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Early Puberty Trend during the COVID-19 Pandemic in Singapore: A Retrospective Review in a Single Tertiary Centre

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Abstract

Objectives. We aimed to study the trend of referrals for precocious puberty during the COVID-19 pandemic compared to pre-COVID years, explore the differences in the demographic and clinical features, and evaluate the contributing factors.

Methodology. The cases referred for assessment of PP from 2018-2021 to our endocrine centre were grouped into pre-COVID (2018-2019) and COVID (2020-2021) years. Cases fulfilling the diagnosis of PP included the onset of thelarche <8 years in females and 4mls testicular volume <9 years in males. The PP was further differentiated as Isolated Thelarche (IST) and Central Precocious Puberty (CPP). Early menarche was defined as menarche <10 years old.

Results. There were more referrals for PP and more diagnosed as CPP during the COVID-19 pandemic, predominantly among females. There were more endocrine tests done and more cases received treatment. None of the abnormal magnetic resonance imaging (MRI) pituitary findings required surgical intervention. The body mass index (BMI) was found to be positively associated with the risk of getting CPP with a crude-odd ratio (COR) of 1.8, *P* <0.001, and early menarche (COR 2.1, *P* <0.001).

Conclusion. We found a significant increase in the referrals of PP and diagnosis of CPP during the COVID-19 pandemic. Higher BMI was found to be associated with CPP and early menarche.

Key words: precocious puberty, early puberty, early menarche, COVID-19, obesity

INTRODUCTION

The secular trend toward earlier puberty has been observed worldwide, with many countries reporting earlier thelarche and menarche among girls. Two epidemiological studies (PROS and NHANES III) from the USA in the mid-1990s, which noted earlier sexual maturation in girls reported onset of puberty may be as early as 7.7 years in girls and as early as 7.6 years in boys.[1] The Danish study in the 1990s on the other hand, could not detect the downward secular trend in the timing of puberty.[2] Given the differences and limited epidemiological data among the countries, pubertal changes before age 8 years in girls and 9 years in boys continued to be used as the cut-off age for early or precocious puberty (PP) referrals.

The reported incidence rate of precocious puberty varies among the countries; however, most reported an increasing trend for the past 2 decades. The study of data from Danish national registries from 1998-2017 reported a sixfold increase in the incidence for girls, from 2.6 per 10,000 to 14.6 per 10,000, and a 15-fold increase for boys, from 0.1 per 10,000 to 2.1 per 10,000.[3] Similarly, the studies from Korea reported the annual prevalence of central precocious puberty (CPP) in girls and boys from 2008-2020 increased from 141.8 to 3439.9 (24.3 times) and from 2.7 to 206.5 (76.5 times) per 100,000 persons.[4] The mechanisms underlying the increasing trend in the incidence of CPP are uncertain, however, the nutritional status (overweight or obesity) has been highlighted as a major influence, especially in girls.

For the past 2 years during the COVID-19 pandemic, the incidences of PP seemed to be further accentuated and were reported in many parts of the world.[5-8] Similarly, being one of the country's main tertiary endocrine referral centres, we noticed a significant increase in the new referrals for precocious puberty and early menarche to our clinic. This prompted us to perform an audit to investigate this phenomenon.

METHODOLOGY

This is a cross-sectional study with the objective to study the change in the trend of cases referred for precocious puberty

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and early menarche during the COVID-19 pandemic, explore the differences in their demographic and clinical features and evaluate the possible contributing factors.

As PP is a condition with a low prevalence of about 0.02%,[9] the calculated sample size for the study was tremendously large. As such, we decided to collect all the cases that were referred during the study period. We screened through the new case endocrine clinic referral database and selected all the cases referred for PP, from the year 2018 to 2021. Missing data constituted less than 10% of the samples and hence, were excluded during the analyses.

We grouped the referrals into pre-COVID (year 2018-2019) and COVID (year 2020-2021), and retrospectively extracted the clinical data of PP cases from our electronic medical records. Cases fulfilling the diagnosis of PP were onset of puberty before 8 years in females (breast development i.e., thelarche); and less than 9 years in males (testicular enlargement i.e., increase in volume to 4 ml). Patients with thelarche of infancy presenting before 2 years old; isolated premature adrenarche; underlying structural abnormalities or oncological diseases that may directly interfere with pubertal development were excluded from the audit.

Ethics Review Board approval was exempted from the audit.

