16, 2020; accepted April 9, 2020.

doi: 10.1097/JCMA.0000000000000360.

<zdoi: 10.1097/JCMA.0000000000000360>

for testicular maturation.[14–16] However, limited information on the trends in male puberty in Taiwan is currently available. The most recent data on testicular volume (TV) in Taiwanese boys were published in 1998.[17]

Skeletal maturity has been widely used as a biological indicator of individual physiological maturity. In a previous study, when bone age (BA) was considered, the accuracy of the prediction of menarche was higher than that of the prediction based on chronological age (CA) alone.[18] To determine whether the secular trend of earlier pubertal timing is ongoing in our population, we investigated the current timing of menarche in girls and the timing of pubertal change in TV in boys and compared the age at appearance of signs of sexual maturation by using biological markers and a skeletal maturity scale.

2. METHODS

2.1. Data sources

In this retrospective study, we collected and analyzed the medical records of patients who visited a pediatric endocrine clinic at Chen-Hsin General Hospital and observed hand or wrist radiographs for BA assessment from October 1, 2010, to March 31, 2018. Personal details of the participants consisted of sex, date of birth, date of image for BA determination, disease and medication history, and information of menarche or TV. CA was calculated. Medical records of patients with congenital malformation of the left hand, genetic diseases, or endocrine diseases were excluded from the data analysis. The selection process is illustrated in Fig. 1. All data were collected following the regulations of the institutional review board and ethics committee [No. (658)107A-30].

2.2. Study variables and interobserver and intraobserver reliability

Skeletal age was estimated for each of the radiographs using the Greulich and Pyle (GP) atlas.[19] Age estimation was undertaken by a single pediatric endocrinologist (Y.-S.Y.). The reliability and validity of BA estimation by this pediatrician were tested. Intraobserver accuracy was tested using a subset of 50 selected radiographs each of girls and boys. The second assessor was a senior pediatric radiologist (T.Y.C.). An interobserver test was devised using the same 100 selected radiographs. The second observer was blinded to CA and was only informed of the sex of the individual. Correlation analysis was conducted using the

