

Age at Pubertal Development in a Hispanic-Latina Female Population: Should the Definitions Be Revisited?



Ana Pereira MD, PhD¹, Camila Corvalan MD, PhD¹, Paulina M. Merino MD², Valeria Leiva MS¹, Verónica Mericq MD^{2,*}

¹Institute of Nutrition and Food Technology, Faculty of Medicine, University of Chile, Santiago, Chile

²Institute of Maternal and Child Research, Faculty of Medicine, University of Chile, Santiago, Chile

ABSTRACT

Study Objective: To assess pubertal events in a Hispanic female population and to create normograms of puberty.

Design: Longitudinal.

Setting: University facility.

Participants: Five hundred forty-nine girls from the Growth and Obesity Chilean Cohort study.

Interventions: Follow-up twice a year beginning at age 6 years.

Main Outcome Measures: Breast development, pubic hair development, and age. Breast development (B2, B3, and B4) and pubarche (P2) were determined. Age at menarche was obtained from the adolescents and their mothers. Age and growth velocity at peak height velocity were calculated.

Results: In girls, B2, B3, and B4 occur at median ages of 9.2, 10.2, and 10.9 years, respectively. The median age at P2 was 9.7 years. The mean age at peak height velocity and the growth velocity were 10.6 years (SD = 1.1) and 8 cm/y, respectively. The mean age at menarche was 11.9 years (SD = 1.1); only 2.8% (15 /530) of girls experienced menarche after 14 years and 1.9% before 10 years. The mean interval time between B2 and menarche was 2.5 ± 1.0 years. Transient thelarche occurred in 8.6% of girls.

Conclusion: This longitudinal cohort shows that thelarche occurred 1.2 months later than previously reported in cross-sectional studies. Conversely, we found that pubic hair appeared 12 months earlier and menarche occurred 9 months earlier than previously reported. These findings are important in setting normalcy data and avoiding unnecessary clinical consultations.

Key Words: Puberty, Female, Secular trend, Menarche

Introduction

Puberty results from the awakening of complex neuroendocrine machinery, the primary mechanism for which is still unclear. The acquisition of secondary sexual characteristics is characterized by changes in body composition, increased growth rate, completion of longitudinal growth, and finalization with the acquisition of reproductive capacity. In girls, the usual sign of puberty initiation is breast development (thelarche; B2). The development of pubic hair (pubarche; P2) is also incorporated in puberty assessment but should not be used as a sole marker of puberty onset because it depends on an adrenal androgen production increase (adrenarche) more than a gonadal/ovarian source.¹ Individual variability in pubertal timing involves mainly genetic factors, but influences by external signals might play essentially permissive roles. In specific situations, these environmental signals might be crucial in a subset of the population.²

Marshall and Tanner provided data that established norms for several decades; according to these data, the mean age of breast development was 11.2 years.³ Later, this

study was critiqued because the sample was on the basis of underserved children, which is not representative of the general population. A much earlier appearance of secondary sexual characteristics was reported by a large cross-sectional study in 1997 by Herman-Giddens in the United States,⁴ which led to the Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society to propose new guidelines in 1999 to evaluate the age of puberty.⁵ Because of the cross-sectional nature of the study and the fact that observations stopped at age 12 years, there was still some uncertainty around those findings. A more contemporary and multisite/ethnic cohort study, conducted by the Breast Cancer and the Environment Research Program (BCERP), from Biro et al, which was aimed to assess the association between obesity and thelarche, recruited girls at age 6 years ($n = 1239$).⁶ Surprisingly, the authors reported a more substantial proportion of young girls attaining B2 earlier than previously described, varying according to race/ethnicity and body mass index (BMI) percentile. The proportions of non-Hispanic white, Hispanic, and black girls presenting breast development before the age of 8 years were 10.4%, 10.9%, and 23.4%, respectively, indicating that the secular trends in the onset of breast development might have continued since the National Health and Nutrition Examination Survey (NHANES) III and the study from Herman-Giddens et al,⁴ with data collected in the 1990s.⁷ Similar data of a secular

The authors indicate no conflicts of interest.

