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ORIGINAL ARTICLE

What is the best method for estimating final height in patients with precocious puberty?

¿Cuál es el mejor método de estimación de talla final en pacientes con pubertad precoz?

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What do we know about the subject matter of this study?

In many cases, precocious puberty can cause a height below the genetic target. There are validated height prediction methods to guide the treatment decision. Those methods that use bone maturation age are expected to be more accurate.

What does this study contribute to what is already known?

Genetic target height is an easy to apply method, which showed similar results of final height compared with methods that use bone maturation age, so it is very useful in clinical practice.

Abstract

Central precocious puberty is the premature activation of the hypothalamic-pituitary-gonadal axis, leading to an early epiphyseal fusion and, in many cases, heights below the genetic target. Therefore, a proper adult stature prediction is essential for the treatment decision. **Objective:** To compare the concordance of final height using height prediction made by two validated methods versus the genetic target height in girls who consulted due to central precocious puberty. **Patients and Method**: Retrospective, non-concurrent cohort study including 93 girls with central precocious puberty, who were not treated with LHRH analogs and had reached their final adult height. The data was obtained from the clinical records. To predict height, the Bayley-Pinneau method and the Roche-Wainer-Thissen method were applied, and the results were compared with the genetic target height. The concordance between the estimated final height and the final height obtained was evaluated using the Bland-Altman method. **Results:** When comparing the final height obtained with that predicted by the Bayley-Pinneau method, there was a mean difference of 1.01 cm, and using the Rocke-Wainer-

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Thissen method, there was a difference of +0.96 cm. The calculation of the genetic target height showed a difference of +0.05 cm with respect to the final height. **Conclusion:** The prediction of height made by the Bayley-Pinneau and Roche-Wainer-Thissen methods was adequate and, contrary to expectations, it was similar to the calculation of the genetic target height that does not use the age of bone maturation. This also presented better concordance and less dispersion of the results with respect to the final height obtained.

Introduction

In girls, precocious puberty is suspected with the appearance of the breast buds and/or pubic hair before the age of 8[1]. It is a frequent cause of consultation in Pediatric Endocrinology, both from families and referred by their pediatricians.

Precocious puberty can be of central origin, which depends on the activation of the Hypothalamus-Pituitary-Gonad (HPG) axis; or it can be peripheral (PPP), which is independent of the axis and can be of ovarian or adrenal origin or produced by exogenous steroid administration. Clinically, both can present the same signs, breast bud, and/or pubic and axillary hair, and apocrine odor[2].

The premature activation of the HPG axis, which occurs in central precocious puberty (CPP), causes an increased secretion of gonadotropins (LH and FSH), which stimulate the production of estradiol responsible for both breast development and accelerated pubertal growth, and ends with the fusion of the growth plate approximately two years after menarche. Because of this early process, affected patients may reach a final height smaller than expected[1,2].

The treatment of choice is the gonadotrophin-releasing hormone analogs (GnRHa), which halt pubertal progression, produce a variable regression in the development of secondary sexual characteristics, and decrease the advancement of skeletal maturation, which could benefit the achievement of final height if performed on time[3]. However, it is an invasive and high-cost treatment since it requires regular injections, which means that it is not always well tolerated by patients and their families; furthermore, not all patients require it.

One of the main concerns of parents, and therefore an important factor in deciding treatment, is the eventual compromise of final height. Clinical experience has shown that not all cases of CPP present deterioration of their final height[1], so it is very important to have an adequate method to accurately predict the final height that these patients will reach. Among the methods developed and most widely used to predict final height in children are those developed by Bayley-Pinneau (BP) and Roche-Wainer-Thissen (RWT).

The BP method was developed in 1952 and is still one of the most widely used. It is based on the close correlation between the bone age established from the Greulich-Pyle (GP) atlas and the calculation of the percentage of adult height attained at that time[4]. The RWT methodology, published in 1975, also uses bone age plus longitudinal growth data and is based on multiple regression equations applied to children aged between one and sixteen years[5]. On the other hand, the calculation of the genetic target height (GTH), is a method of predicting height that is easy to calculate and very useful for clinical practice. The final height estimate is obtained by calculating the average parental height, adjusted to the patient's sex from a 13cm difference, which is added to the average in girls or subtracted in boys[6].

