Original Article

Turner Syndrome Growth Charts: A Western India Experience

Vaman V. Khadilkar[1,2], Madhura B. Karguppikar[1], Veena H. Ekbote[1], Anuradha V. Khadilkar[1,2]

[1]Growth and Endocrine Unit, Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, [2]Department of Health Sciences, Savitribai Phule Pune University, Pune, Maharashtra, India

Abstract

Background and Objectives: Disease specific growth charts are useful to monitor growth and disease progress in specific disorders such as Turner syndrome. As there is a paucity of data on spontaneous growth of Indian girls with Turner syndrome, the objectives were to construct reference curves for height and assess height velocity in Indian girls with Turner syndrome from 5 centers from western India. **Material and Methods:** Three hundred forty-eight readings of height and weight on 113 genetically proven girls with Turner Syndrome from 5 centers from western India were collected and retrospectively analyzed. Data were collected over the last 2 decades (GH treatment naive girls were included). The method described by Lyon *et al*. was used to compute smoothed standard deviations and percentiles for height. For computing growth velocities, longitudinal data were used on 104 untreated girls (longitudinal readings for height for a minimum of 3 years were used). Midparental height z scores (MPHZ) were computed. **Results:** In girls with Turner syndrome, the mean adult height was found to be 140.1 cm. Height velocity was low at all ages compared to normal girls with a notable difference beyond the age of 10 years where normally, a growth spurt is expected. The MPH Z-score correlated positively with the height Z-score. The 3rd, 50th, and 97th height percentiles of Turner girls at all ages were lower than normal girls' charts. **Conclusion:** Turner syndrome charts for height are presented; these charts may be used to monitor growth in girls with Turner syndrome.

Keywords: Children, growth chart, Turner syndrome, western India

Introduction

First described by Turner (1938) and Ulrich (1930), Turner syndrome is a relatively common chromosomal aberration seen in approximately 1:2500 female live births.[1] It is broadly classified as classic Turner syndrome where one of the X chromosomes is completely missing and mosaic Turner syndrome where two cell lines coexist. Karyotype is the gold standard for the diagnosis of Turner syndrome.[2]

Clinically, Turner girls may present with lymphedema, shield chest, short 4th metacarpal/metatarsal, a wide carrying angle, short stature, amenorrhea, and premature ovarian insufficiency. They often have comorbidities such as hypothyroidism and cardiac and renal defects. Growth faltering is a major concern in girls with Turner syndrome.

Growth charts for normal children are not suitable in syndromic children because their growth pattern in terms of height, weight, and body mass index (BMI) significantly differ. Growth abnormalities in girls with Turner syndrome can be better identified if monitored using disease specific charts, e.g., if a girl with Turner syndrome develops hypothyroidism or celiac disease, it is easy to appreciate downward height deviation on a Turner growth chart than on a normal girl's chart. Since the production of Turner syndrome charts by Ranke *et al*. in 1983, they have been widely used to monitor the growth of Turner girls across the world, especially where local Turner charts are not available.

In a comprehensive review of Turner syndrome growth studies by Bertapelli *et al*. in 2014, the need to construct Turner curves for different ethnic groups has been emphasized.[3] There is a paucity of data on spontaneous growth of Indian girls with Turner syndrome. The objectives of our study were thus 1) to construct reference percentile curves for height for

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_123_20

Address for correspondence: Dr. Anuradha V. Khadilkar, Jehangir Hospital, 31, Sassoon Road, Pune - 411 001, Maharashtra, India.
E-mail: anuradhavkhadilkar@gmail.com

Submitted: 12-Mar-2020 **Revised:** 25-Apr-2020
Accepted: 07-Jul-2020 **Published:** 27-Aug-2020

How to cite this article: Khadilkar VV, Karguppikar MB, Ekbote VH, Khadilkar AV. Turner syndrome growth charts: A western India experience. Indian J Endocr Metab 2020;24:333-7.