* Address correspondence to: Verónica Mericq, MD, Institute of Maternal and Child Research (IDIMI), Faculty of Medicine, University of Chile, Santa Rosa 1234, 2° piso, PO box 226-3, Santiago, Chile; Phone: +562 29770850

E-mail address: vmericq@med.uchile.cl (V. Mericq).

trend in thelarche has become available from Europe within a rather short period (approximately 20 years).^{8–11}

Interestingly, data from Europe and North America suggest that the age at menarche has only changed marginally, indicating that the pubertal period between thelarche and menarche might have lengthened.^{12,13} However, Biro et al have recently reported data from the BCERP cohort that has shown an earlier age at menarche and a shorter interval between B2 and menarche in Hispanic adolescents than in white and Asian girls.¹⁴

In Chile, all contemporary data come from cross-sectional studies. The first study on this subject was published in 1886 and described an age at menarche of 16 years.¹⁵ More contemporary assessments reported in 2002 that among low-middle-income girls, 16.7% of the girls aged 7–7.99 years ($n = 36$) had palpable breast tissue equivalent to Tanner stage B2.¹⁶ In 2004, a larger cross-sectional study in Chile that included 758 girls aged 5.8–16.1 years reported that the mean age at Tanner stage 2 breast development and pubic hair was 8.9 and 10.4 years, respectively,¹⁷ and the age at menarche was 12.7 years. Interestingly, in the group aged 7.0–7.99 years ($n = 77$), 13 girls were B2, and none of them were P2. Thus, we believe that some of these events do not represent true pubertal initiation with a progressive nature.

In the Growth and Obesity Chilean Cohort Study (GOCS), we followed low-middle-income children born in 2002–2003 in Santiago, Chile, since they were 3.5 years of age, and collected longitudinal information on a number of clinical outcomes. Thus, the objective of the present work was to describe pubertal events in the female participants of this cohort and to create normograms of puberty that might allow clinicians to plot each patients' transition to evaluate its normalcy in Hispanic girls.

Materials and Methods

The primary aim of the GOCS was to assess the association between early growth and the development of adiposity and metabolic risk.¹⁸ Briefly, in 2006 we recruited 1190 (50% girls) children between 3.0 and 4.9 years of age who were attending the Chilean National Nursery School Council Program from the southeastern area of Santiago. The GOCS includes children with the following characteristics: singleton births only; gestational age 37–42 weeks; birth weight of 2500 to 4500 g (data retrieved from medical registries); and no physical or psychological conditions that could severely affect growth. We did not observe significant differences in age, sex, birth, and anthropometry at enrollment between participants and nonparticipants.¹⁹ In Chile, 5% of the population identify as indigenous (Mapuche is the predominant group),²⁰ and in our cohort, 18.2% of the girls have at least 1 indigenous surname among their parents' and grandparents' surnames (8 in total).²¹

Thereafter, annual evaluations have been conducted, and since 2009, we started collecting data on Tanner staging every 6 months as well as registering age at menarche.

The Ethics Review Board of the Institute of Nutrition and Food Technology of the University of Chile approved the study protocol. All parents or guardians of the children

provided written informed consent, and the girls gave their assent.

Pubertal Development

At age approximately 7 years, a single pediatric endocrinologist (V.M.) assessed pubertal staging.³ Then, secondary sex characteristics were evaluated every 6 months by a female dietitian trained specifically for this purpose, with permanent supervision by the pediatric endocrinologist (V.M.). The sexual maturity staging criteria and definitions used in the study were the 5 stages of breast and pubic hair development determined using palpation and visual inspection, as described by Marshall and Tanner (Tanner staging).³ Concordance among dietitians and between dietitians and the pediatric endocrinologist was 0.9 for breast stages.²²

Transient thelarche was defined as a B2 disappearing at a subsequent visit.

Age at menarche was self-reported. Mothers and girls were advised to call researchers, and telephonic follow-up was performed every 6 months starting at breast Tanner stage 4 (B4); a questionnaire was developed to differentiate vaginal infections or other genitourinary conditions from first menses.

Anthropometric Measures

Weight and height were collected using standardized protocols (barefoot and light clothes) by 2 dietitians with inter- and intrarater correlation coefficients greater than 0.80 for all measurements. Weight was measured with a portable electronic scale (Seca 770) with a precision of 0.1 kg, and height was measured with a portable stadiometer (Harpender 603) to the nearest 0.1 cm. BMI was calculated by dividing weight (in kilograms) by height in meters squared. We estimated height for age and BMI for age on the basis of the World Health Organization 2007 growth reference.²³ A complete description of anthropometry methodology is reported elsewhere.²⁴ Birth weight was obtained from medical records, and the quality of the data was previously assessed.²⁵ The peak height velocity (PHV) was defined as the highest velocity in growth that occurred in girls older than 7 years of age, and the age at onset of growth spurt (OGS) was the lowest height velocity before the PHV.

