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RESEARCH ARTICLE

Increase of Consultations for Premature Thelarche and the Post-Diagnostic of Precocious and Accelerated Puberty in Pediatric Endocrinology in Alava, due to the Lockdown Measures Endured in 2019 as a result of the COVID-19 Pandemic

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ABSTRACT

Introduction: As a result of the COVID 19 pandemic and home confinement measures, many of our routine and daily habits have been affected and modified. But, have these factors conditioned a real increase in Precocious (PP) and Accelerated Puberty (AP)?

Objectives: This is an observational and retrospective study in which the incidence of medical consultations due to Premature Thelarche is compared between March to December 2019 and 2020. The medical consultations took place in the Pediatric Endocrinology (PE) consultation of our hospital, HU Araba - Vitoria.

Patients and Methods: The analysis included 75 cases of young girls who consulted for Premature Thelarche in 2019 and 97 girls who consulted in 2020 for the same reason. Different variables such as somatometry, hormones, ultrasound examination and treatment were analyzed for each of the patients.

Results: In 2019, 75 first visits of PE were due to Premature Thelarche in young girls (accounting for 2.46% of the total number of first visits carried out in Pediatrics Outpatient Clinics (POC) and 16.77% of PE first visits). However, in 2020, 97 first visits were due to PE (3.52% the total first time visits of OC and 23.3% in PE). It was found that in 2020, the number of first time visits due to Premature Thelarche increased by 28% compared to 2019 ($p = 0.0001$ mean comparison).

In 2019, out of the 75 consultations due to premature Thelarche, 40% were diagnosed with an earlier physiological puberty. Conversely in 2020, out of the 97 consultations, 61.77% had a normal physiological puberty. These figures represent an OR of 1.54 ($p = 0.02$ t Student for independent samples). It was evaluated whether the patients had experienced > 3 kg weight gain in the 6 months prior to the medical visit. In 2020, 31.57% of patients experienced weight gain, whereas 68.42% did not. In 2019 patients who experienced weight gain accounted for 12.16% and 87.83% did not experience significant weight gain ($p = 0.01$ t Student for independent samples).

Conclusion: Our data shows an increase in the incidence of the referrals from Primary Attention to Pediatric Endocrinology to examine advanced Thelarche during the period of lockdown measures (2020), and an increase in the number of diagnostics of PP and AP in young girls in our hospital when compared to figures of 2019. Furthermore, in 2020 there was a greater number of patients who experienced weight gain increase 6 months prior to the medical consultations.

We hypothesize that lockdown inflicted sedentary lifestyles together with changes in dietary habits, promoting weight gain in patients. This effect could have caused a body fat mass increase in girls, suggesting a "trigger effect" in the activation of the gonadal axis, causing a rise in the number of early puberty cases.

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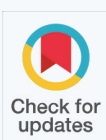
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- Premature Thelarche
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Abbreviations

PP: Precocious Puberty; AP: Accelerated Puberty; PT: Premature Thelarche; PE: Pediatric Endocrinology; POC: Pediatrics Outpatient Clinics; OR: Odds Ratio

Introduction

Puberty is a complex biological process in which children undergo a series of hormonal changes leading to the maturation of secondary sexual characteristics, reaching their adult size and reproductive capacity [1-4]. All these hormonal changes are due to the activation of the hypothalamic pituitary-gonadal axis, which is regulated by a large number of elements, including genetic and environmental determinants [5-8].

According to the Spanish Society of Pediatric Endocrinology, we understand as Precocious Puberty (PP), the beginning of the appearance of secondary sexual characteristics before the age of 8 in girls and 9 in boys; and as Accelerated Puberty (AP) when it appears between 8 and 9 years of age in girls and between 9 and 10 years of age in boys [9,10]. However, for some years, it has been observed and described that the age of onset of puberty is being advanced, especially in girls [2-4,11-15]. Although some of these cases can be explained by genetic/family factors, most of them lack a family history of precocious puberty, believing that this increase could be justified by nutritional, lifestyle and/or environmental changes, although these are not well known [14-22].

During the COVID 19 pandemic and the lockdown experienced due to it, many routines and habits of our lives have been affected and modified. That is why, at the beginning of this study and in relation to the onset of puberty, this question was asked: "Have all the restriction measures applied during COVID-19 been able to condition an increase in precocious puberty and early puberty? And has this happened in our Autonomous Community?" As background to our study we found the article "Increased incidence of precocious and accelerated puberty in females during and after the Italian lockdown for the coronavirus 2019 (COVID-19) pandemic" [6], in which they describe a higher incidence of Central Precocious Puberty (CPP) in Italy, as well as a faster progression of puberty in girls who had previously been diagnosed with this diagnosis.