Given that the target height does not use bone age for its calculation, it should be more useful in patients with normal bone maturation, i.e., a difference between bone and chronological age of less than one year. In the other two methods analyzed, the prediction is based on bone age, which represents very well the biological maturity of an individual, so they would be expected to be more accurate in patients with advanced bone maturation, as occurs in girls with CPP. However, they do not consider parental height.

Currently, there is little information on the comparison of the height prediction obtained by the BP and RWT methods with the prediction made by GTH in girls with CPP who have reached their final height. Knowing the advantages and limitations of these calculations could be very useful for predicting the final height compromise and, therefore, making the treatment decision in girls with CPP.

The objective of this work was to compare the agreement between the prediction of final height obtained by BP, RWT, and GTH calculation methods in relation to the actual final height achieved in girls with CPP, in order to define which of them provides more accurate information.

Patients and Method

Study design

Partially concurrent retrospective cohort study. Data were collected from 120 female patients aged

between 6.5 and 9.5 years who consulted due to suspected precocious puberty in the UC Health Network between 1987 and 2005, seen by two pediatric endocrinologists. Patients treated with GnRHa were previously excluded in order to have the final height not modified by the treatment. For the analysis, we included patients in whom it was possible to evaluate their final height at the time of the study, which was defined as growth < 1 cm in the last year and a bone age ≥ 15 years[7].

Measurements

Of the 120 patients who met the criteria and agreed to participate, 93 were included; 39 of them were able to attend in person to have their final height measured with a high-precision stadiometer (Harpenden®) in the medical office. The data of the remaining 54 patients were obtained by telephone with precise measurement instructions at home. For this purpose, they were asked to be measured by a third party, placing their whole body with both feet together on a smooth surface. With the body and head on the wall, a hardcover book was placed at a 90-degree angle to the wall. A line was marked at that point and then, without the patient, was measured with a metal measuring tape from the floor to the mark. This procedure, guided by telephone, was repeated three times, and the average of these three measurements was recorded as the final height.

Clinical data

The data necessary to make the diagnosis of CPP and the estimate of final height were obtained within the first three months of the first consultation and were collected by reviewing clinical records. The diagnosis of CPP was confirmed by a suggestive clinical picture plus: a) GnRH test (peak LH > 5 mIU/ml by ECLIA method); or b) Ultrasound with uterine growth > 3.6 mm and ovarian > 2 cc and basal LH > 0.3 mIU/ml by ECLIA method (n); or both criteria. In the first consultation, chronological age, bone age (using GP Atlas for carpal radiography), weight, and height measured with the methodology described above were recorded for each patient. In addition, in the same consultation, the mother's height and mostly the fathers' height (56%) were measured with the same high-precision stadiometer. In the rest of the cases, the father's height was obtained from the mother's report. The carpal radiography was analyzed and the bone age report was confirmed or corrected, in all cases by the two treating endocrinologists highly experienced in the area.

No concordance study was performed between the bone age diagnoses and, in case of discrepancy between the reports, the one made by the treating endocrinologist was always used.

Methods

For each patient, the three methods for estimating final height were applied.

The BP method uses tables according to sex, chronological age, and bone age. The formula used was: *Final adult height = (current height/ percentage of adult height achieved) x100*. The height obtained in centimeters according to sex was divided by a different factor according to whether bone maturation was normal (bone age +/- 1 year regarding chronological age), accelerated (bone age > 1 year advanced regarding chronological age), or delayed (bone age delayed > 1 year regarding chronological age). For the RWT method, a linear function was used according to height, weight, bone age assessed by the GP method, and average parental height. The genetic target height was calculated using the formula: *GTH child: (father's height (cm) + mother's height (cm) + 13) /2*.

The accuracy of a height prediction method is considered good if the final height achieved is +/- 3 cm in relation to the prediction.

Statistical analysis

To evaluate the agreement between continuous variables, the Bland and Altman method was used between the final height estimated by the three methods and the final height achieved. For this, the average between the height obtained by the estimation method and the actual final height was placed on the x-axis; and the difference between them was placed on the y-axis. If the estimation was perfect, it would be on the 0 line. However, since this is unlikely, they are calculated and distributed towards an upper line when there is an overestimation or a lower one if there is an underestimation with respect to the known final height. The upper and lower lines represent the 2 SDs.

Ethical aspects

This project was approved by the research ethics committee of the Pontifical Catholic University of Chile. Informed consent signed by the patients or their legal representatives was obtained before participating in the study.

Results

Ninety-three patients were included, with an average age at the first consultation of 8.3 ± 1.2 years (6 years 5 months to 9 years 5 months), and average bone age of 9.9 ± 1.7 years.