Statistical Analyses

A new event or progression in the Tanner stages occurs within a time interval; thus, the true moment of occurrence of the event is unknown. In other words, the age at onset of any of these stages might occur at any point in the interval in which a girl's Tanner stage changes at the subsequent visit (eg, age at B2 was considered the age between the last visit at B1 and the subsequent visit at B2). In the case that at the first visit, the girl was already at Tanner stage 2 or higher, we assumed that she was at Tanner stage 1 at age 5 (in 2006–2007, girls did not have signs of puberty initiation). Thus, the age of any pubertal event was the midpoint of the

age at 2 consecutive visits. Because the event might occur at any moment within the interval, we estimated the median and 95% confidence interval for age at the different Tanner stages for breast and pubic hair by using interval-censoring analysis. We also performed a sensitivity analysis using the midpoint of the interval as the age of onset of puberty, and the results were similar (data not shown).

Age at OGS and PHV were calculated according to Aks-glaede et al.²⁶ Height velocity was estimated as the difference between 2 subsequent height measures (in centimeters) divided by the difference in time (per year), and the age was assigned as the midpoint of the period. PHV was defined as the period in which the height velocity was the highest in girls after 8 years of age. Age at OGS was calculated as the period of minimum height velocity immediately before the age of PHV. Data were considered implausible and were excluded from the analyses in the following situations: when the difference in the velocity of PHV and OGS was less than 2 cm per year; and when last recorded visit was the PHV and it was less than 7 cm per year.

The puberty nomograms for breast development, pubic hair development, and menarche were on the basis of the longitudinal data using the methodology of van Buuren²⁷ and van Buuren and Ooms²⁸ (stage-line diagrams). On the basis of the nomograms, age-specific SD scores were calculated. All statistical analyses were carried out using Stata version 15.0 (StataCorp).

Results

From the total number of girls recruited in 2006, 549 had at least 1 sexual maturation evaluation (Tanner or menarche recording) between 2009 and 2017. The retention rate of the cohort in 2017 was 80%, and the median number of visits during the study period was 10 visits (interquartile range, 10–14). From these girls, we were able to detect thelarche in 426, pubarche in 444, menarche in 530, and PHV in 417. The mean BMI z-score and height z-score at B2 was 0.8 (SD = 1.1) and 0.1 (SD = 1.0); at B4 of 1.0 (SD = 1.2) and 0.2 (SD = 1.0); and at menarche 1.0 (SD = 1.1) and 0.4 (SD = 0.9), respectively. The prevalence of obesity and overweight at B2 was 14% and 33%, respectively.

On the basis of the entire cohort, girls experienced thelarche, breast Tanner stage 3 (B3) and stage 4 (B4) at median ages of 9.2, 10.2, and 10.9 years, respectively (Table 1). Of these girls, 39 girls were B2 at the first Tanner stage evaluation, and in 37 girls, we detected transient thelarche (8.6%).

The median age at pubarche was 9.7 years (Table 1). In 350 girls, we were able to detect B2 and P2. In 185 girls (52.9%), thelarche preceded pubarche, whereas in 88 girls (25.1%), P2 occurred before B2 (Table 2).

The median age at PHV and growth velocity was 10.6 years (interquartile range, 9.8–11.3) and 8 cm/y, respectively. The complete data are shown in Table 1. The mean age at menarche was 11.9 years (SD = 1.1); only 15 girls experienced menarche after the age of 14 years (2.8%) and 10 girls before the age of 10 years (1.9%; data not shown). Despite girls' and mothers' menarche age being

Table 1

Estimated Median Age of Secondary Sex Characteristics in Breast, Pubic Hair Tanner Staging, Menarche, and Peak Height Velocity

| Variable | n | Median | 95% CI |
|---------------------------------|-----|--------|-----------|
| Breast Tanner staging (years) | | | |
| B2 | 426 | 9.2 | 9.0-9.3 |
| B3 | 386 | 10.2 | 10.1-10.3 |
| B4 | 388 | 10.9 | 10.8-11.0 |
| Pubarche Tanner staging (years) | | | |
| P2 | 444 | 9.7 | 9.6-9.8 |
| IQR | | | |
| PHV | | | |
| Age at PHV, years | 417 | 10.6 | 9.8-11.3 |
| Age at OGS, years | 417 | 8.3 | 7.5-8.8 |
| Velocity at PHV, cm/y | 417 | 8.3 | 7.5-9.2 |
| Velocity at OGS, cm/y | 417 | 4.8 | 4.2-5.3 |
| Menarche | | | |
| Menarche, years | 530 | 11.9 | 11.2-12.6 |