This study is a retrospective observational analytical study in which the incidences of first consultations made for Premature Thelarche between the months of March and December 2019 and between the same periods of time in 2020 at the Pediatric Endocrinology (PE) consultation are compared from our hospital. In addition, the increase in the diagnosis of Precocious (PP) and Accelerated Puberty (AP) in the cases evaluated for this reason is compared, with the aim of demonstrating that the sensation that there has been in Primary Care as well as in the EP service about the increase

in the incidence of these pathologies during confinement and the COVID was a reality. Other studies that have already been published refer to it (23,33).

Patients and Methods

First, the total number of first consultations that had been made to the pediatrics Outpatient Clinics (OC) from March to December 2019 and in the same period of time in 2020 was requested. Subsequently, the first consultations made to the Pediatric Endocrinology Service were evaluated retrospectively, to figure out in how many of this patients the cause of referral was PT.

Male patients referred for this reason and patients who had dropped out of follow-up were excluded from the study. Patients younger than 24 months were also excluded. The patients included in our study were all female and were aged between 6 and 9 years at the time of the first consultation.

Study design

The study includes 77 patients who consulted for Premature Thelarche in 2019 and 99 in 2020.

Once the girls who had consulted for the first time for PT in any of the previously described periods were selected, different characteristics recorded during the first consultation were retrospectively reviewed.

From each of them, the following was collected: the age at which they attended the first consultation, their origin, family history of precocious puberty, weight, height, Body Mass Index (BMI), whether or not they had adrenarche and whether it had been prior or after onset of Thelarche, month in which they consulted, Bone Age (BA) at the first visit, the difference between bone age and chronological age, and whether they had experienced weight gain in the last 6 months or not. If available, the existence of disruptors and the results of the abdominal ultrasound were noted. Basal FSH, LH, and E2 laboratory values were also recorded.

Once all these data were collected, the successive consultations of those who had had data of early puberty were reviewed, assessing which ones had undergone the Procrin test and which ones had not and the diagnosis of all of them was recorded, the options being: isolated thelarche, precocious puberty, accelerated puberty and physiological puberty (normal physiological development).

Aspects of the different variables assessed

Body Mass Index (BMI) was calculated by dividing the patient's weight in kilograms by the square of the height in meters.

For the calculation of the Bone Age (BA), Rx of the left hand was performed in the first consultation and the Greulich and Pyle method was used.

To calculate the difference between BA and Chronological Age (CA), the decimal age to which the BA and CA corresponded, respectively, was first calculated, taking into account the years and months that the girls were when they consulted and subsequently the BA minus CA was subtracted.

Ultrasound: girls who had an abdominal ultrasound were classified as prepubertal or pubertal, considering pubertal those whose ovarian volume was greater than 4-4.5 ml, uterine corpus length > 3 cm, and/or body/neck ratio uterus was 2:1.

Laboratory analysis: all the analytics were extracted by the same nursing group and on an empty stomach.

The gonadal axis stimulation test performed was PROCIN (leuprolide acetate: GnRH analogue): a single dose of 500 ug subcutaneously. This test was carried out after explaining to the parents what the procedure consisted of, the purpose with which it was being carried out, and after signing the informed consent. All of them were performed in a day hospital, collecting FSH and LH values on admission, 3 hours and 24 hours after administering PROCIN. E2 values were also collected at admission and 24 hours after administration.

Weight gain in the last 6 months: In this study, this concept was defined as an increase of > 3 kg during this period of time. It was decided to consider as significant weight gain an increase of more than 3 kg in the last six months, because, physiologically, from one to one and a half years of life there is a slowing down of the growth rate until it increases considerably before puberty and menarche. Therefore, taking into account the age of our patients, the growth rate should be low and therefore the weight gain was attributed to an increase in fat mass and consequently in BMI. In addition, an increase of more than 3 kg in 6 months meant, in most cases, a percentile increase in weight.

Concepts and definitions

Physiologic puberty was defined as pubertal changes beginning after age 9 years.

Isolated Thelarche was defined as breast enlargement without other associated hypothalamus-pituitary-gonadal axis activation data.

Precocious Puberty (PP) was defined as the development of pubertal changes before the age of 8 with an EO > 2 SD for age, with a stimulated LH > 6 IU/L or a baseline LH value of > 1.1 IU/L in the presence pubertal signs and a stimulated LH/FSH ratio > 0.6 with associated clinical evidence of development of secondary sexual characteristics.

pubertal signs and a stimulated LH/FSH ratio > 0.6 with associated clinical evidence of development of secondary sexual characteristics.