The average breast Tanner stage at the time of the study was II. Table 1 shows the distribution of patients according to Tanner stages.

Figure 1 shows the average height prognosis and its

standard deviation obtained from the three estimation methods, compared with the patients' actual final height.

Figures 2, 3, and 4 show the agreement between each method and the final height.

Figure 2 shows the comparison between the height prediction by the BP method and the final height achieved. The difference between the estimated and observed methods was -1.01 cm on average, with a maximum over- and underestimation of 10.7 cm and -15.5 cm, respectively. Since the sample had a normal distribution, tested by Kolmogorov-Smirnov, 95% of the measurements were between 8.87 cm (+2DS) and -10.89 cm (-2DS).

Figure 3 compares the height predicted by the RWT method with the final height achieved. An average difference of +0.96 is observed between the estimated and observed results, with a maximum over- and underestimation of +14.9 cm and -11 cm, respectively. 95% of the measurements were between 9.65 cm (+2DS) and -7.72 cm (-2DS).

Figure 4 shows the comparison between the height predicted by the GTH method and the final height achieved, showing an average difference of +0.05 cm, with a maximum over- and underestimation of 7.5 cm and -5.5 cm, respectively. 95% of the measurements were between 6.19 cm (+2DS) and -6.10 cm (-2DS).

In this study, 56% of the fathers could be measured in person in the same way as the patients, the rest were measured according to the height reported by the mother. We did not have both measurements in the same individual for comparison.

Discussion

The prediction of final height remains a complex task for pediatricians and endocrinologists. Its calculation for the follow-up of the same individual is useful in clinical practice since it allows assessing the growth potential of patients over time, which is particularly important in cases of early pubertal development. Female precocious puberty is probably the most frequently observed pubertal disorder and motivates many consultations in families that are not always well informed. In these patients, an accurate method for predicting final height is essential, as treatment may not always be necessary.

So far, the method most commonly used by pediatric endocrinologists is BP, which is based on the concept that the prediction obtained has an inaccuracy of +/- 5 cm in patients without growth disorders[4]. The main disadvantage of this method is that in patients with delayed or advanced bone maturation of more than two years, the accuracy decreases significantly. Our study showed that BP obtained an average underestimation of 1.01 cm, but presented a wide dispersion in the results, with greater inaccuracy than expected. This finding is consistent with previous studies[8,9].

Similar results were obtained using the RWT method. It is important to note that this method is more cumbersome to apply; it requires collecting a

Table 1. Tanner stage at the time of diagnosis

Tanner	Nº patients (%)
I*	4 (4.3)
II	68 (73.1)
III	19 (20.4)
IV	2 (2.1)

*history of telarche

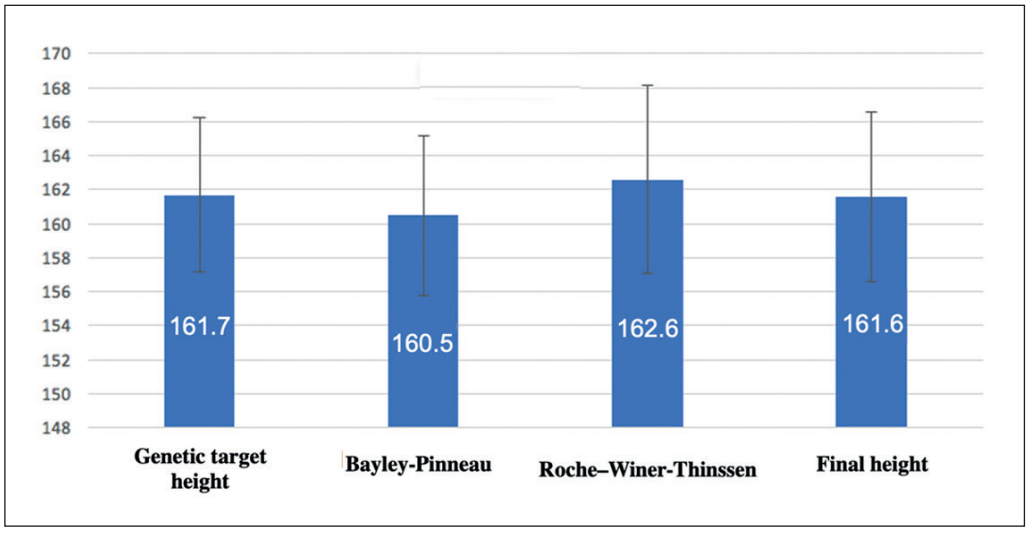

Figure 1. Final height obtained by the methods of estimation of stature and final height.