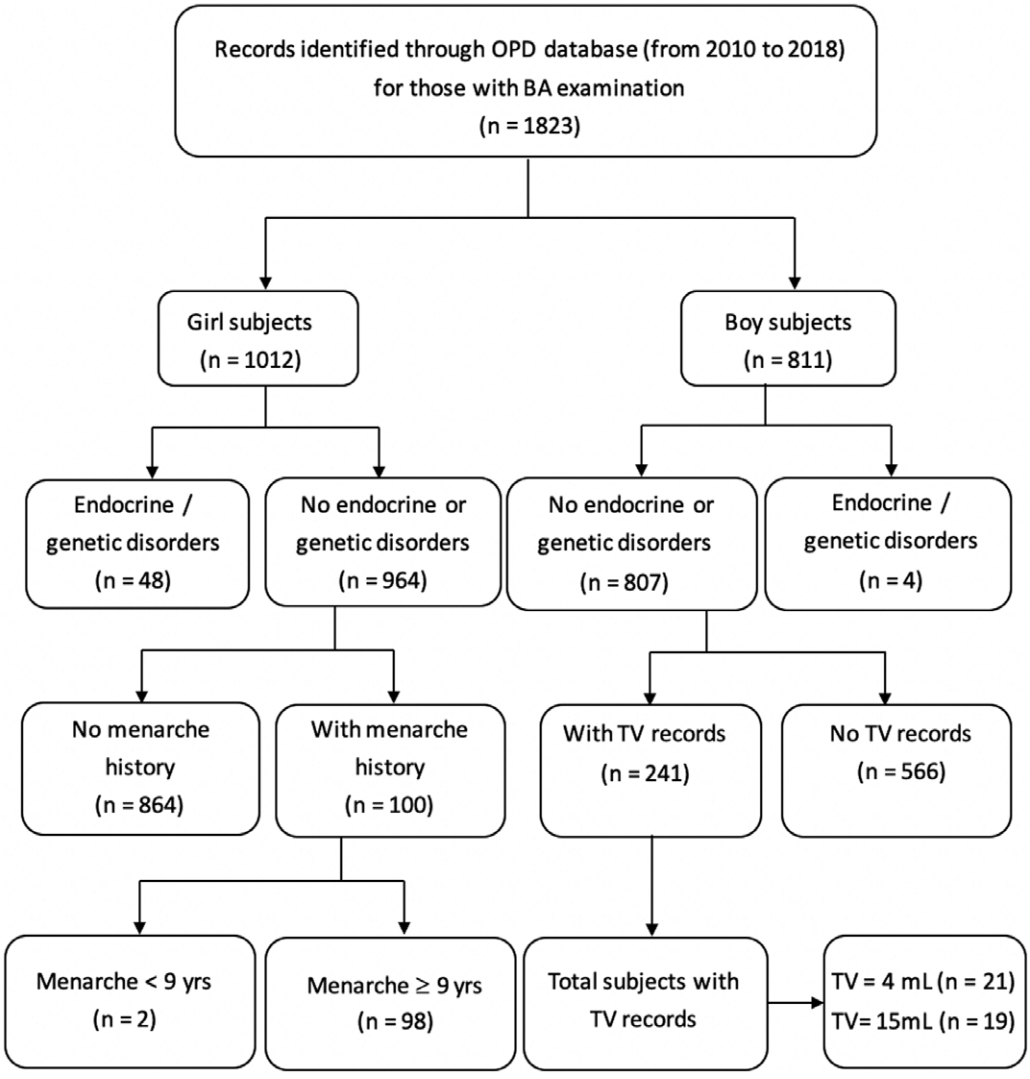

Fig. 1 Flowchart of the selection process. BA = bone age; OPD = outpatient department; TV = testicular volume.

data with estimated BA. The correlation coefficient for intraobserver comparison was 0.993 ($p < 0.001$), and that for interobserver comparison was 0.992 ($p < 0.001$).

The commonly used markers of the timing of female puberty are thelarche and menarche. Thelarche is the first appearance of breasts and is defined as Tanner B2 stage. This obvious pubertal sign might not be easily noted in girls with slight obesity because of the presence of fat tissue. Menarche is a late maturational event; however, it is a unique marker of late puberty. In this study, we used menarche to evaluate the secular trend in pubertal onset. All of the information on menarche was further confirmed by the participants' mothers. The mean CA of menarche in this study was compared with the data of four previous Taiwanese studies.[10–13]

Among boys, the first sign of pubertal development is an increase in TV. According to Tanner and Whitehouse,[20] TV equals to 4 mL represents the first sign of the onset of puberty. The genital rating was defined as follows: stage 1: TV < 4 mL (prepubertal phase); stage 2: 4–8 mL (early pubertal phase); stage 3: 9–14 mL (middle pubertal phase); stage 4: 15–20 mL (late pubertal phase); and stage 5: TV > 20 mL (mature phase). Because there was no male equivalent event to female menarche, TV of 15 mL was chosen as a sign for beginning of the late pubertal phase. TV was measured by the same pediatric endocrinologist using the Prader's orchidometer method.[21] Only data of the left testis were recorded. All participants with abnormal growth of testes including cryptorchidism, single testis, and varicocele were excluded. All the data were further analyzed and compared with data from Chin et al[17] for Taiwanese children in 1998. Subsets of data from boys with TV of 4 or 15 mL were further evaluated, and the data were used for the statistical analysis of BA and CA.

2.3. Statistical analysis

The statistical software SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used to analyze all the data. Descriptive statistics, namely the means and SDs of CA and BA, were calculated. Differences in BA and CA were analyzed using the paired *t* test. Pearson's correlation coefficient was used to investigate intra- and interpersonal correlations of estimated BA and to compare ages and TV during the pubertal period. A linear regression model was used to study the secular trend in menarche timing, and the Student *t* test was used for comparison of TV in this study with data reported in the study by Chin et al[17] (1998). Statistical significance was defined as $p < 0.05$.

