**Original Article**

# An investigation of the anthropometric measurements in males with 47,XXY (Klinefelter Syndrome) from birth to five years of age and the impact of early hormonal treatment (EHT)

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## Abstract

**Aim:** 47,XXY (KS) is the most frequently occurring sex chromosome aneuploidy (SCA) with an incidence rate of 1:500 to 1:650 live male births. 47,XXY is characterized by androgen insufficiency and hypogonadism, diminished phallus size, hypotonia, and increased stature. This investigation examines the relationship between Early Hormonal Treatment (EHT) and growth in boys with 47,XXY from birth to 5 years.

**Methods:** A cohort of 134 males with 47,XXY was seen as part of a natural history study and anthropometric measurements were completed at each evaluation for height (HT), weight (WT), and head circumference (HC). Data was analyzed for these factors in the group receiving testosterone as EHT (T group) and a no treatment (No-T) control group.

**Results:** Significant differences in HC were observed between the T group and No-T group for birth to 12 months. There was no other significant difference in HC for boys between the ages of 13 to 60 months. Only significant

differences were observed in the birth to 12 months group for HT between the T group and No-T group. There were only significant differences in WT in the birth to 12-month age range between the T group and the No-T group, as well as in the 12-24-month age range.

**Conclusion:** EHT is not associated with reducing or advancing growth in children with 47,XXY over 2 years old. After 24 months of age there is no discernible difference between boys with 47,XXY with EHT and without EHT.

**Keywords:** 47XXY, Klinefelter Syndrome, early hormonal treatment, growth, height, weight, head circumference

## INTRODUCTION

Klinefelter Syndrome, or 47,XXY, is the most common Sex Chromosomal Aneuploidy (SCA), with an incidence rate of about 1 in 500 male births[1]. This variation is caused by the presence of an additional X chromosome in males and is highly underdiagnosed, with only 10% to 25% of males receiving a diagnosis throughout their lifetime[1]. A diagnosis of Klinefelter Syndrome often occurs for several reasons: via prenatal testing or genital abnormalities identified at birth, in adolescence in association with delays in pubertal development, or in adulthood while being tested for infertility[2]. Underdiagnosis occurs partially because of a highly variable phenotype. The neurodevelopmental presentation of 47,XXY often includes executive dysfunction, language-based learning disorders, and increased anxiety. Physically, 47,XXY typically presents with characteristic androgen deficiency, reduced fertility, gynecomastia, hypergonadotropic hypogonadism, hypotonia, and increased height[3].

Individuals with 47,XXY typically reach the 30th percentile in height before age 2, and ultimately reach the 75th to 90th percentile by age 18. Mean weight and head circumference measurements are typically at the 50th percentile[2]. A study on the clinical presentation of Klinefelter Syndrome by Pacenza *et al.* found that the average height of 94 males with 47,XXY was above the 50th percentile at $178.8 \pm 9.0$ cm[4]. Regardless of hormonal replacement therapy status, it is rare for post-pubertal males with 47,XXY to remain below the 25th percentile in height[5,6]. One study found that body weight and body mass index did not significantly differ between individuals with 47,XXY and individuals with a normal karyotype[7]. However, this population often outwardly presents as less athletic in appearance secondary to hypogonadotropic hypogonadism. Their BMI levels tend to fall within a typical range due to the commensurate muscle-to-fat ratio, with decreased muscle mass and increased body fat[6].

The cause for these characteristic growth patterns and body proportions is unclear due to a lack of research; however, there are some working hypotheses. Tanner *et al.* proposed that an unequal growth rate caused by possible incomplete activation of the extra X chromosome may account for these characteristics[8]. This hypothesis has been reaffirmed in later publications[9]. However, it has also been hypothesized that these proportional differences are caused by hormonal deficiency, as prepubertal hypoandrogenism typically presents as increased long bone growth and eunuchoid proportions, a feature commonly associated with 47,XXY[10].

Hormonal replacement therapy (HRT) is the suggested treatment for 47,XXY because of the androgen deficiency associated with the disorder. There are currently three types of HRT that exist in literature: Early Hormonal Treatment (EHT), which is typically given during "minipuberty" in infancy, Hormonal Booster Treatment (HBT), which is typically given at or around 5 years of age, and Testosterone Replacement Therapy (TRT), typically administered regularly beginning at puberty and into adulthood.