1–18-year old Turner syndrome Indian girls from western India, 2) to assess height velocity, and 3) to compare these growth parameters with available international data on Turner syndrome girls.

Material and Methods

This was an observational, retrospective study. Deidentified data on 113 genetically proven growth hormone treatment naïve Turner girls from 5 centers from western India was collated for the study. Estrogen replacement therapy was started beyond the age of 13 years (mean age 13.8 years) and no patient had received hormone replacement therapy before the first height measurement. Girls with comorbidities and untreated hypothyroidism were excluded ($n = 3$); growth data on girls from 2000–2019 was included in the study. Three hundred and forty-eight readings on a total of 113 Turner syndrome girls were available for analysis. The population that visited the tertiary level center had mixed ethnic population, their ethnic origins were traced and these were: 77 from west (68.3%), 11 from south (9.7%), 15 from north (13.2%), 6 from central (5.3%), and 4 (3.5%) from east Indian origin. Midparental height (MPH) records were available on 88 children. Height could be measured only for 88 couples and, hence, those have been included for analysis. In other patients, height for only one of the parents was available and these were not included for analysis for MPH. Since this was a retrospective study where data was deidentified, a waiver was obtained from the institutional ethics committee.

All data were entered in Microsoft excel and cleaned; data was analyzed using the LibreOfficeCalc v6.0.3.2 and PSPP Gnu software v1.0.1. Age wise means and standard deviation (SD) for height, weight, and BMI were computed. Height, weight, and BMI were converted to Z-scores using Indian reference data.[4] MPH was computed (father's height + mother's height/2–6.5) and Z scores for girls' height and MPH were calculated.[5] Correlation analysis between Z-score of girls' height and MPH was carried out.

The means of the height were smoothed using the cubic spline method.[6] For generating smoothed height percentiles, the method described by Lyon *et al*. was used.[7] For computing growth velocities, longitudinal data from 101 (out of 113 GH naive girls with Turner syndrome in whom longitudinal readings for height were available for a minimum of 3 years) was used. Growth velocity was calculated as change in height over change in time and annualized velocities were computed. The data used in computing growth velocities had a minimum interval of 6 months between 2 readings. The age at height velocity was rounded off to the closest full year. As the number of readings for height velocity were insufficient to generate percentiles at younger ages, medians and SD of height velocity were computed.

To compare height percentiles created for Turner girls with Indian reference data, percentiles generated in the current study and Indian Academy of Paediatrics charts were plotted together.[4] To compare with available international data, the 50th percentile from the current study was plotted against the 50th centile of other available studies.

Results

A total of 113 girls with Turner syndrome at a mean age of 13.3 years from western India were studied. The karyotype abnormalities detected were 45x in 53.9%;45x, 46 × x in 16.8%; 46 × i in 15%;45x, 46 × i in 6.1%;45 × p in 4.4%;45x, 46 × y in 2.6%, and 45x, 47 × xx in 0.8%. The Y-cell line contributed to 2.6% of the data (3 patients). Reanalyzing the data after excluding these did not make a significant difference to the results; hence, they were retained in the analysis. Age wise data on mean height, weight, and BMI are presented in Table 1. The number of observations under the age of 5 years was 22, between 5 and 10 years were 45, and between 10 and 18 were 281, making a total of 348 observations for 113 subjects. The height Z scores of the Turner girls were <−2SD at all age groups while the weight and BMI Z scores ranged from −1.4 to −2.8 and −1.4 to 0, respectively. Mean height Z score was −2.8 (0.47), whereas mean midparental height Z score (MPHZ) was −0.6 (0.99). The height Z score and MPH Z-score were significantly, positively correlated (correlation coefficient 0.26, $P = 0.016$).

Of the 113 girls, 2 girls entered puberty and 1 menstruated spontaneously. The mean age of onset of puberty was 11.8 years and that of menarche was 13.8 years. Puberty was induced using hormone replacement therapy in 39 girls at a mean age of 13.8 years.