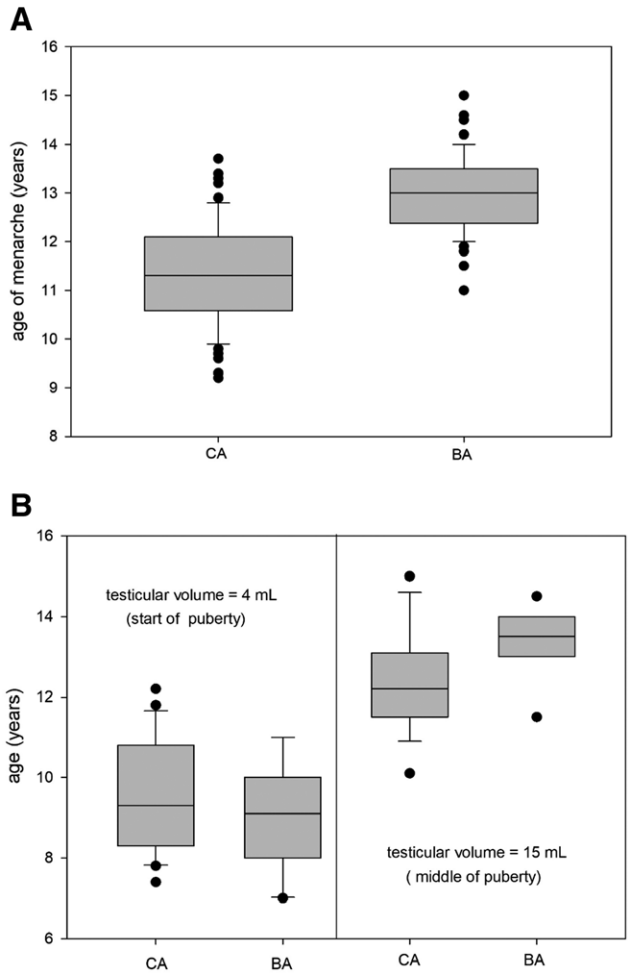

Fig. 2 Recent pubertal timing in Northern Taiwanese children. A, Comparison of age at menarche between chronological age (CA) and bone age (BA) in girls (n = 98). The mean CA was 11.35 ± 1.06 years, and the mean BA was 12.95 ± 0.80 years; $p < 0.001$. B, Comparison of age at the start and middle of puberty between CA and BA in boys. When testicular volume (TV) was 4 mL (n = 21), the mean CA was 9.50 ± 1.38 years, and the mean BA was 9.04 ± 1.28 years; $p = 0.119$. When size of TV was 15 mL (n = 19), the mean CA was 12.32 ± 1.22 years, and the mean BA was 13.46 ± 0.68 years; *p* value = 0.001.

3. RESULTS

In total, 241 TV records of boys and the menarche timing data of 98 girls were collected from 1823 children. Furthermore, X-ray examination of the left hand of the wrist bone was conducted to determine the participants' CA and BA. The girls' mean CA at the start of menarche was 11.35 ± 1.06 years (n = 98), and the mean BA at the start of menarche was 12.95 ± 0.80 years (n = 98). CA and BA differed significantly at menarche, $p < 0.001$ (Fig. 2A). CA and BA were compared in the boys at the start of puberty when TV was 4 mL (n = 21). The mean CA was 9.50 ± 1.38 years, and the mean BA was 9.04 ± 1.28 years. CA and BA at the start of male puberty ($p = 0.119$) did not differ significantly. CA and BA were compared in the boys at stage 4 of puberty when TV was 15 mL (n = 19). The mean CA was 12.32 ± 1.22 years, and the mean BA was 13.46 ± 0.68 years. CA and BA differed significantly in stage 4 of male puberty ($p = 0.001$) (Fig. 2B).