EHT consists of testosterone injections administered during minipuberty in infancy. In typically developing boys, this minipuberty generally occurs between 1-6 months of age, and has an impact on brain development, maturation of sexual organs, and the promotion of social behaviors[11-13]. One study by Cabrol *et al.* included 38 infants with 47,XXY, and measured testosterone levels during minipuberty[14]. They found that testosterone concentrations were significantly lower in infants with 47,XXY compared to controls. Therefore, administering EHT mimics the testosterone surge that occurs in typically developing infants, and may mitigate the impact of androgen deficiency associated with 47,XXY.

The impact of HRT on the growth patterns of males with 47,XXY has been under-investigated and is not well understood at this time. However, there are long-held beliefs that testosterone replacement in young children may affect growth patterns or initiate puberty, though there are not any substantive studies in research literature documenting these findings. These beliefs have impacted families seeking care from their pediatric medical providers. Notably, there have not been any longitudinal comprehensive studies looking at the effect of HRT on growth in individuals with 47,XXY between infancy and the preschool years. Additionally, in these studies, cohorts have been small and there have been few natural history studies on anthropometric parameters in males with 47,XXY. The present study aims to evaluate the effect of testosterone on growth velocity and proportion in males with 47,XXY from birth to five years of age, as well as to expand on the literature discussing their anthropometric patterns.

## MATERIALS AND METHODS

134 boys aged from birth to 60 months were enrolled in this study. All participants had a prenatal diagnosis of 47,XXY and had been referred by their primary care physician, parents, or other ancillary healthcare providers for neurodevelopmental evaluation, including anthropometric measurements of height, weight, and head circumference. Head circumference measurements were obtained by encircling the cranium with a measuring tape, one centimeter above the eyes and against the occipital region of the head. Length and weight were obtained in a supine position for those under 2 years of age. In children above three years, height was measured using a sliding measurement tool in a standing position and weight was obtained by standing on a standard upright scale. At the time of enrollment, prenatal, perinatal, and postnatal history, as well as family demographics and a three-generation family history, were collected.

Each patient's visit, including head circumference, height, and weight measurements at the time of the visit, was treated as an individual data point. This would serve as the most accurate method of ascertaining the association between growth velocity and testosterone administration. Patients under 2 years of age were seen once every 6 months and patients between 2 years of age and 5 years were seen once every year. There were 268 data points. 175 data points received testosterone injections as treatment, and 93 points did not participate in EHT and instead served as the "no treatment" (No-T) group.

Patients were evaluated by pediatric endocrinologists throughout the United States and local to their communities to determine the need for HRT. EHT was administered between the ages of 4- and 15-months. EHT consisted of three intramuscular injections of 25 mg of testosterone enanthate given over three months. Treatment was typically given at 4, 5, and 6 months of age but may be given up to 24 months[15].

The statistical analysis was completed in MATLAB R2019b using the statistics toolbox. A *t*-test was completed for analysis to compare two groups of males, those who received EHT and those who did not (T *vs.* No-T). *P*-values of $< 0.05$ were considered statistically significant.

## RESULTS

Data points were bifurcated into two groups for analysis based on their testosterone status (T or No-T). Birth data, before the administration of testosterone, was also included. Normative control data for height, weight, and head circumference was obtained from the World Health Organization's (WHO) child growth standards for boys from birth to 60 months of age[16]. To reduce confounding factors, a biostatistician blinded to participants' identities and hormonal treatment statuses completed data analysis.

When comparing head circumference in centimeters, only those from birth to 24 months of age showed a significant difference between the T group (M = 42.8, $P$ = 0.028) and the No-T group (M = 39.9). The same finding was true for height in centimeters, T group (M = 67.3, $P$ = 0.047) and the No-T group (M = 62.2). Comparing weight in kilograms, the birth to 12-month-old (T-group: M = 8.5, $P < 0.05$; No-T group: 6.4) and the 13- to 24-month-old (T-group: M = 11.5, $P$ = 0.048; No-T group: M = 13.2) showed significant differences. There is one noted outlier with a significantly higher weight in comparison to the other subjects of that age [Figure 1]. This anomaly may be explained by the subject's family history of increased weight and size. No significant differences were found between 1.0 years of age and 5 years of age for head circumference and height [Table 1]. In Figures 1-3, growth curves shown in red and pink reveal typical childhood growth patterns for all periods. No significant differences were found between 2 and 5 years of age in weight. All groups showed normalization with their typically developing peers by 5 years of age [Figures 1-3].