CI, confidence interval; IQR, interquartile range; OGS, onset of growth spurt; PHV, peak height velocity.

significantly correlated, the magnitude was low ($r = 0.12$; $P = .01$). The mean interval time between B2 and menarche was 2.5 ± 1.0 years (Table 2).

Finally, in Figure 1, we plotted these pubertal characteristics (± 2 SD) and the growth of Chilean girls.

Discussion

In this ongoing longitudinal study we examined the timing of the onset and subsequent development of secondary sex characteristics in a cohort of Chilean girls and adolescents. We observed that the median onset of breast development occurred 1.2 months later than previously reported in our country in the latest cross-sectional study.¹⁷ Conversely, we found that pubic hair appeared 12 months earlier and menarche occurred 9.6 months earlier than previously reported.^{17,29}

This discrepancy could be attributed to the presence of a transient thelarche in the former study, which cannot be detected in a cross-sectional study. Indeed, isolated thelarche (ie, thelarche that does not progress and is not accompanied by the sequence of pubertal events) seems to be prevalent.^{30,31} In the present study, we detected 8.6% of girls who experienced these phenomena. The worldwide decline in the age of B2 and the larger interval between B2 and menarche could be attributed in part to this fact.

Table 2

Timing between Sexual Maturation Events

| Variable | n | % |
|--------------------------------------------|-----|-------|
| Girls who had a B2 or P2 or both diagnosis | 520 | 100.0 |
| Girls who were detected B2 but not P2 | 76 | 14.6 |
| Girls who were detected P2 but not B2 | 94 | 18.1 |
| Girls who were detected P2 and B2 | 350 | 67.3 |
| B2 and P2 diagnosed at same time | 77 | 22.0* |
| B2 before P2 | 185 | 52.9* |
| P2 before B2 | 88 | 25.1* |
| Mean | | SD |
| Time between B2 to menarche, years | 2.5 | 1.0 |
| Time between B2 to B3, years | 1.3 | 0.7 |
| Time between B3 to B4, years | 1.0 | 0.6 |

* Percentage in relation to girls who were diagnosed with B2 and P2.

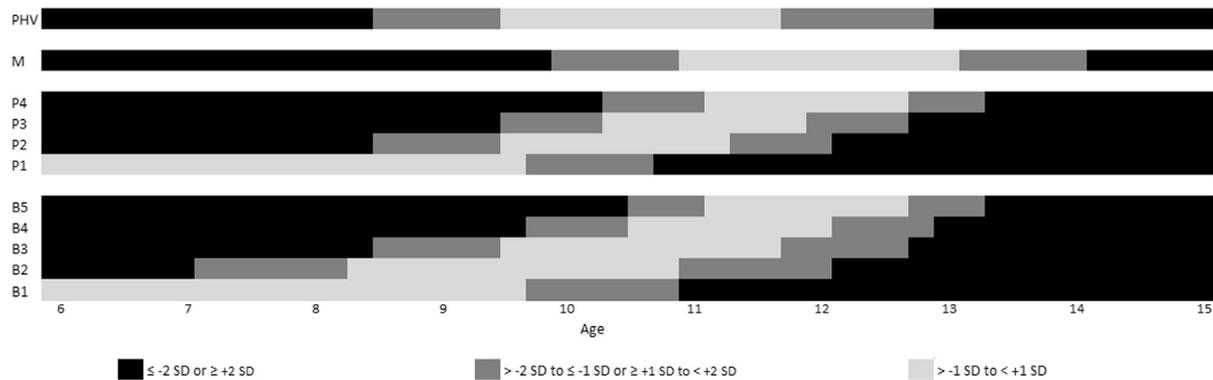


Fig. 1. Description of pubertal development and growth in Chilean girls; breast, pubic hair, menarche and PHV. The different pubertal stages are described in the y-axis: B1 to B5 are breast Tanner stages, P1 to P4 are pubic hair stages, and M corresponds to age at menarche. The x-axis represents the age of the participants. Black squares correspond to the age distribution of the different pubertal stages between less than or equal to -2 SD or greater than or equal to 2 SD. Dark gray squares correspond to the age distribution of the pubertal stages between greater than -2 SD and less than or equal to -1 SD or greater than or equal to 1 SD and less than 2 SD. Light gray squares correspond to the age distribution of the pubertal stages between greater than -1 SD and less than 1 SD. PHV, peak height velocity.