Data collection

Information collected included patient's demographic data; anthropometric measurements; Tanner staging at presentation; risk factors for precocious puberty (family history of PP, small for gestational age, prematurity, use of supplements, or other conditions such as a history of head injury/infection; twin pregnancy or adopted children); biochemical investigations including baseline luteinizing hormone (LH), follicular stimulation hormone (FSH), estradiol (E2), testosterone, and peak LH level during luteinizing hormone-releasing (LHRH) stimulation test (LH level was taken at 0, 30 and 60 minutes); radiological investigations including bone age x-ray, pelvis ultrasound, magnetic resonance imaging (MRI) of the pituitary; and treatment with gonadotrophin-releasing hormone agonist (GnRHa) injection.

Definition

The precocious puberty cases were further divided into isolated thelarche (IST) and central precocious puberty (CPP) after assessment. IST was diagnosed if the patient had thelarche with no significant bone age advancement (less than 1 year), no pubertal progression, baseline LH <0.5 and/or peak LH <5 IU/L during the LHRH stimulation test. CPP was diagnosed based on pubertal progression with significant bone age advancement (more than 1 year), LH baseline >0.5 IU/L, and/or LH peak >5 IU/L during the LHRH stimulation test. Early menarche was taken as menarche before the age of 10 years.

Statistics

Statistics analysis was performed using SPSS Statistics software version 22. Descriptive data were expressed as mean ± standard deviation (SD) and number (n) and proportion (%) for categorical variables unless otherwise stated.

Continuous variables were analysed with the independent t-test for normally distributed data and Mann Whitney Test for non-normally distributed data. The association of categorical variables was analysed with the Pearson chi-square test or Fisher's exact test, as appropriate. Simple binary logistic regression was used to determine the association between the variables. A value of P <0.05 is considered statistically significant.

RESULTS

There were 968 cases referred to New Case Endocrine Clinic from year 2018-2019 and 1069 cases from year 2020-2021. Cases referred for PP were 224 (21%) during the 2-year COVID-19 pandemic, versus 128 (13%) cases during the pre-COVID years with an increment of 8%, p <0.001. The cases that fulfilled the definition of CPP were noted to be more during COVID years with 122 (54%) cases versus 49 (38%) cases during pre-COVID years, p = 0.002. Cases of IST also increased from 23 (18%) pre-COVID to 44 (20%) cases during COVID-19 years, though the increment was not significant (Table 1).

The predominant PP referrals were females. The males comprised only 4 (6%) and 5 (3%) cases in pre-COVID and COVID years. The referrals were mostly from government hospitals and clinics (71%) compared to private centres (29%), and the proportions were very similar over the years. The majority of the patients were Chinese (74%), followed by Indian, Malay, Caucasian, and others. The age of presentation to the clinic ranges from the median age of 7.61 (interquartile range, IQR 1.64) to 7.75 (IQR 1.72) for females, and mean age 8.57 (± 2.00 standard deviation, SD) to 8.96 (± 0.89 SD) for males (Table 2).

The age of pubertal onset among female patients was quite similar during the pre-COVID years (median age 6.9, IQR 1.3) and COVID years (median age 7.0, IQR 1.0), and the majority presented with breast Tanner stage 2 (54-55%). There were more cases referred for early menarche during the COVID years, with 39 (24%) versus 15 (22%) cases, though the proportion of increment was not significant. The mean age of menarche for those with early menarche was about the same for pre-COVID and COVID years, with a mean age of 8.86 ± 0.94 SD versus 8.97 ± 0.53 SD. The onset of puberty for those cases with early menarche was median age 7.0 (IQR 0.80) during pre-COVID years, and age 7.5 (IQR 0.60) during COVID years, p <0.05 (Table 2).

The mean body mass index (BMI) standard deviation score (SDS) as well as the obese group of patients had increased

Table 1. Comparison of new case endocrine referrals pre-COVID and COVID years

Variable	Pre-COVID years, n (%)	COVID years, n (%)	*p*
New case endocrine referrals			**0.001**
a) Precocious puberty	128 (13)	224 (21)	
b) Other endocrine cases	840 (87)	845 (79)	
Total	968 (100)	1069 (100)	
Final diagnosis			**0.002**
a) Central precocious puberty (CPP)	49 (38)*	122 (54)*	
b) Isolated thelarche (IST)	23 (18)	44 (20)	
c) Not PP	56 (44)*	58 (26)*	
Total	128	224	

* = column proportions differ significantly from each other)