Table 2 illustrates the height percentiles for Turner girls from 1–18 years and Figure 1 depicts a comparison of height percentiles of Turner girls with World Health

Table 1: Turner Girls' Mean height, weight, and BMI with WHO/IAP *Z* scores

Age	Height (SD)	Weight (SD)	BMI (SD)	Htz	Wtz	BMIz
1	67.1 (3.2)	6.6 (0.3)	14.6 (0.8)	−2.9	−2.8	−1.4
2	76.8 (3.6)	8.6 (1.1)	14.5 (0.4)	−2.6	−2.9	−0.9
3	85.3 (4)	10.4 (0.4)	14.3 (0.6)	−2.4	−2.7	−0.9
4	91.7 (4.3)	11.9 (0.6)	14.2 (1.2)	−2.4	−2.7	−0.8
5	96.8 (4.5)	13.2 (1)	14.1 (1.5)	−2.1	−1.5	−0.1
6	101.4 (4.8)	14.6 (2.2)	14.1 (1.6)	−2.2	−1.5	−0.2
7	105.8 (5)	16.3 (3.1)	14.4 (2.8)	−2.3	−1.5	−0.2
8	110 (5.2)	18.2 (4.7)	14.8 (3.2)	−2.4	−1.5	−0.1
9	113.9 (5.4)	20.3 (7.8)	15.5 (7.1)	−2.6	−1.5	−0.1
10	117.8 (5.5)	22.5 (5.4)	16.2 (2.8)	−2.7	−1.6	−0.1
11	121.4 (5.7)	24.8 (5.8)	17 (3.1)	−3.0	−1.7	−0.2
12	124.8 (5.9)	27 (3.9)	17.6 (2.1)	−3.2	−1.8	−0.2
13	128.2 (6)	29.2 (5.7)	18 (2.4)	−3.4	−1.9	−0.3
14	131.4 (6.2)	31.5 (6.9)	18.4 (3.3)	−3.5	−2.0	−0.4
15	134.6 (6.3)	33.8 (7.2)	18.8 (2.8)	−3.4	−1.9	−0.4
16	137.4 (6.5)	36.2 (4.6)	19.3 (4.2)	−3.3	−1.8	−0.4
17	139.2 (6.5)	38.8 (5.4)	20 (2.6)	−3.2	−1.6	−0.2
18	140.1 (6.6)	41.5 (7.9)	21 (4.5)	−3.3	−1.4	0.0

Table 2: Height percentiles for Turner syndrome girls

Age	3rd	10th	25th	50th	75th	90th	97th
1	61.1	63.0	65.0	67.1	69.2	71.2	73.1
2	70.0	72.1	74.4	76.8	79.2	81.5	83.7
3	77.7	80.1	82.6	85.3	88.0	90.5	92.9
4	83.5	86.1	88.8	91.7	94.6	97.3	99.9
5	88.1	90.9	93.7	96.8	99.8	102.7	105.4
6	92.3	95.2	98.2	101.4	104.6	107.6	110.4
7	96.3	99.3	102.4	105.8	109.1	112.2	115.2
8	100.1	103.2	106.5	110.0	113.4	116.7	119.8
9	103.7	107.0	110.3	113.9	117.5	120.9	124.1
10	107.3	110.6	114.1	117.8	121.5	125.0	128.3
11	110.6	114.0	117.6	121.4	125.3	128.9	132.3
12	113.7	117.2	120.9	124.8	128.7	132.4	136.0
13	116.8	120.4	124.2	128.2	132.2	136.0	139.7
14	119.7	123.4	127.3	131.4	135.5	139.4	143.1
15	122.6	126.4	130.4	134.6	138.9	142.9	146.7
16	125.2	129.0	133.1	137.4	141.8	145.8	149.7
17	126.7	130.7	134.8	139.2	143.6	147.7	151.6
18	127.6	131.5	135.7	140.1	144.5	148.7	152.6

Organization (WHO, under 5) and Indian reference data (5–18 years).[4] The 3rd, 50th, and 97th percentiles of Turner data at all ages were lower than those of normal Indian girls and this effect was more pronounced after the pubertal age.