However, nutritional status could be a confounder when puberty onset is evaluated. In the previously mentioned Chilean study, the percentage of obese girls was 24.4%, and the percentage of overweight girls was not reported. In our sample, 47% were either obese or overweight at B2, which reflects the country's current nutritional status.³²

Another important confounder is ethnicity. Local ancestry estimation requires reference panels from the ancestral populations, which correspond to native American, European, and African populations for Latinos. A recent assessment of the contribution of the 3 continental populations in Chile indicated that its composition was 40.4% native, 57.1% European, and 2.5% African.³³ Nevertheless, in a survey within the same cohort, we aimed to evaluate the prevalence of precocious puberty (thelarche or pubarche) in children with Mapuche ancestry vs nonindigenous Chilean children (according to surnames).³⁴ We observed no differences in the prevalence of these events in girls even after adjustment for socioeconomic status, body mass index, waist circumference, insulin-like growth factor 1 and dehydroepiandrosterone sulfate at 7 years. However, in our cohort, ethnicity was not a determinant of puberty, and socioeconomic status and BMI were not confounders; we cannot rule out that these 3 factors might influence age differences in pubertal onset worldwide. Nevertheless, the large decline in age at P2 and menarche within a period of 10 years is worrisome. Both events cannot be transient and thus represent a true advancement in the onset of puberty. An increase in obesity prevalence has been blamed as causal in this earlier maturation. We aim in future research to assess the role of adiposity (measured using different indicators) in determining early puberty in Chilean children.

The BCERP cohort of pubertal development in Hispanic adolescents showed a similar median age of breast development (9.3 years),⁷ age at menarche (11.8 years), and a similar interval between B2 and menarche (2.3 years) compared with our population.¹⁴

In Venezuela, the Caracas Mixed-Longitudinal Study had a subsample of girls followed until completion of puberty who showed a later median age of B2 of 10.3 years (range, 7.4–12 years) and of menarche at 12.5 years (range,

9.6–16 years). However, these girls were recruited between 1976 and 1982, more than 3 decades ago, and thus, these findings might not represent current trends. In a Cuban cross-sectional descriptive study of 100 girls aged 13–15 years in urban and rural areas, thelarche appeared at 11.4 years and 10.4 years and menarche at 12.4 and 11.4 years in rural and urban areas, respectively. The data were obtained between 2009 and 2010, but pubertal development was assessed using a questionnaire. This fact might explain the short time between B2 and menarche, and the assessment of age at B2 might be less reliable.³⁵ In another cross-sectional study in Colombia that was aimed to analyze weight, height, and BMI variability according to pubertal development and type of school in adolescents from Medellín,³⁶ the authors report a mean age of B2 at 10.9 (± 1.2 years). The number of girls included in the sample was 828, but recruitment was performed in 1998–1999, and the authors did not report the age range of girls included.

Endocrine disruptors have also been associated with earlier maturation, and this exposure has also been evaluated within our cohort.³⁷ We observed that increased urinary levels of phenols or phthalates at specific stages (breast Tanner stage 1 and Tanner stage 4) were associated with an earlier menarche.

Assessment of age at OGS and at PHV on the basis of growth charts has previously been carried out in a number of studies with different methodologies.^{38,39} We decided to use the method described by Aksglaede et al,²⁶ which has a high agreement between estimated age at PHV on the basis of 12-month measurements and 3–4 monthly measurements. PHV occurred at a later stage of puberty, between B3 and B4, and approximately half a year before menarche, which is consistent with Marshall and Tanner's description.³ Interestingly, the magnitude of PHV is greater than what Biro et al reported⁴⁰ in white (7.23 cm/y) and black girls (7.18 cm/y).