Table 2. Clinical characteristics of patients with precocious puberty during pre-COVID and COVID years

Variables	Pre-COVID years, n (%)	COVID years, n (%)	*p*
Gender			0.459^
a) Female	68 (94)	161 (97)	
b) Male	4 (6)	5 (3)	
Total	72 (100)	166 (100)	
Referral centre			>0.997
a) Government	51 (71)	119 (72)	
b) Private	21 (29)	47 (28)	
Ethnic			0.968^
a) Chinese	53 (74)	123 (74)	
b) Malay	4 (6)	11 (7)	
c) Indian	7 (10)	17 (10)	
d) Caucasian	4 (5)	6 (4)	
e) Others	4 (5)	9 (5)	
Age of Presentation			
a) Female	7.61 (1.64)ǂ	7.75 (1.72)ǂ	0.398ᵛ
b) Male	8.96 ± 0.89°	8.57 ± 2.00°	0.728*
Onset of puberty			
a) Female	6.9 (1.3)ǂ	7.0 (1.0)ǂ	0.074ᵛ
b) Male	8.6 (1.4)ǂ	8.5 (1.4)ǂ	0.532ᵛ
Breast Tanner Stage			0.567
2	37 (54)	89 (55)	
3	24 (36)	48 (30)	
4	5 (7)	21 (13)	
5	2 (3)	3 (2)	
Patients with menarche at presentation			0.724
a) Yes	15 (22)	39 (24)	
b) No	53 (78)	122 (76)	
Age of menarche	8.86 ± 0.94°	8.97 ± 0.53°	0.539*
Onset of puberty in early menarche	7.00 (0.80)ǂ	7.50 (0.60)ǂ	0.035ᵛ
BMI SDS			
a) Female	0.26 ± 1.24°	0.43 ± 1.10°	0.307*
b) Male	0.62 ± 0.76ǂ	1.87 ± 0.33°	0.012*
Height SDS			
a) Female	0.87 ± 0.96°	0.93 ± 1.04°	0.692*
b) Male	1.04 ± 1.66°	2.19 ± 1.50°	0.312*
Weight SDS			
a) Female	0.65 ± 1.08°	0.79 ± 1.02°	0.374*
b) Male	0.93 ± 0.85°	2.25 ± 0.65°	0.033*
Weight category			0.383
a) Obese	9 (12)	33 (20)	
b) Overweight	13 (18)	29 (17)	
c) Not overweight/obese	50 (70)	104 (63)	
Overweight/Obese			
a) Female	21 (31)	57 (35)	0.509
b) Male	1 (20)	5 (100)	0.048^
Family history PP			0.861
a) Yes	9 (12)	22 (13)	
b) No	63 (88)	143 (87)	
Risk factors of PP			0.059^
a) SGA	2 (3)	11 (7)	
b) Prematurity	5 (7)	13 (8)	
c) Supplements	2 (3)	12 (7)	
e) Others	3 (4)	9 (5)	
f) No	60 (83)	121 (73)	
Received treatment			0.048
a) Yes	11 (15)	45 (27)	
b) No	61 (85)	121 (73)	

°mean ± SD; ǂmedian (interquartile range); *Independent-Samples T-test; ^Fisher's Exact test; ᵛMann-Whitney test

Table 3. Association of overweight/obesity with diagnosis of CPP, IST and early menarche

Factors	Overweight/Obese, n (%)	OR (95% CI)	*p*-value
CPP			
No	16 (19)	Ref	-
Yes	68 (81)	2.1 (1.1 - 4.0)	0.023
IST			
No	68 (81)	Ref	-
Yes	16 (19)	2.1 (1.1 - 4.0)	0.023
Early Menarche			
No	44 (56)	Ref	-
Yes	34 (44)	3.4 (1.8, 6.2)	<0.001

Ref = reference; OR = odds ratio; CI = confidence interval

Table 4. Diagnostic features of patients with precocious puberty during pre-COVID and COVID years