Accelerated Puberty (AP) was defined with the same characteristics as PP but in girls between 8 and 9 years old.

Statistical analysis

Statistical analyzes were performed using the SPSS program 13.0. Some of the characteristics analyzed in this study were continuous quantitative and others nominal categorical. To compare the latter between the two years, a legend was created in a way that a number corresponded to one of the options of the variable. For example, in the case of the ultrasound variable, 0 was assigned: if it was not done, 1: if it had prepubertal characteristics, and 2: if it had pubertal characteristics.

The categorical variables studied were described with frequencies while the quantitative variables by means and ranges.

Student's t-test was used to evaluate and compare variables.

All statistical tests were two-tailed and $p < 0.05$ was considered statistically significant.

Results

In 2019, 3,037 first consultations were made to the different subspecialties of Pediatrics, of which 447 were to Pediatric Endocrinology (PE), which accounted for 14.71% of the POCs. In 2020, a total of 2,746 first consultations were made, with 416 to Pediatric Endocrinology, which represents 15.14%, that is, 0.43% more than in 2019.

If we focus on the first consultations made to PE for Premature Thelarche in girls, we observe that in 2019 there were 75, which represents 2.46% of the first POCs consultations and 16.77% of the first PE consultations. However, in 2020, there were 97 first consultations made for this reason, representing 3.52% of visits to POC and 23.3% in PE. Comparing both years, in 2020 there were 28% more first consultations for premature thelarche than in 2019 ($p = 0.0001$ mean comparison). We therefore understand that there is a significant difference, observing a higher frequency of first consultations for PT in 2020 compared to 2019 [33-40].

When studying the correlation between the related samples, we observed that there could be a difference between what happened in 2019 and 2020 in the distribution by sex (in 2019, 2.6% men and 97.4 women; and in 2020, 2% men and 98% women; $p < 0.05$), in the presence of a family history (in 2019, 84% did not have family history of pubertal disturbances compared to 15.6% who did and in 2020, 76% did not have family history of pubertal disturbances and 24% did; $p = 0.011$) and in the month they consulted (although looking at the months in both samples, it is observed that the months with the most consultations were

between August and December, being August and October in 2019 both months with 13 consultations and in 2020 October with 19 consultations). In the rest of the variables studied, no significant differences were observed, so we deduce that the children who consult in both years have similar characteristics, except in the frequency of consultations, which were higher in 2020 (38-42).

In 2019, out of the 75 consultations for PT, 18 (24%) were for AP and 12 (16%) for PP, that is, 40% of the consultations for PT were diagnosed as having a pubertal developmental disorder.; while in 2020, out of the 97 consultations for this diagnosis, 35 (36%) were AP and 25 (25.77%) were PP, that is, of the total number of patients with PT, 61.77% were diagnosed as having a pubertal developmental disorder; which means an OR of 1.54 ($p < 0.05$ Student's t for independent samples) (Figures 1-4).

On the other hand, assessing the mean BMI of the girls who consult in both years, we observe that it was around the 50th percentile; however, in 2020, 19.58% (19 cases) had a BMI > 19.5 (p85, overweight) and 7.2% (7 cases) had a BMI >

21.5 (p95, obesity), compared to 17.33% (13 cases) with BMI > 19.5 in 2019 and 9.3% (7 cases) with BMI > 21.5. ($p < 0.05$ Student's t for independent samples).

When evaluating whether there had been a weight increase >3 kg in the 6 months prior to the consultation, we see that in 2020 31.57% experienced this increase compared to 68.42% who did not; and in 2019, 12.16% did see their weight change compared to 87.83% who did not. ($p = 0.0001$ Student's t for independent samples).

Our data shows that there has been an increase in the first consultations made to PE for premature Thelarchia during the period of confinement, as well as a subsequent increase in the diagnostic incidence of PP and AP in our hospital compared to the same period in 2019. In addition, the increase in the OR in the diagnosis of PP and AP in 2020, compared to 2019, was similar (OR of PA in 2020 vs. 2019: 1.5 and OR of PP in 2020 vs. 2019: 1.6).

Comparing 2019 vs. 2020 of total visits.