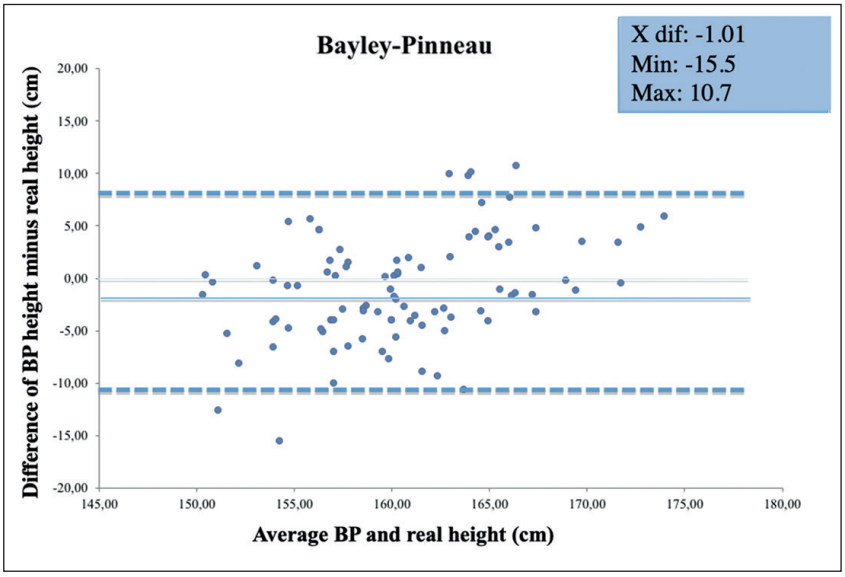

Figure 2. Comparison of size estimation by the Bayley-Pinneau method VS Real height.

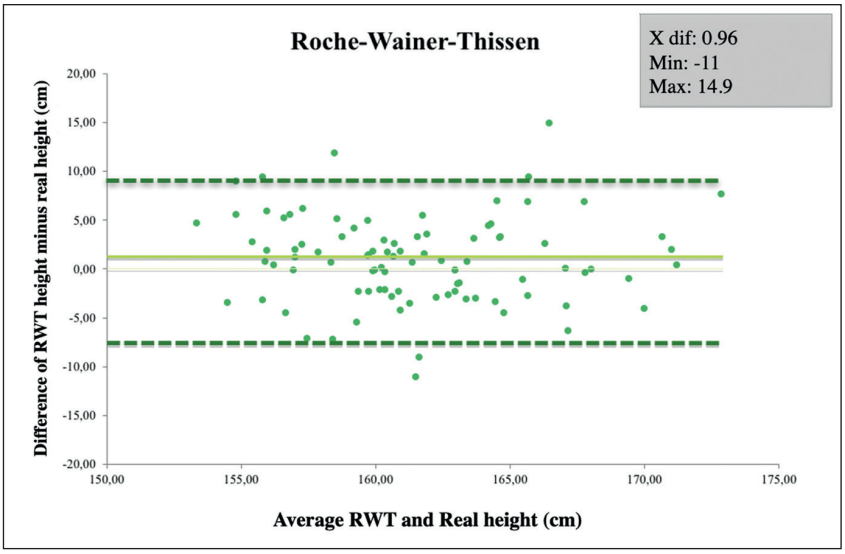

Figure 3. Comparison of height estimation using the Roche-Wainer-Thissen method VS Actual height.