Height velocity means and SD of the present study in comparison with that of normal Indian girls is presented in Table 3.[8] Turner girls had the highest growth velocity in infancy, it dropped to 6.8 cm in the third year; the mean height velocity from 4–9 years was 4.9 cm/year beyond which it was <4 cm/year due to lack of the pubertal growth spurt.

Figure 2 illustrates the comparison of mean height of girls from current study with those reported by Ranke *et al*., Isojima *et al*., and Low *et al*. It was observed that Indian Turner syndrome girls were shorter at all ages when compared with Ranke *et al*.'s study but were comparable with Asian studies of Low *et al*. and Isojima *et al*.[9-11]

Discussion

In this retrospective, mixed longitudinal study, we present height percentiles and height velocity on 113 girls with Turner syndrome from 5 centers from western India. The number of girls included in previous global studies that have produced Turner syndrome charts ranged from 55 to 1447: 150 German girls by Ranke *et al*.[9]; 249 English girls by Brook *et al*.[12]; 55 Finnish girls by Lenko *et al*.[13]; 70 French girls by Rosenberg and Tell[14]; 1447 Japanese girls by Isojima *et al*.[11]; and 203 from Hong Kong in a study by Low *et al*.[10] Subgroup analysis of growth patterns based on karyotypes in our study did not reveal differences; other studies have also not observed major difference in growth patterns between the subtypes of Turner syndrome.[9]

We found that the MPH Z-score correlated positively with the girls' height Z score, and a similar positive correlation has been

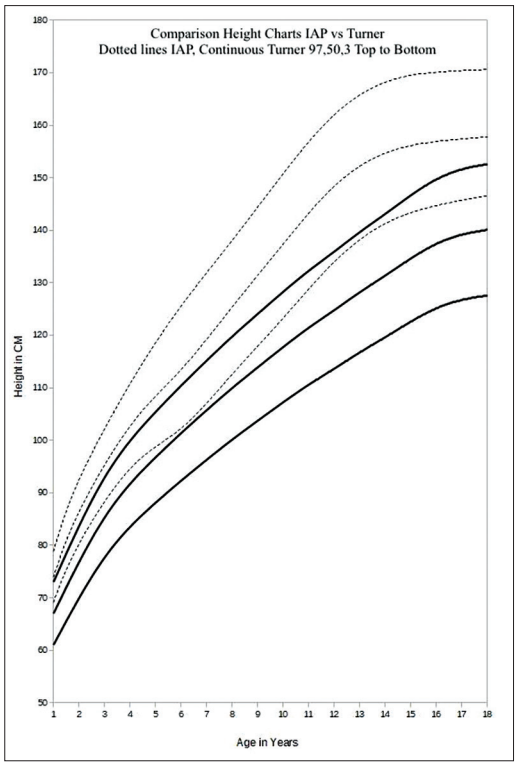

Figure 1: Comparison of height charts: Turner syndrome vs. WHO-IAP

reported by Naeraa and Nielsen.[15] Mean height velocity of Turner girls was lower than that of normal Indian girls' reference data from 5 to 12 years of age. However, 13 year onwards, mean height velocity was either comparable or the growth rates of normal girls were lower possibly because they had attained adult height early as compared to Tuner girls who lack puberty and continue to grow at a low rate for a longer time. The hallmark of growth in Turner syndrome is lack of the pubertal spurt as described by many researchers. The same pattern of absence of pubertal spurt was observed in Turner girls in our study. Height velocity was observed to be lower than 4 cm beyond the age of 10 years where normally the pubertal growth spurt is expected.

Human growth is influenced by several genetic and environmental factors. Growth curves follow a recognizable pattern in normal as well as in syndromic children. The lower than average final height in girls with Turner syndrome is multifactorial due to intrauterine growth retardation, stunting between age 2–11 years, and lack of significant pubertal spurt.