•AP 24% vs. 36% ($p: 0.0032$ chi square for independent samples); 18/75 vs. 35/97

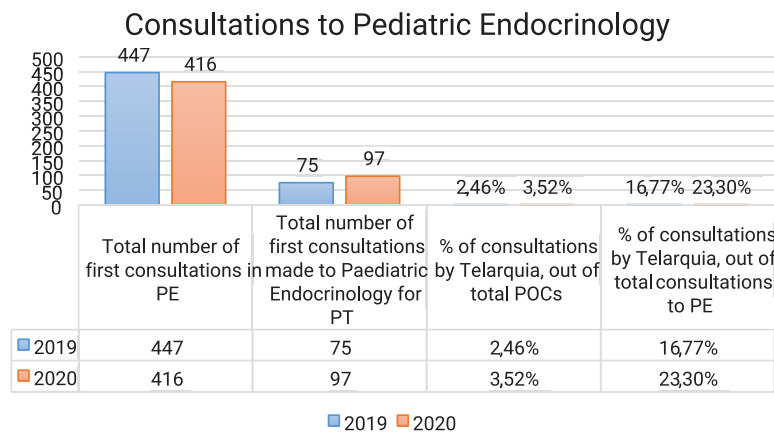


Figure 1 Total number and proportion of consultations to pediatric endocrinology 2019 vs 2020.

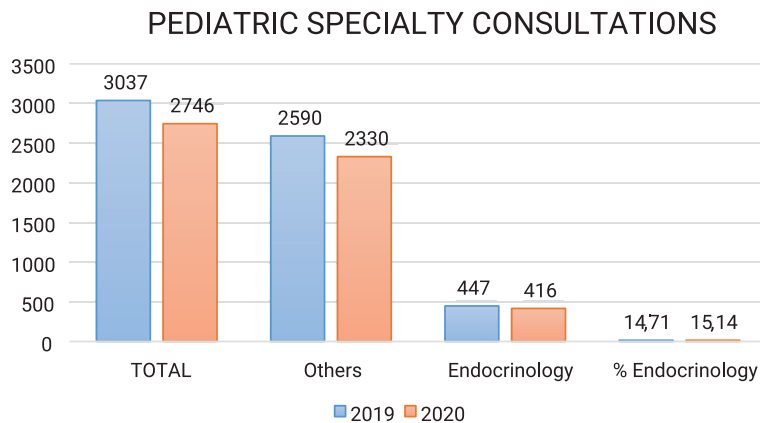


Figure 2 Total and proportion of pediatric specialty consultations 2019 vs 2020.

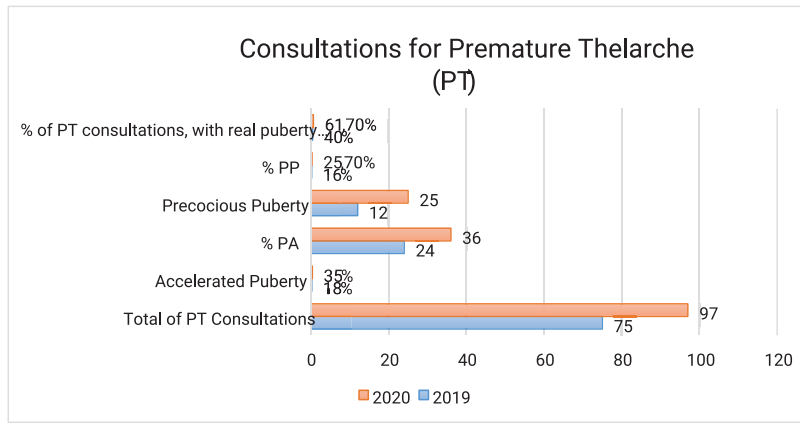


Figure 3 Total number of consultations for Premature Thelarche and diagnosis of PP and PA, 2019 vs 2020.

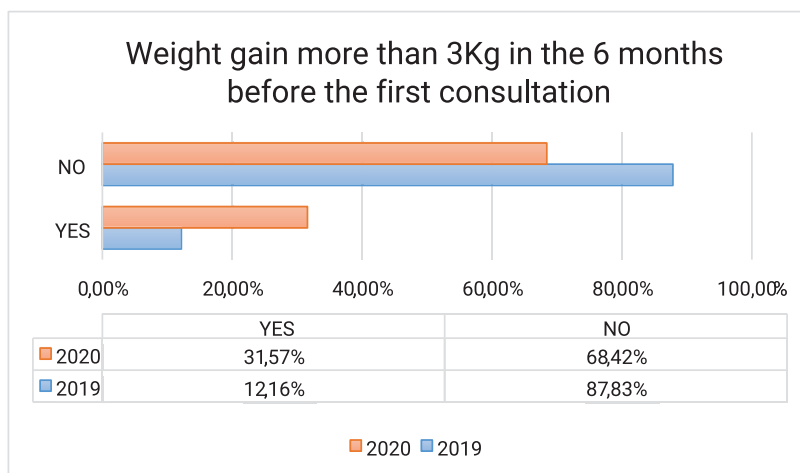


Figure 4 Total number of consultations for Premature Thelarche and diagnosis of PP and PA, 2019 vs 2020.