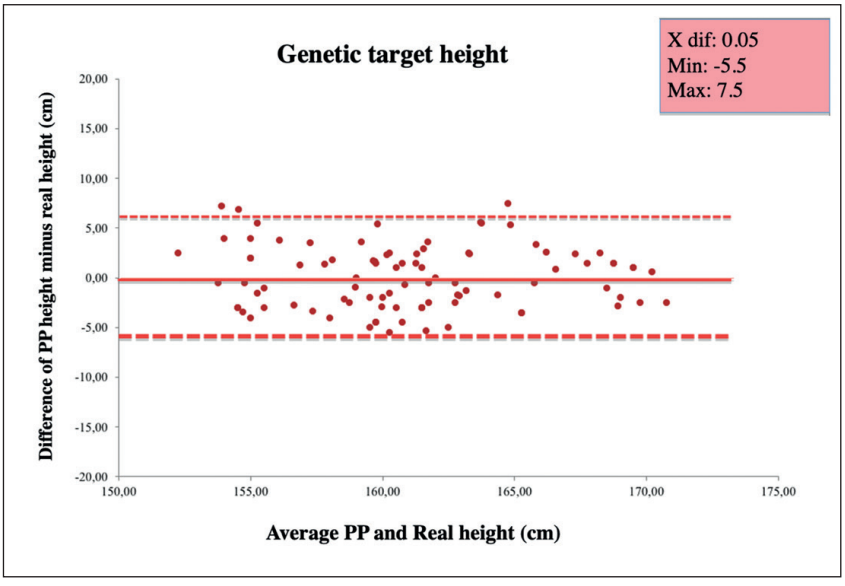

Figure 4. Comparison of height estimation by parent average height method VS actual height.

larger amount of data, comparing them with reference tables, and finally, adding up the results to obtain the final height estimate. On average, this method overestimated the height of our patients by 0.96 cm, showing a significant dispersion in the precision of the heigh calculation prediction with respect to the patients' actual final height.

Contrary to expectations, the simplest method, which does not use bone age and considers the average corrected height of the parents +/- 13 cm, was the one that presented the best concordance, with an average difference very close to zero, also presenting less dispersion in the results, despite that father's height could only be measured in person in slightly more than 50% of the cases. This emphasized the importance of parental height in this prediction, which is not included in the other methods.

In this study, we can observe that the three methods showed accuracy in height prediction. Although the target height was the one that presented the highest concordance with the final height achieved, when comparing it with the BP and RWT methods, the results were similar. Consequently, the comparison of the target height with the height prediction obtained by the BP and RWT methods in girls consulting due to acceleration of biological maturity is an adequate method to evaluate the need to stop puberty, since it allows defining whether there is a possible compromise in the final height and, therefore, providing the most accurate information possible to parents to make the treatment decision. It should be considered that it is important to repeat the application of these methods in successive check-ups, as well as the evaluation of pubertal development and the follow-up with the growth curve.

Regarding our findings, it should be noted that the methods used were developed from the analysis of populations without growth pathologies. This aspect should be considered since, when applied to patients with precocious puberty in whom the pubertal growth spurt and bone age are advanced with respect to chronological age, the accuracy in predicting final height may be different from the healthy population, which could contribute to explain in part the large dispersion observed in our results. The other factor that undoubtedly contributes to explaining the greater variation observed in the first 2 methods is the use of bone age for their calculation, which is subjective and operator-dependent.

Currently, new automated methods have been developed, which suggest greater accuracy in their results. Among them, BoneXpert software (Denmark) stands out, which is based on the GP atlas but has improvements in calculations and clinical data, and calculations for determining bone age by the Tanner-Whitehouse-3 and GP methods[10]. For its calculation, it uses sex, chronological age, height, bone age, the parents' height, and adapts it to mainly European reference populations. This method includes an automated system for reading carpal radiographs, which reduces operator-dependent variability, improving the effectiveness of the prediction. It is currently the main height prediction system for clinical use in Europe and has gradually acquired preference in our country, although studies evaluating the effectiveness of this method with respect to conventional models are very scarce in the literature[11]. Likewise, there are prediction models based on age at first menstruation[12], mathematical models validated in Europe[13], and methods based on bone markers[14] that suggest a certain greater accuracy in their results, surpassing conventional models, but there are no well-designed studies to demonstrate this.

Limitations

The limitations of this work are that in 58% of our patients, their height was measured remotely as described since it is very difficult to achieve attendance in person in more adult patients who are already free of the problem that led them to consult us. However, we should point out that the instructions for measuring at home were very precise and both the patients and those who performed the measurement report have complied with them adequately. Another limitation is the reliability of the bone age report, which is questionable in any operator-dependent examination. However, we can point out that all x-rays were reviewed by two of the investigators who participated in this study, highly experienced in pediatric endocrinology.

Possibly, these patients would have reached a different height than the current ones if they had been treated. This, and what motivated the treatment decision, were not the objectives of this study, partly because it is very difficult to analyze retrospectively, and includes psychosocial and economic aspects in addition to height prognosis. Another limitation to consider was that we were able to get only 40% of the former patients to attend.