We provide a nomogram that might be very useful in the evaluation of puberty for primary practitioners and pediatricians in Latin America, and researchers from other parts of the world should also provide similar referral figures for their countries. This tool might allow for the easy recording of secondary sex characteristics and prevent unnecessary

consultations. The incorporation of Tanner assessment, together with other components of pubertal maturation, such as the increase in growth velocity, might also allow us to rule out isolated thelarche, which seems to be highly prevalent.

This work is not exempt of limitations. We observed a weak positive correlation between girls' and mothers' age at menarche. This finding could be attributed to method bias because maternal age at menarche was self-reported in 2010. Another limitation is that appearance of B2 occurred within the last visit at B1 and the first visit at B2; to avoid this error we used interval-censoring analysis, and the estimated error should be small because the time interval between visits was no more than 6 months. The strength of our results is on the basis of the longitudinal nature of the study, including anthropometry, maternal age at menarche, and Tanner staging using inspection and palpation of all secondary sex characteristics. All of these data allowed us to characterize pubertal events during this period: secondary sex characteristics and growth velocity. We believe our findings are important not only for pediatric endocrinologists but also for primary practitioners in setting normalcy data and avoiding unnecessary consultations.

Acknowledgments

Fondo Nacional de Desarrollo Científico y Tecnológico, Chile Grants 1140447, 1120326 and 11170670. World Cancer Research Fund International, United Kingdom 2010/245 supported this work. Sponsors were not involved in study design, collection, analysis and interpretation of data; manuscript writing or submission decision.

We thank GOCS families and children for their participation.