## DISCUSSION

Our findings show that EHT does not have a significant effect on growth patterns for boys with 47,XXY between 2 and 5 years of age. Differences in growth during the infant period (birth-1.0 years) were likely related to EHT; however, no significant differences were noted between 24-60 months of age in height, weight, or head circumference. To the best of our knowledge, this is the largest study to analyze growth in response to HRT in boys with 47,XXY at these ages.

It is important to note that the presented study has some limitations. First, this is not a randomized controlled trial, and thus we are unable to determine causality. We are also unable to generalize our findings due to ascertainment bias and a large percentage of individuals who are undiagnosed with 47,XXY. This specific limitation is a common challenge for all research studies investigating this population.

Potential confounding factors have been minimized for this study. We compared No-T groups and T-groups and there were no significant differences in maternal or paternal age, birth weight, and parental educational status [Table 2]. There were five subjects, in both the T and No-T group, with significantly smaller head circumference measurements in comparison to their same-age peers [Figure 3]. These subjects had no indications of their neurodevelopmental dysfunction to explain this presentation; however, parental head circumference was not taken, which could have helped determine if the condition was familial. While our study investigated height, weight, and head circumference, we did not evaluate body mass index (BMI) or extremity length. BMI as a measure of growth may have limitations in this population however, as many of these boys fall into a normal range for BMI at this age.

Previous studies indicate that at birth, males with 47,XXY are smaller in height, weight, and head circumference than average, and that these children have been shown to accelerate in growth at age three, and again at the onset of puberty[17-19]. Davis *et al.* described that a cohort of 20 infants with 47,XXY exhibited increased arm span[19], leg length, and overall stature compared with their typically developing peers[20]. However, our findings show that after 24 months of age, there is no discernible difference in height,

**Table 1. Anthropometric growth patterns of boys with 47,XXY: comparing testosterone (T) *vs.* No testosterone (No-T)**

| | | Birth-12 mo. | | 13-24 mo. | | 25-36 mo. | | 37-48 mo. | | 49-60 mo. | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | T (*n* = 44) | No-T (*n*= 43) | T (*n* = 48) | No-T (*n* = 16) | T (*n* = 35) | No-T (*n* = 11) | T (*n* = 24) | No-T (*n* = 10) | T (*n* = 24) | No-T (*n* = 13) |
| HC (cm) | Mean | 42.8 | 39.9 | 47.5 | 47.8 | 48.6 | 48.6 | 50.3 | 50.3 | 49.3 | 53.2 |
| | SD | 6.8 | 5.2 | 1.3 | 1.8 | 5.6 | 1.3 | 1.8 | 2.0 | 6.8 | 3.6 |
| | *P*-Value | 0.028* | | 0.47 | | 0.49 | | 0.48 | | 0.13 | |
| HT (cm) | Mean | 67.3 | 62.2 | 81.8 | 86.9 | 91.7 | 89.7 | 109.5 | 97.3 | 110.7 | 106.9 |
| | SD | 12.7 | 6.4 | 5.6 | 15.7 | 4.6 | 6.1 | 43.2 | 5.3 | 8.1 | 4.6 |
| | *P*-Value | 0.047* | | 0.065 | | 0.11 | | 0.5 | | 0.09 | |
| WT (kg) | Mean | 8.5 | 6.4 | 11.5 | 13.2 | 14.3 | 13.2 | 16.6 | 15.5 | 20.0 | 18.0 |
| | SD | 1.7 | 1.6 | 1.9 | 3.9 | 2.0 | 2.1 | 2.0 | 1.9 | 0.5 | 3.7 |
| | *P*-Value | < 0.05* | | 0.048* | | 0.07 | | 0.35 | | 0.14 | |

*$P < 0.05$.