Regarding the strengths of our study, we should point out that parental height was recorded based on stadiometer measurement in the consultation room in most cases. Although new carpal x-rays were available during the evolution of almost all our patients and these would probably improve the performance of the methods in predicting final height, we decided not to include them in the study since we consider that, in cases of early precocious puberty, the moment close to the first consultation is the one in which the eventual treatment is decided.

Conclusions

Our study shows that the 3 methods of height prediction in female CPP, although they achieve a very good average concordance (around 1 cm) with the final height achieved, present a large dispersion (6 to 10 cm), which complicates the individual prediction of the cases. None of the height prediction methods studied provides an accuracy capable of establishing absolute certainty, so it requires great caution in sharing these results with families and being aware that prognostic error is always possible. This could be minimized with regular check-ups of the patients and by performing the height prognosis on several occasions, but this analysis is not part of our study.

However, despite these limitations in height prediction, the simplest method, GTH, was comparable with the GP and TW2 methods and presented the highest concordance in their results. The greater dispersion observed in the traditional methods is probably influenced by the subjectivity and variability of the bone age report, included in both methods, which is operator-dependent, and does not include parental height information.

Based on our results, for a better estimation of final height in girls with precocious puberty, we always recommend calculating GTH plus one of the current prediction methods, probably BP due to its simplicity. In case of discrepant results, we advise being more cautious to communicate the predictions to the family and to decide on puberty-stopping treatments.

Based on our results, we recommend calculating GTH for estimating final height in patients with CPP, since it is an easy method to implement, does not require laboratory tests or imaging, and shows good agreement with final height. Given that patients with CPP may present alterations in bone maturation, it is also recommended to simultaneously apply one of the other two current methods. If when comparing GTH versus BP or RWT the results are similar, the prediction will be more reliable.

It should be noted that the new height prediction methods available promise advantages in terms of measurement accuracy over conventional methods. Further studies are needed to compare which of these new methods would be the best tool for estimating final height in women with precocious puberty.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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References

1. García H, Youlton R, Burrows R, et al. Consenso sobre el diagnóstico y tratamiento de la pubertad precoz central. Rev. méd. Chile 2003;131(1):95-110.
2. Hermanussen M, Aßmann C, Groth D, et al. Final height, target height and the community. Georgian Med. News 2014;(230):30-4.
3. Walvoord E, Hirsch O. Combined Use of Growth Hormone and Gonadotropin-releasing Hormone Analogues in Precocious Puberty: Theoretic and Practical Considerations. Pediatrics. 1999;104:1010-4.
4. Bayley N, Pinneau S. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. J Pediatr. 1952;40:423-41.
5. Roche A, Wainer H, Thissen D. The RWT method for the prediction of adult stature. Pediatrics. 1975;56:1026-33.
6. Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2:9 years allowing for height of parents. Arch Dis Child. 1970;45:755-62.
7. Macedo DB, Cukier P, Mendonca BB, et al. Advances in the etiology, diagnosis and treatment of central precocious puberty. Arq Bras Endocrinol Metabol. 2014;58(2):108-17.
8. Lopez MC, Ramos CO, Latronico AC, et al. Applicability of a novel mathematical model for the prediction of adult height and age at menarche in girls with idiopathic central precocious puberty. Clinics (Sao Paulo). 2018;73:e480.
9. Tarim O. Height predictions by Bayley-Pinneau method may misguide pediatric endocrinologists. Turk J Pediatr. 2013;55(1):485-92.
10. Thodberg HH, Kreiborg S, Juul A, et al. TheBoneXpert method for automated determination of skeletal maturity. IEEE Trans Med Imaging. 2009;28:52-66.
11. Lepe G, Villacrés F, Silva Fuente-Alba C, et al. Correlación en la determinación de la edad ósea radiológica mediante el método de Greulich y Pyle versus la evaluación automatizada utilizando el software BoneXpert. Rev. Chil. Pediatr. 2018;89(5):606-11.
12. Giabicani E, Lemaire P, Brauner R. Models for Predicting the Adult Height and Age at First Menstruation of Girls with Idiopathic Central Precocious Puberty. PLoS ONE. 2015; 10(4):e0120588.
13. Lemaire P, Duhil de Bénazé G, Mul D, et al. A mathematical model for predicting the adult height of girls with idiopathic central precocious puberty: A European validation. PLoS ONE. 2018;13(10):e0205318.
14. Vincent A, Souberbielle J, Brauner R. Comparison of two bone markers with growth evolution in 74 girls with central precocious puberty. BMC Pediatrics. 2018;18:2.