In boys, TV increased by only 1–2 mL during the first 9 years of life. After that period, TV increased markedly from 9.5 to 15 years of age. Subsequently, the slope of the curve progressively declined. The result is shown in Fig. 3. Correlation between age and TV was divided into three age groups, namely group 1 (<9.5 years), group 2 (9.5–15 years), and group 3 (>15 years). The correlation coefficients of CA and TV in groups 1, 2, and 3 were 0.615, 0.511, and 0.390, respectively. The correlation coefficients of BA and TV in groups 1, 2, and 3 were 0.617, 0.843, and 0.193, respectively. In group 2 (9.5 to 15 years old), BA and TV ($\gamma = 0.843$) showed a stronger correlation than CA and TV ($\gamma = 0.511$).

Compared with the four Taiwanese studies on menarche, a linear correlation between the mean age at menarche and the year of the study with a correlation coefficient of –0.986 ($p < 0.001$) was observed in the present study (Fig. 4). The regression equation for CA of menarche (Y) on year (X) was as follows: Y = 98.773 – 0.043 X. The decline rate was approximately 0.43 years per decade in the past 30 years. Compared with 1998 data from Chin et al[17] of Taiwanese children, significant differences were observed in different age groups in the present study (Table 1). In boys, an advance of more than 1 year in onset age was observed over the past 20 years.

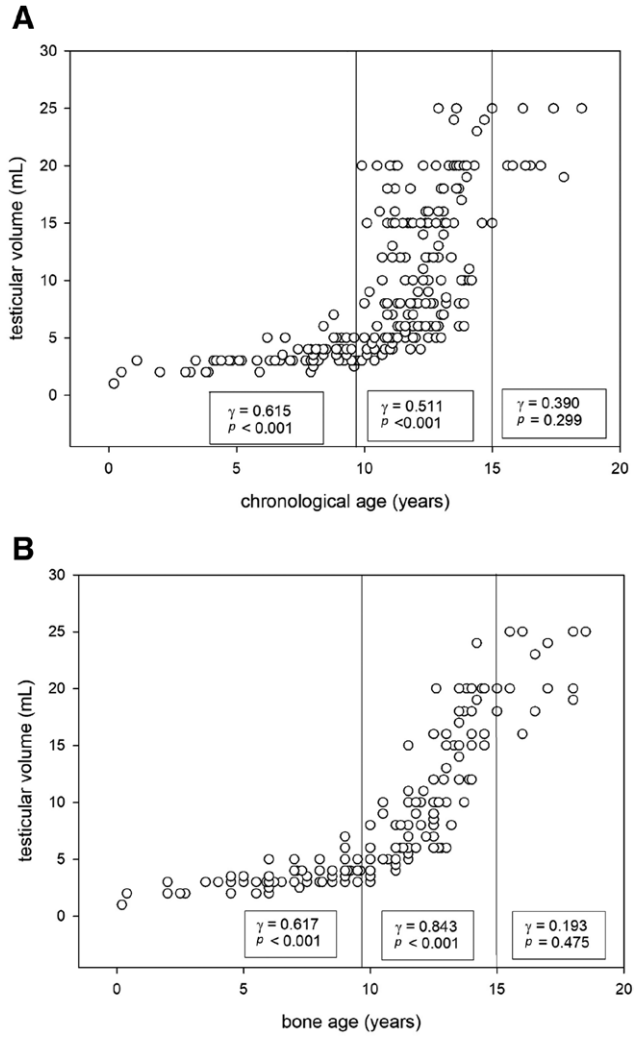

Fig. 3 Testicular volume (TV) versus chronological age (CA) or bone age (BA) (n = 241). Group 1: age <9.5 years, group 2: age 9.5–15 years, and group 3: age >15 years. A, The correlation between TV and chronological age. B, The correlation between TV and bone age.