**Table 2. Demographics**

| | T (*n* = 175) | | No-T (*n* = 93) | | |
|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | ***P*-Value** |
| Birth weight (kg) | 3.10 | 0.575 | 3.04 | 1.12 | 0.72 |
| Maternal age (years) | 35.35 | 5.47 | 34.81 | 5.11 | 0.565 |
| Paternal age (years) | 36.60 | 6.03 | 36.66 | 5.60 | 0.955 |
| Maternal education scale | 5.22 | 1.17 | 5.46 | 0.78 | 0.256 |
| Paternal education scale | 4.91 | 1.61 | 5.23 | 1.54 | 0.333 |

Maternal and Paternal Education Scales: 1: Didn't finish high school; 2: High school; 3: Some college, didn't finish; 4: 2-year college, associates; 5: College; 6: Grad school; 7: MD, PhD, Law school.
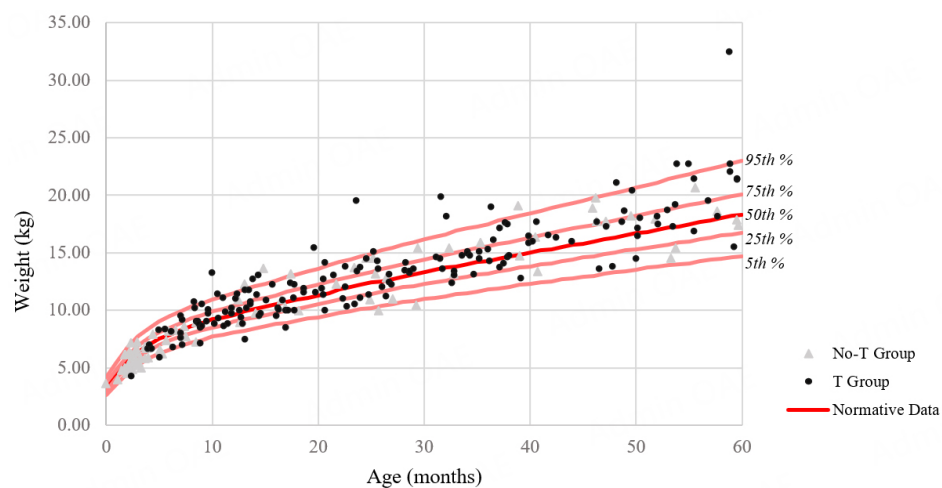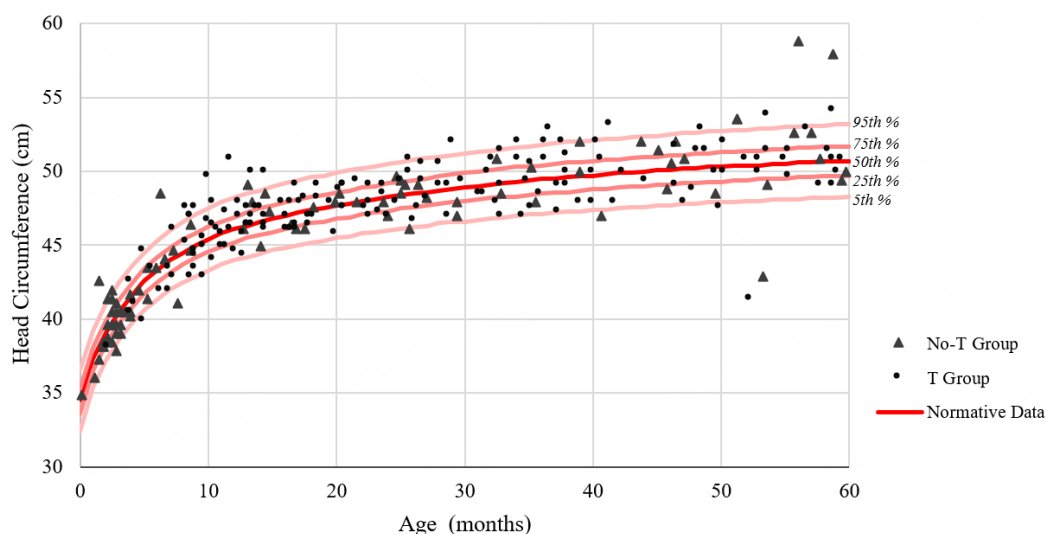


**Figure 1.** Weight (kg) in males with 47,XXY from 0-60 months. The No-T group and the T group are represented by triangles and circles, respectively. The bright red line represents the 50th percentile of typical child weight as obtained by the World Health Organization. The surrounding pink lines represent the preceding and following percentiles.