Most reasons for lower final height in Turner girls may be attributed to the haploinsufficieny of SHOX gene in these girls.[9,16] We found that girls with Turner syndrome at all ages were shorter than healthy Indian girls [Figure 1]. Further, associated disorders such as hypothyroidism and celiac disease may compromise growth in these children. Hence, plotting them on Turner syndrome specific growth charts is critical to identify such deviations. Also, growth hormone is being increasingly used in India to treat Turner girls and monitoring of growth during therapy would be more appropriate if plotted on Turner charts.

Table 3: Comparison of mean height velocity (SD) of Turner syndrome girls with normal Indian girls from 2-17 years (figures in parentheses are the standard deviations)

Age (years)	Height Velocity (cm/year)	
	Turner Girl	Normal Girl
2	12	-
3	6.8±1.1	-
4	5.2±1.0	-
5	5±1.2	6.6±0.9
6	4.6±1.7	6.2±1
7	4.5±0.1	5.7±1
8	5.5±0.1	5.7±1.3
9	4.8±0.3	6.0±1.6
10	3.7±0.9	6.5±1.9
11	3.7±0.7	6.4±1.9
12	3.3±0.9	5.1±2.2
13	3.6±1.0	3.2±2.0
14	2.9±0.9	1.9±1.3
15	2.0±0.7	1.1±0.8
16	1.8±0.5	0.8±0.5
17	1.8±0.9	0.4±0

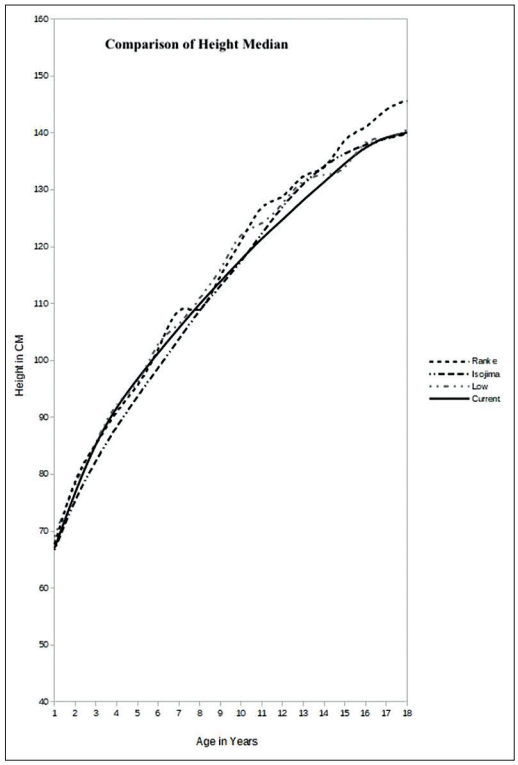

Figure 2: Comparison of 50th centile for height: present study vs. international data

When compared to Ranke *et al*.'s data and data from Rongen-Westerlaken *et al*.,[17] Turner girls' mean adult height was lower in our study population, whereas, it was comparable to that reported by Lyon *et al*., Brook *et al*., and Low *et al.* (146.8 cm in Ranke *et al*.'s, 146.9 cm in Karlberg *et al*.'s, 141.7 cm in Brook *et al*.'s, 139.2 cm in Lyon *et al*.'s, 142 cm in Low *et al.*'s, 141.2 cm in Isojima *et al*.'s, and 140.1 cm in our data). The studies by Ranke *et al*. and Brook *et al*. are more than 3 decades old and there are no data available on the secular trend in these populations. However, a Japanese study on secular trend in height in Turner syndrome suggests that mean adult height in untreated Turner girls has increased by 3 cm over a 15-year period.[10] The height of Indian Turner girls in our study at adult was 17.7 cm shorter than that of national girls' average,[4] while the height of Japanese Turner syndrome girls has been reported to be 20 cm shorter than that of their normal counterparts.[10]