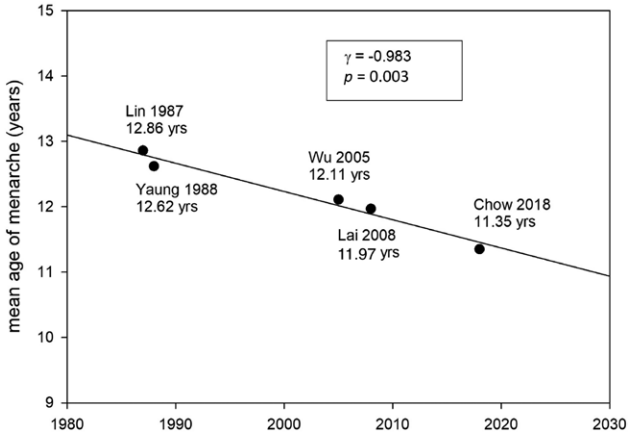

Fig. 4 Correlation between mean ages of menarche among girls in different studies in Taiwan.

4. DISCUSSION

4.1. Clinical implications

The accelerated tempo of growth and maturation has been suggested to be persistent during the past century in many countries.[5,6,8,22–24] In the present study, the mean age at menarche was 11.35 years. Compared with previous results obtained over the past 30 years in Taiwan,[10–13] a shift of 0.43 years per decade for the mean age at menarche was observed in the present study (Figure 4). An apparent ongoing secular trend was confirmed for female adolescents in Taiwan. A recent report in mainland China showed that the age at menarche declined from 14.25 years in girls born before 1976 to 12.60 years in girls born after 2000, with a decline rate of 0.51 years per decade.[23] The secular trend in female maturation appears persistent in these two areas.

Compared with the data of boys from the study by Chin et al[17] in 1998, the findings of this study suggest that Taiwanese boys currently mature significantly faster than they did 20 years ago (Table 1). In short, the enlargement of the testis starts and proceeds approximately 1 year earlier in boys currently than it did 20 years ago. Because few studies are available and low reliability of the male puberty marker, additional studies are needed to confirm this finding. Previous studies have confirmed the existence of ethnic differences in the size of the penis and testis.[8] Compared with recent TV data from mainland China, the pubertal timing of boys in Taiwan is probably 1 year earlier than that in boys in Chongqing.[16] At TV of 4 or 15 mL, the medians of CA are 9.25 and 12.41 years in Taiwanese boys and 10.55 and 13.42 years in boys in Chongqing. A clear difference in the timing of the early and the late stage of male puberty between these two populations is observed. Establishing normal growth curves and tables for Taiwanese male pubertal development will be valuable for clinicians.

Table 1

Comparison of the current data of testicular growth with data reported in a study by Chin et al[17] in 1998

	Current study	Chin et al[17] 1998	
Age (y)	Left testicular volume (mean ± SD, mL)	Left testicular volume (mean ± SD, mL)	*p*
7–8	3.2 ± 0.5 (n = 16)	2.0 ± 0.8 (n = 31)	<0.001
8–9	4.3 ± 1.1 (n = 14)	2.0 ± 0.6 (n = 31)	<0.001
9–10	4.5 ± 3.9 (n = 18)	4.0 ± 1.7 (n = 30)	0.612
10–11	7.8 ± 4.8 (n = 29)	4.1 ± 2.2 (n = 30)	<0.001
11–12	9.6 ± 5.0 (n = 46)	6.8 ± 2.5 (n = 30)	0.002
12–13	11.0 ± 4.9 (n = 40)	9.0 ± 4.0 (n = 31)	0.063
13–14	14.1 ± 5.9 (n = 33)	11.0 ± 3.5 (n = 31)	0.013

Tanner[25] (1987) introduced the concept of "tempo" to refer to the overall pace of somatic maturation, which includes the rate of growth, skeletal maturation, and the timing of puberty. Our study also evaluated skeletal maturation by using BA at puberty in both sexes. In female adolescents, we found that the data of BA at menarche were less variable than those of CA. In male adolescents, the data of BA at stage 4 of puberty (TV = 15 mL) were also less variable than those of CA. During the age at which rapid enlargement of testis occurs (9.5–15 years), the correlation between age and TV was significantly stronger with BA than with CA. These findings suggest an internal synchronization of sexual development and skeletal maturation during pubertal somatic growth. Clearly, BA is a reliable clinical tool for monitoring and predicting the progress of pubertal change.