•PP 16% vs. 25.77% (p: 0.0049 chi square for independent samples); 12/75 vs. 25/97

In conclusion, we could say that in 2020 an acceleration of puberty was seen regardless of age, increasing the incidence in a statistically significant way almost equally in both PP and PA.

The rest of the girls studied were given other diagnoses: isolated Thelarche, lipomastia or normal puberty.

We can also observe that in 2020 there were more girls who consult with BMI > p85 , that is, with overweight or obesity; just as patients with an increase in weight gain in the last 6 months consult more frequently.

Discussion

The main objective of this study was to assess if the subjective feeling in pediatric endocrinology of Alava about the increase of consultations for PT was real, as well as the increase in definitive diagnoses of PP and AP in girls from that region. The results show a statistically significant

increase in the incidence of consultations and, also, in the incidence of definitive diagnoses of pubertal advancement during the pandemic, which is in line with other studies [6,17,23,35]. These findings are probably related to the changes observed in children's daily routines during this time [26,28-31].

It is known that pubertal development is largely dependent on genetic factors, but the role of environmental factors is also well known [40] and it is this last point the one that has probably conditioned the increased incidence of AP and PP during confinement.

The virulence and lethality of the disease produced by the 2019 coronavirus led governments to take very restrictive and limiting decisions for today's society, which caused important changes in the daily routines of all people, including children. Specifically, Spain went into a state of alarm on 14 March 2020, establishing few days later the lockdown of the population which, among other things, prevented children from leaving the house, that is, they could not go to school, play sports or go to the park to play. This altered children's lives, leading to less physical exercise

and changes in eating schedules and probably diet, as they spent more time at home and more time in front of digital screens [28–31].

All these increased sedentary behaviors can lead to weight gain and to an increase in body mass index. This, in turn, may lead to an increase in fat mass, which could be an inducer of puberty, favoring the development of precocious puberty in girls [5,25–27,32,37]. In this study, weight gain of more than 3 kg in the last 6 months before PT consultation was found to be statistically significant; however, this data has its limitations, because it would have been correct to take into account BMI, as well as growth velocity and body composition, and not only weight gain. Therefore, these data suggests that there was an increase in weight in the girls who consulted, but it would not be correct to conclude that this gain was due to an increase in body fat. It is true, however, and according to other studies, that lockdown favored sedentary lifestyles and sedentary lifestyles favoured an increase in body fat which in turn favored the onset of puberty [6,17].

These results seem to suggest a correlation between environmental factors and the early onset and progression of puberty.

On the other hand, it could be thought that the anxiety generated by this pandemic in the population may have made parents look more closely at their children's health because of the risk of disease and be more aware of the physical changes they were undergoing, which is why girls have consulted for early puberty at a younger age and the number of consultations had been higher [17,41–45]. We have seen this reflected in our study, where we observed a clear increase in the number of consultations for suspected PP or AP during confinement.

Therefore, our study may hypothesize that a sedentary lifestyle that favors the use of screens, decreased physical exercise, increased intake and changed dietary habits may account for the timing and pace of pubertal development [17,24].

Perhaps if healthier lifestyle habits had been adopted during lockdown, we would not have observed an increase in pubertal disorders during the pandemic.

Nevertheless, it would be advisable for parents to pay attention to pubertal body changes in their children, and to consult them if any abnormalities are suspected.

On the other hand, we should not forget that this study has several limitations. In addition to the one already discussed in the previous paragraphs about the variable of weight gain, another one would be the small size of the sample.

Conclusion

In conclusion, despite its limitations, this study shows

some of the collateral effects that confinement may have had and that could have gone unnoticed initially. Our data suggests a significant increase in the incidence of PE consultations for PT as well as new cases of both precocious and accelerated puberty in girls in Alava during confinement due to the COVID-19 pandemic, and the increase in both pathologies has been similar.

Nevertheless, we believe that further multi-center research is needed to analyze all the variables that may have been involved in early pubertal development during the pandemic in order to confirm this phenomenon on a larger scale and to establish the causal relationship with specific pathogenic factors.

Conflict of Interest

The authors declare that they have no conflict of interest.

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