Girls with Turner syndrome in our study were lighter at all ages when compared to Ranke *et al*., Karlberg *et al*., and Isojima *et al*.'s data (weight at 18 years in the current study is 41.5 kg, Ranke *et al*.'s 49 kg, Karlberg *et al*.'s 46 kg, and Isojima *et al*.'s 42.9 kg, respectively). When compared with healthy Indian girls, Turner girls were 12.3 kg (mean) lighter at 18 years.[4] Mean BMI was seen to be lower in the present study in comparison with healthy Indian girls. Not many studies have presented BMI for Turner girls; however, Indian Turner girls had a lower BMI than Swedish[17] and Egyptian girls.[18] These differences suggest that it is critical to have ethnic specific growth curves for Turner girls as quoted by El-Bassyouni *et al*. "Local (Turner) reference growth curves are more appropriate to use than International standards."[18] The presented growth curves for Indian girls with Turner syndrome may thus be used to monitor growth in these girls (please see examples).

Some limitations of this study are the number of patients is modest and are only from western India, although it is comparable to other studies conducted on girls with Turner syndrome. We have not reported data on biochemical/hormonal parameters and the study is retrospective. Thus, larger prospective, multicentric studies are required for assessing growth in Indian girls with Turner syndrome. In addition, midparental height could not be obtained for all patients included in the study and, hence, the analysis was carried out with the available readings (88 children, i.e., 77.8%).

Conclusion

In conclusion, Turner syndrome height charts presented in this study may be used to monitor growth in girls with Turner syndrome. These data may be more appropriate for identifying deviations in growth parameters of Turner syndrome girls.

Clinical Use of Turner Syndrome charts [Figure 3]:

- **Case a**: Girl diagnosed in neonatal period with pedal edema, karyotype 45x. She was just below the 50th percentile on Turner chart till 3 years after which growth was above the 50th percentile. Her MPH was 151 cm. She was growing on the 3rd percentile of the IAP charts.
- **Case b**: Girl diagnosed with clinical features of Turner at 9 years of age (46xx, 46xi) and received growth hormone for 7 years and reached adult height of 156 cm (MPH 162 cm). She crossed percentiles from being on the 50th for

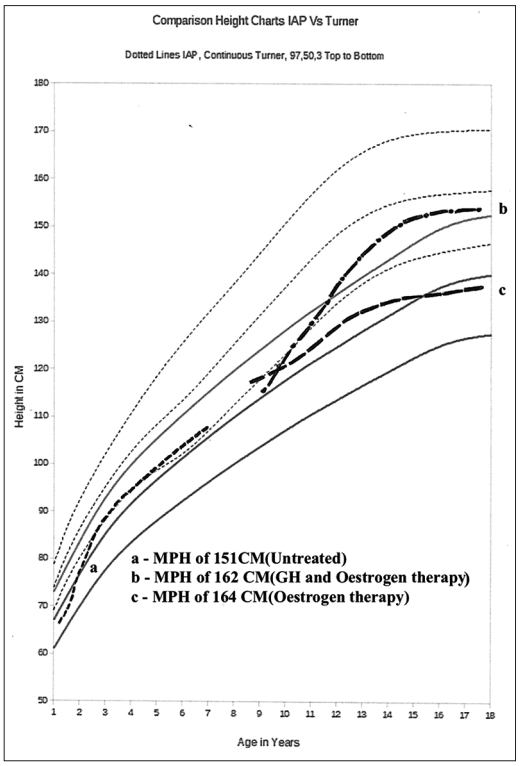

Figure 3: Growth patterns of 3 karyotype proven Turner cases plotted on Turner growth charts (present study)

the Turner syndrome chart (below 3rd percentile of IAP chart) to above the 97th of the Turner chart and just below the 50th percentile of IAP charts.