References

- Abreu AP, Kaiser UB: Pubertal development and regulation. *Lancet Diabetes Endocrinol* 2016; 4:254
- Rzeczkwaska PA, Hou H, Wilson MD, et al: Epigenetics: a new player in the regulation of mammalian puberty. *Neuroendocrinology* 2014; 99:139
- Marshall WA, Tanner JM: Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969; 44:291
- Herman-Giddens ME, Slora EJ, Wasserman RC, et al: Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings Network. *Pediatrics* 1997; 99:505
- Kaplowitz PB, Oberfield SE: Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society. *Pediatrics* 1999; 104:936
- Biro FM, Galvez MP, Greenspan LC, et al: Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. *Pediatrics* 2010; 126:e583
- Biro FM, Greenspan LC, Galvez MP, et al: Onset of breast development in a longitudinal cohort. *Pediatrics* 2013; 132:1019
- Juul A, Teilmann G, Scheike T, et al: Pubertal development in Danish children: comparison of recent European and US data. *Int J Androl* 2006; 29:247
- Mul D, Fredriks AM, van Buuren S, et al: Pubertal development in The Netherlands 1965–1997. *Pediatr Res* 2001; 50:479
- Aksglaede L, Sorensen K, Petersen JH, et al: Recent decline in age at breast development: the Copenhagen Puberty Study. *Pediatrics* 2009; 123:e932
- Rubin C, Maisonet M, Kieszak S, et al: Timing of maturation and predictors of menarche in girls enrolled in a contemporary British cohort. *Paediatr Perinat Epidemiol* 2009; 23:492
- Sorensen K, Mouritsen A, Aksglaede L, et al: Recent secular trends in pubertal timing: implications for evaluation and diagnosis of precocious puberty. *Horm Res Paediatr* 2012; 77:137
- Ramnitz MS, Lodish MB: Racial disparities in pubertal development. *Semin Reprod Med* 2013; 31:333
- Biro FM, Pajak A, Wolff MS, et al: Age of menarche in a longitudinal US cohort. *J Pediatr Adolesc Gynecol* 2018; 31:339
- Diaz E: Breves observaciones sobre la aparición de la pubertad en la mujer chilena y las predisposiciones patológicas del sexo [Brief observations of puberty onset and its pathological predisposition in Chilean women]. Santiago de Chile, Universidad de Chile, 1886
- Gaete X, Unanue N, Ávila A, et al: Cambios en la edad de inicio de la pubertad en niñas de la comuna de Santiago: implicancias para el diagnóstico de la pubertad precoz [Changes in the age of puberty in girls in the district of Santiago: implications for the diagnosis of precocious puberty]. *Rev Chil Pediatr* 2002; 73:363
- Codner E, Unanue N, Gaete X, et al: Age of pubertal events in Chilean school age girls and its relationship with socioeconomic status and body mass index [Cronología del desarrollo puberal en niñas escolares de Santiago: relación con nivel socio-económico e índice de masa corporal]. *Rev Med Chil* 2004; 132:801. [in Spanish].
- Corvalán C, Uauy R, Stein AD, et al: Effect of growth on cardiometabolic status at 4 y of age. *Am J Clin Nutr* 2009; 90:547
- Kain J, Corvalán C, Lera L, et al: Accelerated growth in early life and obesity in preschool Chilean children. *Obesity (Silver Spring)* 2009; 17:1603
- INE: Social Statistics of Indigenous people in Chile- CENSO 2002. Santiago, National Institute of Statistics (INE), 2005
- Fernández JR, Redden DT, Pietrobelli A, et al: Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. *J Pediatr* 2004; 145:439
- Pereira A, Garmendia ML, González D, et al: Breast bud detection: a validation study in the Chilean growth obesity cohort study. *BMC Womens Health* 2014; 14:96
- de Onis M, Garza C, Victora CG, et al: The WHO Multicentre Growth Reference Study: planning, study design, and methodology. *Food Nutr Bull* 2004; 25:S15
- Corvalán C, Uauy R, Mericq V: Obesity is positively associated with dehydroepiandrosterone sulfate concentrations at 7 y in Chilean children of normal birth weight. *Am J Clin Nutr* 2013; 97:318
- Kain J, Galván M, Taibo M, et al: Evolution of the nutritional status of Chilean children from preschool to school age: anthropometric results according to the source of the data. *Arch Latinoam Nutr* 2010; 60:155. [in Spanish].
- Aksglaede L, Olsen LW, Sorensen TI, et al: Forty years trends in timing of pubertal growth spurt in 157,000 Danish school children. *PLoS One* 2008; 3:e2728
- van Buuren S: Growth charts of human development. *Stat Methods Med Res* 2014; 23:346
- van Buuren S, Ooms JC: Stage line diagram: an age-conditional reference diagram for tracking development. *Stat Med* 2009; 28:1569
- Hernández MI, Unanue N, Gaete X, et al: Age of menarche and its relationship with body mass index and socioeconomic status. *Rev Med Chil* 2007; 135:1429. [in Spanish].
- Mogensen SS, Aksglaede L, Mouritsen A, et al: Diagnostic work-up of 449 consecutive girls who were referred to be evaluated for precocious puberty. *J Clin Endocrinol Metab* 2011; 96:1393
- Sømod ME, Vestergaard ET, Kristensen K, et al: Increasing incidence of premature thelarche in the Central Region of Denmark - challenges in differentiating girls less than 7 years of age with premature thelarche from girls with precocious puberty in real-life practice. *Int J Pediatr Endocrinol* 2016; 2016:4
- MINSAL: Obesity a National Problem: evaluation of the law on nutritional composition and its advertising. Santiago, Chile, Ministry of Health, 2017
- Eyheramendy S, Martínez FI, Manev F, et al: Genetic structure characterization of Chileans reflects historical immigration patterns. *Nat Commun* 2015; 6:6472
- Fernández M, Pereira A, Corvalán C, et al: Precocious pubertal events in Chilean children: ethnic disparities. *J Endocrinol Invest* 2019; 42:385
- Osorio Mora M, González Balmaceda A, Mora de Zayas M, et al: Puberty in adolescent of rural and urban areas. *Rev Cubana Ginecol Obstet* 2012; 38:7
- Giraldo GA, Uscátegui PRM, Restrepo CMT, et al: Variabilidad del peso, la estatura y el índice de masa corporal según desarrollo puberal y tipo de colegio en adolescentes de Medellín, Colombia [Weight, height and body mass index variability according to both puberal development and to the type of school in adolescents of Medellín, Colombia]. *Rev Chil Nutr* 2012; 39:136. [in Spanish].
- Binder AM, Corvalán C, Calafat AM, et al: Childhood and adolescent phenol and phthalate exposure and the age of menarche in Latina girls. *Environ Health* 2018; 17:32
- Persson I, Ahlsson F, Ewald U, et al: Influence of perinatal factors on the onset of puberty in boys and girls: implications for interpretation of link with risk of long term diseases. *Am J Epidemiol* 1999; 150:747
- Virani N: Growth patterns and secular trends over four decades in the dynamics of height growth of Indian boys and girls in Sri Aurobindo Ashram: a cohort study. *Ann Hum Biol* 2005; 32:259
- Biro FM, Huang B, Crawford PB, et al: Pubertal correlates in black and white girls. *J Pediatr* 2006; 148:234