Variables	Pre-COVID years, n (%)	COVID years, n (%)	*p*
Baseline blood investigations done			0.285
a) Yes	39 (54)	101 (62)	
b) None	33 (46)	63 (38)	
LHRH test done			**0.043**
a) Yes	8 (11)	37 (22)	
b) No	64 (89)	129 (78)	
Done LHRH test			
a) Female	7 (88)	37 (100)	0.278
b) Male	1 (12)	0	0.382^
LHRH test results			0.133^
a) Positive	7 (88)	22 (60)	
b) Negative	1 (12)	15 (40)	
USS pelvis done			0.846
a) Yes	24 (35)	59 (37)	
b) None	44 (65)	102 (63)	
Ovary volume (ml)			
a) IST	0.55 ± 0.05°	1.37 ± 0.54°	0.097*
b) CPP	3.00 ± 2.36°	2.84 ± 1.09°	**0.001***
MRI pit			0.064
a) Done	20 (28)	67 (40)	
b) Not Done	52 (72)	99 (60)	
MRI pit			0.260
a) Normal	12 (60)	49 (73)	
b) Abnormal	8 (40)	18 (27)	
Abnormal MRI pit			
a) Female	7 (44)	17 (27)	0.207
b) Male	1 (25)	1 (20)	0.722^

°mean ± SD; *Independent-Samples T-test; ^Fisher's Exact test; ; ᵛMann-Whitney test

from pre-COVID to during the COVID years, though the majority of referred cases were not overweight or obese. The proportion of overweight/obese patients for both genders has increased over the years, but we noticed a significant increment among the male patients during the COVID year, with an increase in both the weight SDS and BMI SDS (Table 2). We found that the obese/overweight patients were significantly higher among those diagnosed with CPP as compared to IST, with 68 (39.8%) versus 16 (23.9%), p <0.05; and was found to be positively associated with the risk of getting CPP with odd ratio (OR) 2.1, P = 0.023; as well as early menarche (OR 3.4, P <0.001) (Table 3).

The majority of the patients did not have any obvious risk factors for PP. About 12-13% of them had a family history of PP, and 7-8% were born prematurely. More patients in COVID years who were born small for gestational age presented with PP 11 (7%) versus 2 (3%) and taking supplements either oral or topical with 12 (7%) versus 2 (3%) cases in pre-COVID years (Table 2). None of the risk factors were found to be significantly associated with PP or CPP.

More baseline hormonal tests were done during the COVID years though the differences were not statistically significant. A more significant number of LHRH stimulation tests was done during the COVID years, with 37 (22%) vs 8 (11%) cases in pre-COVID years, and more proportion were carried out in female patients (Table 4). There was a significantly higher proportion of patients who received GnRHa treatment during COVID years with 45 (27%) versus 11 cases (15%), p <0.05 (Figure 1).

More ultrasound pelvis and MRI pituitary imaging were done during the COVID years, though these were not statistically significant. Ovarian volume was noted to be smaller in the IST group as compared to the CPP group during the pre-COVID year but with a slight difference during the COVID years. Eight (40%) and 18 (27%) of the MRI pituitary done during pre-COVID and COVID years were found to be abnormal, with female predominance (Table 4). However, none of them revealed pathological brain lesions that required surgical intervention. There were 7 cases with macroadenoma or microadenoma; five with Rathke's cyst; two with hypothalamic hamartoma; five with slight pituitary enlargement and others with

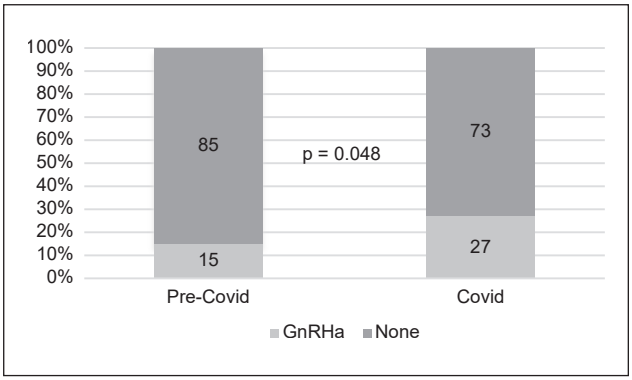

Figure 1. Percentage of patients started on GnRHa during pre-COVID and COVID years.

incidental findings such as pineal cyst, arachnoid cyst and non-specific lesions in the brain.