- **Case c**: A 9-year-old girl was diagnosed with short stature and phenotypic features of Turner syndrome and did not receive growth hormone therapy (46xx, 45x, MPH 164 cm). She was above the 50th percentile of the Turner chart, but crossed to being under the 50th percentile at 18 years. She was always below the 3rd percentile of IAP charts.

Acknowledgements

We acknowledge Dr. Aniket Kumbhojkar, Dr. Hari Mangtani, Dr. Hemchand Prasad, Dr. Prashant Patil, Dr. Rahul Jahagirdar, Dr. Saurabh Uppal, and Dr. Shalmi Mehta for their contribution.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Cui X, Cui Y, Shi L, Luan J, Zhou X, Han J. A basic understanding of Turner syndrome: Incidence, complications, diagnosis, and treatment. Intractable Rare Dis Res 2018;7:223-8.
2. Bondy C. Recent developments in diagnosis and care for girls in Turner syndrome. Adv Endocrinol 2014;2014:1-9. doi: 10.1155/2014/231089.
3. Bertapelli F, Barros-Filho Ade A, Antonio MÂ, Barbeta CJ, de Lemos-Marini SH, Guerra-JuniorG. Growth curves for girls with Turner syndrome. Biomed Res Int 2014;2014:1-8. doi: 10.1155/2014/687978.
4. Khadilkar VV, Khadilkar AV. Revised Indian Academy of Pediatrics 2015 growth charts for height, weight and body mass index for 5-18-year-old Indian children. Indian J Endocrinol Metab 2015;19:470-6.
5. Wright CM, Cheetham TD. The strengths and limitations of parental heights as a predictor of attained height. Arch Dis Child 1999;81:257-60.
6. Ward R, Schlenker J, Anderson GS. Simple method for developing percentile growth curves for height and weight. Am J Phys Anthropol 2001;116:246-50.
7. Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. Arch Dis Child 1985;60:932-5.
8. Khadilkar V, Khadilkar A, Arya A, Ekbote V, Kajale N, Parthasarathy L, *et al*. Height velocity percentiles in Indian children aged 5-17 years. Indian Pediatr 2019;56:23-8.
9. Ranke MB, Stubbe P, Majewski F, Bierich JR. Spontaneous growth in Turner's syndrome. Acta Paediatrica 1988;77:22-30.
10. Isojima T, Yokoya S, Ito J, Horikawa R, Tanaka T. Trends in age and anthropometric data at start of growth hormone treatment for girls with Turner syndrome in Japan. Endocr J 2008;55:1065-70.
11. Low LC, Sham C, Kwan E, Karlberg J, Tang G, Cheung PT, *et al*. Spontaneous growth in Chinese patients with Turner's syndrome and influence of karyotype. Acta Paediatrica 1997;86:18-21.
12. Brook CGD, Murset G, Zachmann M, Prader A. Growth in children with 45 XO Turner's syndrome. Arch Dis Child 1974;49:789-95.
13. Lenko HL, Perheentupa J, Söderholm A. Growth in Turner's syndrome: Spontaneous and fluoxymesterone stimulated. Acta Pædiatrica 1979;68:57-63.
14. Rosenberg D, Tell G. Syndrome de Turner. A propos d'une statistique de 60 observations. Pediatrie 1972;27:831-50.
15. Naeraa RW, Nielsen J. Standards for growth and final height in Turner's syndrome. Acta Pædiatrica 1990;79:182-90.
16. Fukami M, Seki A, Ogata T. SHOX Haploinsufficiency as a cause of syndromic and nonsyndromic short stature. Mol Syndromol 2016;7:3-11.
17. Rongen-Westerlaken C, Corel L, Van den Broeck J, Massa G, Karlberg J, Albertsson-Wikland K, *et al*. Reference values for height, height velocity and weight in Turner's syndrome. Acta Paediatrica 1997;86:937-42.
18. El-Bassyouni HT, Afifi HH, Aglan MS, Mahmoud WM, Zaki ME. Growth curves of Egyptian patients with Turner syndrome. Am J Med Genet A 2012;158A: 2687-91.