Children with early puberty are at risks of accelerated skeletal maturation and short adult height, early sexual debut, potential sexual abuse, and psychosocial difficulties. Altered pubertal timing also causes concerns regarding the development of reproductive tract cancers later in life. For example, an early age of menarche is a risk factor for breast cancer.[1] Young age at

male puberty is associated with an increased risk of testicular cancer.[26] Although genetic factors remain the major determinant of pubertal timing,[27] the secular trend of early onset of puberty appears to coincide with improved public health, improved nutrition, and increased environmental pollution. Exposure to endocrine-disrupting chemicals in early life has been implicated to affect pubertal development in girls.[14] The data of our population are sufficient to suggest a trend toward an earlier menarche in girls. Additional investigations are warranted to determine the cause.

4.2. Methodological considerations

Several methods can be used for evaluation of skeletal age.[28] Currently, the main clinical methods for BA assessment are the GP and Tanner and Whitehouse methods. The GP method has the advantage of being quick and easy to use. Some authors have suggested that new GP standards should be established for children today, and the standards should vary according to the ethnicity of the children.[29] Other authors argue that a unified international standard of bone maturity should be maintained for comparing health, nutrition, and quality of life of all children, regardless of their race, nationality, and ethnicity.[30] In this study, we selected the GP method, because it is the most popular method in Taiwan.

The only data of BA at menarche available in Taiwan were published by Lai et al[10] in 2008; however, BA was assigned using National Taiwan University Hospital Skeletal Maturation Index (NTUH-SMI) or the cervical vertebral maturation (CVM) stage of cervical spine and not by using the GP method. The first record of BA at menarche was on page 253 of the GP atlas in 1959.[19] BA was estimated to be 13.5 years. In 1976, Marshall et al[18] reported that girls experienced menarche when their CA was 13.2 years with an SD of 0.84 years and their BA (evaluated using the Tanner-Whitehouse 2 method) was 13.3 years with an SD of 0.39 years. Comparing our BA data at menarche with the data of GP and Marshall, BA at menarche is declining at a rate of 0.09 years per decade. However, this may not be the actual rate of decline, because skeletal maturation may occur at different rates in different ethnic population.[31] Our results, which were obtained using the GP method, may offer reference data for future comparison in the Taiwanese ethnic group.

Currently, limited and insufficient data are available for evaluating secular trends in male pubertal development. Tanner staging is the gold standard for rating pubertal development. It is limited to only a visual inspection of the participants' secondary sexual characteristics and a comparison of findings with photographs. Ultrasonography is the most accurate method. It can define the boundaries between the testis and surrounding extraneous tissues. However, because of high cost, low patient acceptance, and the time required, ultrasonography is not routinely used for clinical TV evaluation. Orchidometry is cost-effective, requires less expertise, and saves time. In a study, Prader's orchidometer exhibited strong correlations even when it was handled by various examiners; consequently, it is an objective and reliable method.[21] Studies have also shown a linear relationship between TVs evaluated through orchidometer and ultrasonography.[32] We selected Prader's orchidometer to measure TV in our study, and only the volume of the left testis was measured. In anthropology, the left side of the body has been routinely used as the standard of somatic measurement.[33]

The strength of our study is that TV and BA were measured by the same observer and that the accuracy and reproducibility of BA assessment were tested. In addition, adequate information is available on menarche timing in the local population over the past 30 years; this information can provide an opportunity to estimate the tempo of the secular trend in menarche. The primary limitation of this study is that our study is a retrospective investigation conducted at a single hospital located in Northern Taiwan; hence, our data do not represent the general Taiwanese population. The second limitation is that our data were obtained from the medical records of patients visiting a pediatric endocrine clinic. This may have introduced selection bias into our results. Our study provides information on current menarche timing with corresponding BA as well as information on current TV development in the Taipei area. A nation-wide study to establish the norms of pubertal development in Taiwanese children and adolescents is also warranted. The third limitation is that there are many factors that might influence pubertal timing, such as socioeconomic status, life setting, family size, family income, parental education, and body mass index. In our retrospective data collection, we did not include these confounding factors to analyze the cause of secular changes, so we hope to include these factors in our future prospective study.