weight, and head circumference between boys with 47,XXY (whether treated with EHT or not) and their typically developing peers [Figures 1-3]. This discrepancy between Davis *et al.*'s findings and ours may be
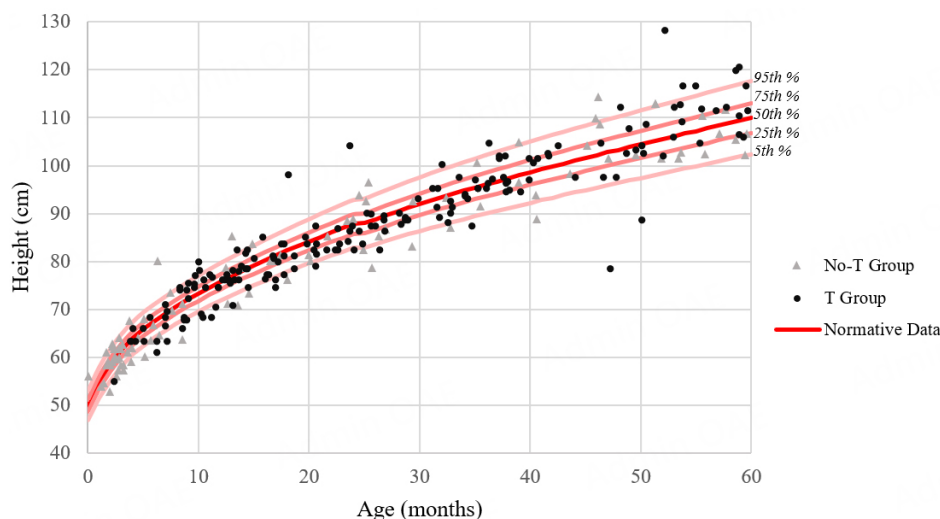
**Figure 2.** Height in males with 47,XXY from 0-60 months. The No-T group and the T group are represented by triangles and circles, respectively. The bright red line represents the 50th percentile of typical child height as obtained by the World Health Organization. The surrounding pink lines represent the preceding and following percentiles.



**Figure 3.** Head Circumference (cm) in Males with 47,XXY from 0-60 months. The No-T group and the T group are represented by triangles and circles, respectively. The bright red line represents the 50th percentile of typical child head circumference as obtained by the World Health Organization. The surrounding pink lines represent the preceding and following percentiles.

due to differences in cohort size. Davis *et al.*'s study had a cohort of 20 infants, which is significantly smaller than our cohort of 134 boys[19].

Since EHT is administered in infancy, the timing of diagnosis has significant implications for children and families. Early detection of sex chromosome aneuploidies, specifically 47,XXY, allows better clinical management among healthcare providers, and ultimately leads to improved outcomes for these individuals based on published studies with substantive cohorts. Further research is warranted to determine the optimal timing and dosages of HRT, as well as how growth is impacted in other age groups.

Our findings further support that EHT neither reduces nor advances physical growth in the child with 47,XXY between the ages 2-5. While EHT is still not considered a standard of care for boys with 47,XXY, there has been an increased focus on its role in treating the associated androgen deficiency. Other studies within this field show that testosterone administered during minipuberty in the first year of life is associated with improved speech and language development, reduced behavioral problems, and increased social skills for boys with this disorder[21,22]. The misconception that EHT may affect the velocity of height in young children with 47,XXY is not supported by the findings in this paper in that all the boys, regardless of EHT status, have similar growth patterns by 2 years of age.

## DECLARATIONS

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### Authors' contributions
Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Schmidt K, Samango-Sprouse C
Performed data acquisition, as well as providing administrative, technical, and material support: Schmidt K, Gropman A, Sadeghin T, Jackson TA, Samango-Sprouse C
Contributed to editorial revisions, development of tables and figures, and updating data analysis: Olaya M

### Availability of data and materials
The data sets presented in this article are not readily available because of privacy or ethical restrictions. Requests to access the data sets should be directed to Samango-Sprouse C at cssprouse@email.gwu.edu.

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### Conflicts of interest
All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate
No animal studies are presented in this manuscript. The studies involving human individuals were reviewed and approved by The Western Institutional Review Board, which also approved this study protocol (#20081226). Written informed consent to participate in this study was provided by the individuals' legal guardian/next of kin. No potentially identifiable human images or data are presented in this study.

### Consent for publication
Not applicable.

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