DISCUSSION

The COVID-19 pandemic has changed the world drastically, not only in terms of COVID infection-related mortality and morbidity rate but also in the lifestyle modification of human beings. The strict lockdown and school closure had caused the children and adolescents to mostly stay indoors, resulting in reduced physical and social interaction, and increased use of electronic devices, which resulted in an overly sedentary lifestyle. People were stressed and confined at home and ate more frequently. All these changes have led to an increasing rate of obesity in many countries, especially among children who were mostly kept protected and confined at home.[10,11] Many endocrine centres around the world have reported an increased incidence of early puberty, faster pubertal progression as well as early onset of menarche during the COVID pandemic, with many publications from Italy, which was one of the hardest-hit countries by COVID-19 infection during the early pandemic.[5,12-15]

The literature and studies have tried to link the causal associations between increased incidence of early puberty with a sedentary lifestyle, obesity, overnutrition, exposure to endocrine-disrupting agents, as well as the use of electronic devices.[5,13] Chen, Yao et al., published a study that suggested an increased incidence of precocious puberty during the COVID-19 pandemic among Shanghai school-aged girls may be associated with decreased serum concentrations of MKRN3 and ghrelin.[6] Kisspeptin and leptin promote the pulsatile GnRH secretion, whereas MKRN and ghrelin suppress it. Rapid weight gain leads to increased concentrations of leptin but decreased concentrations of ghrelin. However, the actual cause remains unknown.

From our study, we found an increase in the number of patients referred and diagnosed with PP during the COVID-19 pandemic years, with more diagnosed as CPP with progressing puberty as compared to IST. There were also more patients referred for early menarche, though the increment was not significant. We noticed that the reported onset of puberty for those with early menarche was significantly later during the COVID years. This may suggest that puberty progressed faster for the PP cases during the COVID years, as reported by some published papers.[12] However, it's difficult to determine the exact onset of puberty for most cases of PP and early menarche, as most parents and patients did not notice the early signs of puberty. This is especially difficult in males where the first sign of puberty is testicular size increment.[8]

In our study, we noticed there were more endocrine stimulation tests (LHRH) performed and more patients treated with GnRHa during the COVID years. LHRH stimulation test usually was performed if the baseline investigations and clinical features were not conclusive of central precocious puberty, typically during the early puberty stages. This may suggest that more cases with early stages of puberty were referred during the COVID years, possibly due to increased awareness of CPP among clinicians and parents. This could be the influence of social media and more exposure to online educational talk during the pandemic years. Similar reasons could explain why more treatment with GnRHa was received during the COVID years, with earlier diagnosis and higher acceptability of the treatment by clinicians and parents.

Our study found higher BMI is associated with a higher risk of CPP and early menarche, which is consistent with some studies.[7,12] We did not notice an increase in cases of PP in males during the COVID years, similar to other reports.[8] However, we noticed the proportion of overweight/obese male PP patients had significantly increased during the COVID years. This is likely related to the increased incidence of obesity during the COVID-19 pandemic.[10,11] Apart from the risk factor of overweight/obese; we did not find other significant risk factors that were associated with PP or CPP.

We found more MRI pituitary done during the COVID years with less proportion of abnormalities detected, though the increment was not significant. The cases of abnormal MRI imaging detected were mostly benign and stable lesions not requiring surgical intervention, as reported by other studies.[5] However, it's difficult to make many conclusions from these data, especially for male patients, due to the small sample size. Patients with significant pituitary lesions usually were referred to with more clinical features than just isolated PP. Besides, we excluded cases with underlying structural abnormalities or oncological diseases that may directly interfere with pubertal development.

The increase in the incidence of precocious puberty with faster progression observed during this COVID-19 pandemic is a worrisome phenomenon. However, it also opened a new window of opportunity for clinicians and researchers to further study the science behind the accelerated pubertal onset and its impact on children and adolescents.

Our study is limited by its retrospective design done in a single centre which reduces the sample size and ability to objectively study the association of various risk factors associated with PP. A prospective multi-centre study in the future should be the way forward.

CONCLUSION

We found an increase in the number of female patients referred and diagnosed with PP during the COVID pandemic years, with more endocrine stimulation tests (LHRH) done, more diagnosis of CPP and administration of GnRHa treatment. More male PP patients were noted to be overweight or obese. Higher BMI was found to be associated with a higher risk of CPP and early menarche. Apart from the risk factor of overweight/obese; we did not find other significant risk factors associated with PP; and there were no other significant differences in the demographic and clinical features of the referred PP cases during the pre-COVID and COVID years.

More causal reasons and environmental factors must have contributed to the increase in PP, as most of the referred PP female cases were not overweight or obese. It would be important to monitor the subsequent trend of puberty in children after the COVID-19 pandemic and consider a more extensive prospective study involving multiple centres.

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Statement of Authorship
Both authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
AL: Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration; **RFV:** Conceptualization, Methodology, Resources, Writing – review and editing, Supervision

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