In conclusion, the current menarche age in adolescents in the Taipei area is 11.35 ± 1.06 years. Comparing our results with data from four crucial Taiwanese studies provides evidence of a stable trend from 1987 to 2018, with a decline rate at approximately 0.43 years per decade. The current timing for male children to enter puberty when their TV reaches 4 mL is 9.50 ± 1.38 years. Compared with Taiwanese data in 1998, an advance of more than 1 year was observed over the past 20 years. BA and TV showed high correlation during puberty. We demonstrated that the maturation process in both female and male adolescents exhibits a secular trend of earlier pubertal timing.

ACKNOWLEDGMENTS

This study was supported by a research grant from Cheng Hsin General Hospital, Taiwan (CHGH 108-16).

REFERENCES

1. Golub MS, Collman GW, Foster PM, Kimmel CA, Rajpert-De Meyts E, Reiter EO, et al. Public health implications of altered puberty timing. *Pediatrics* 2008;**121**(Suppl 3):S218–30.
2. Perry JR, Day F, Elks CE, Sulem P, Thompson DJ, Ferreira T, et al; Australian Ovarian Cancer Study; GENICA Network; kConFab; LifeLines Cohort Study; InterAct Consortium; Early Growth Genetics (EGG) Consortium. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. *Nature* 2014;**514**:92–7.
3. Noll JG, Trickett PK, Long JD, Negriff S, Susman EJ, Shalev I, et al. Childhood sexual abuse and early timing of puberty. *J Adolesc Health* 2017;**60**:65–71.
4. Goldstein JR. A secular trend toward earlier male sexual maturity: evidence from shifting ages of male young adult mortality. *PLoS One* 2011;**6**:e14826.
5. Euling SY, Herman-Giddens ME, Lee PA, Selevan SG, Juul A, Sørensen TI, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. *Pediatrics* 2008;**121**(Suppl 3):S172–91.
6. Wyshak G, Frisch RE. Evidence for a secular trend in age of menarche. *N Engl J Med* 1982;**306**:1033–5.
7. Anderson SE, Must A. Interpreting the continued decline in the average age at menarche: results from two nationally representative surveys of U.S. girls studied 10 years apart. *J Pediatr* 2005;**147**:753–60.
8. Herman-Giddens ME, Steffes J, Harris D, Slora E, Hussey M, Dowshen SA, et al. Secondary sexual characteristics in boys: data from the Pediatric Research in Office Settings Network. *Pediatrics* 2012;**130**:e1058–68.
9. Chang SR, Chen KH. Age at menarche of three-generation families in Taiwan. *Ann Hum Biol* 2008;**35**:394–405.
10. Lai EH, Chang JZ, Jane Yao CC, Tsai SJ, Liu JP, Chen YJ, et al. Relationship between age at menarche and skeletal maturation stages in Taiwanese female orthodontic patients. *J Formos Med Assoc* 2008;**107**:527–32.
11. Wu W-H. Relationship of age at menarche to body height, weight, and body mass index in Tapei schoolgirls. *Tapei City Med J* 2005;**2**:1098–106.
12. Lin JH, Lee JN. [Menstrual cycle and disorder of adolescent girls in southern Taiwan]. *Gaoxiong Yi Xue Ke Xue Za Zhi* 1987;**3**:150–4.

13. Yaung CL, Lai ES. Body height attained at the time of peak height velocity and at menarche: its relation to adult height. *Taiwan Yi Xue Hui Za Zhi* 1988;**87**:563–8.
14. Lee JE, Jung HW, Lee YJ, Lee YA. Early-life exposure to endocrine-disrupting chemicals and pubertal development in girls. *Ann Pediatr Endocrinol Metab* 2019;**24**:78–91.
15. Matsuo N, Anzo M, Sato S, Ogata T, Kamimaki T. Testicular volume in Japanese boys up to the age of 15 years. *Eur J Pediatr* 2000;**159**:843–5.
16. Wang YN, Zeng Q, Xiong F, Zeng Y. Male external genitalia growth curves and charts for children and adolescents aged 0 to 17 years in Chongqing, China. *Asian J Androl* 2018;**20**:567–71.
17. Chin T, Liu C, Wei C. Testicular volume in Taiwanese boys. *Zhonghua Yi Xue Za Zhi (Taipei)* 1998;**61**:29–33.
18. Marshall WA, Limongi Y. Skeletal maturity and the prediction of age at menarche. *Ann Hum Biol* 1976;**3**:235–43.
19. Greulich WW, Pyle SI. *Radiographic atlas of skeletal development of the hand and wrist*. 2nd ed. Standford, CA: Standford University Press; 1959.
20. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Arch Dis Child* 1976;**51**:170–9.
21. Karaman MI, Kaya C, Caskurlu T, Guney S, Ergenekon E. Measurement of pediatric testicular volume with Prader orchidometer: comparison of different hands. *Pediatr Surg Int* 2005;**21**:517–20.
22. Ong KK, Ahmed ML, Dunger DB. Lessons from large population studies on timing and tempo of puberty (secular trends and relation to body size): the European trend. *Mol Cell Endocrinol* 2006;**254–255**:8–12.
23. Meng X, Li S, Duan W, Sun Y, Jia C. Secular trend of age at menarche in Chinese adolescents born from 1973 to 2004. *Pediatrics* 2017;**140**:e20170085.
24. Sørensen K, Aksglaede L, Petersen JH, Juul A. Recent changes in pubertal timing in healthy Danish boys: associations with body mass index. *J Clin Endocrinol Metab* 2010;**95**:263–70.
25. Tanner JM. Issues and advances in adolescent growth and development. *J Adolesc Health Care* 1987;**8**:470–8.
26. Moss AR, Osmond D, Bacchetti P, Torti FM, Gurgin V. Hormonal risk factors in testicular cancer. A case-control study. *Am J Epidemiol* 1986;**124**:39–52.
27. Zhu J, Kusa TO, Chan YM. Genetics of pubertal timing. *Curr Opin Pediatr* 2018;**30**:532–40.
28. De Sanctis V, Di Maio S, Soliman AT, Raiola G, Elalaily R, Millimaggi G. Hand X-ray in pediatric endocrinology: skeletal age assessment and beyond. *Indian J Endocrinol Metab* 2014;**18**(Suppl 1): S63–71.
29. Ontell FK, Ivanovic M, Ablin DS, Barlow TW. Bone age in children of diverse ethnicity. *AJR Am J Roentgenol* 1996;**167**:1395–8.
30. Hochberg Z. Diagnosis of endocrine disease: on the need for national-, racial-, or ethnic-specific standards for the assessment of bone maturation. *Eur J Endocrinol* 2016;**174**:R65–70.
31. Hsieh CW, Liu TC, Jong TL, Tiu CM. Long-term secular trend of skeletal maturation of Taiwanese children between agricultural (1960s) and contemporary (after 2000s) generations using the Tanner-Whitehouse 3 (TW3) method. *J Pediatr Endocrinol Metab* 2013; **26**:231–7.
32. Diamond DA, Paltiel HJ, DiCanzio J, Zurakowski D, Bauer SB, Atala A, et al. Comparative assessment of pediatric testicular volume: orchidometer versus ultrasound. *J Urol* 2000;**164**(3 Pt 2):1111–4.
33. Satoh M. Bone age: assessment methods and clinical applications. *Clin Pediatr Endocrinol* 2015;**24**:143–52.