Transient Postnatal Gonadal Activation and Growth Velocity in Infancy

Panu Kiviranta, MD, PhD,[a,b] Tanja Kuiri-Hänninen, MD, PhD,[a,b] Antti Saari, MD, PhD,[a,b] Marja-Leena Lamidi, MSc,[c] Leo Dunkel, MD, PhD,[d] Ulla Sankilampi, MD, PhD[a,b]

abstract

BACKGROUND AND OBJECTIVE: Transient activation of the hypothalamic-pituitary-gonadal axis with a sex steroid surge is observed in boys and girls during the first months of life. However, the role of sex steroids in the regulation of growth has not been substantiated in infancy. We tested the hypothesis that testosterone (T) surge, known to be higher in infant boys than in girls during the transient postnatal gonadal activation regulates linear growth in infants.

METHODS: To characterize in detail the linear growth velocity (GV) differences between genders in the normal population in early infancy, we evaluated growth of 18 570 healthy infants (51.0% boys) with 162 003 height measurements from birth to 12 months of age. GV was monitored and compared with serially measured urinary T and estradiol levels and serum insulin-like growth factor 1 levels in 84 healthy infants (45% boys) during the first 6 months of life.

RESULTS: GV was significantly faster from birth to 6 months of age in boys than in girls ($P \leq .01$). The greatest GV difference, 4.1 cm per year, was observed at 1 month of age, simultaneously with the peak of postnatal gonadal activation. In the mixed model analysis, GV showed a significant positive association with T in both genders (parameter estimate up to 0.62, 95% confidence interval 0.44–0.81).

CONCLUSIONS: These results provide a new insight into the regulation of growth in infants and elucidate a novel biological role of the transient postnatal gonadal activation in growth regulation.

[a]*Department of Pediatrics, Kuopio University Hospital, Kuopio, Finland;* [b]*Department of Pediatrics and* [c]*Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland; and* [d]*William Harvey Research Institute, Barts and the London, Queen Mary University of London, London, United Kingdom*

Dr Kiviranta carried out the statistical analyses, drafted the first version of the manuscript, and revised the manuscript; Dr Kuiri-Hänninen collected the hormonal data and revised the manuscript; Dr Saari collected the growth data and revised the manuscript; Ms Lamidi modeled the growth of the infants, designed the statistical methods used in the study, and revised the manuscript; Drs Dunkel and Sankilampi coordinated and conceptualized the study and revised the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Leo Dunkel, MD, PhD, William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London, EC1 M 6BQ, London, United Kingdom. E-mail: l.dunkel@qmul.ac.uk

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WHAT'S KNOWN ON THIS SUBJECT: A transient sex steroid surge occurs postnatally in both infant boys and girls, but whether this "minipuberty" has effects on linear growth, analogously to the puberty, remains unclear.

WHAT THIS STUDY ADDS: There is a discernible growth rate difference in infancy, with boys growing faster than girls. A positive association between testosterone level during the first months of life and growth rate was observed, independently of the growth hormone/insulin-like growth factor 1 axis.

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Linear growth is mediated by the proliferative activity of chondrocytes in the growth plates and regulated by many hormones, with growth hormone (GH) and insulin-like growth factor 1 (IGF-1) being the most important regulators. Elevated sex steroid levels stimulate growth both by enhancing GH and IGF-1 synthesis and by direct effects in the growth plate.[1–3] The first, transient, postnatal activation of the hypothalamic-pituitary-gonadal (HPG) axis occurs shortly after birth during the first months of life.[4] In infant boys and girls, the pituitary gonadotropins and sex steroids peak at 1 to 3 months of age, and thereafter, activation of the HPG axis gradually decreases by 6 months of age.[5–8] During this period, often called minipuberty, infant boys have higher androgen levels than girls. The early HPG axis activation has a potential role in priming the reproductive organs for future development, and possibly in programming the gender-typical behavior.[5–9] However, there are no data regarding whether the sex steroids affect linear growth in infancy. Interestingly, some observations indicate that boys have a higher growth velocity (GV) than girls during early infancy.[10–12] The precise timing and magnitude of the sexual dimorphism in growth in infancy, however, remains poorly studied because earlier studies are based on a relatively small number of subjects with long measurement intervals in the first months of life.

We hypothesized that postnatal HPG axis activation in infancy is involved in the regulation of linear growth. Our aim was, first, to characterize normative linear growth during the first year of life in detail in a large population-based cohort of healthy infants to be able to observe possible subtle and transient gender-specific phases of infantile growth; and second, to verify our hypothesis and evaluate the role of sex steroids in infant growth, a prospective observational study with serial sex steroid measurements was conducted.

METHODS

Subjects and Measurements

For detailed characterization of the normative growth in infancy, growth data of 18 570 healthy full-term infants (cohort 1; 51% boys) were analyzed from birth to 12 months. These infants were a subcohort of a larger child population from city of Espoo, previously used in the generation of the new Finnish growth references.[13] In brief, these infants were born from full-term singleton pregnancies, did not have intrauterine growth failure or exposure to maternal smoking, and did not have disorders or take medications that could potentially affect growth. Growth data were obtained from the electronic patient records of free-of-charge well-baby clinic visits that monitor the growth and well-being from infancy to childhood in Finland. During the first year of life, children have 10 scheduled visits: at 2 weeks of age and at 1, 2, 3, 4, 5, 6, 8, 10, and 12 months of age.

To assess the potential role of HPG axis activation in modulating growth in infancy, a cohort of healthy term and near-term newborn infants (cohort 2; n = 84, 45% boys, mean gestational age [SD] 38.0 [2.7] weeks; mean birth weight 2914 [819] g) was recruited at the Kuopio University Hospital, Finland, between August 2006 and March 2008. The infants were measured at 1 week of age (D7) and thereafter monthly until 6 months of age (M1–M6). In both cohorts, length was measured at birth and in the primary care or study visits to the nearest 0.1 cm by using standardized techniques and calibrated equipment described in the nationwide guidelines by the Finnish National Institute for Health and Welfare.[14] Birth size in SD units was determined according to a contemporary Finnish birth size reference.[15]

The Ethics Committee of the local Health Care District approved the study. The study was conducted according to the principles of the Declaration of Helsinki, and written informed consent was obtained from the parents of the subjects participating in the prospective study. Permission for the use of anonymized growth data of Cohort 1 was obtained from the city of Espoo Municipality Institutional Review Board.

Urine and Blood Sampling and Quantitative Hormonal Assays

In the 84 infants participating in the prospective part of the study, a spot urinary sample was collected with a plastic urine collection bag or with clean catch for sex steroid analyses at every visit from D7 to M6. At the D7 and M3 visits, a venous blood sample was drawn for the measurement of serum IGF-1 concentration.

Testosterone (T) and estradiol (E2) levels were measured in the urinary samples. To adjust the results to urine concentration, measured urinary T and E2 levels were corrected for urinary creatinine. An enzymatic method was used to analyze creatinine concentration before the urine was deep-frozen at −72 °C and stored for the later analyses of T and E2, which were measured by high performance liquid chromatography tandem mass spectrometry as described earlier.[5,16] All results from T and E2 analyses under the detection limit of the assay were set to zero to avoid these results to falsely affect the statistical analyses.

Serum IGF-1 concentration was measured using an enzyme-linked immunosorbent assay method (Mediagnost IGF-1 Elisa cat E20, Mediagnost GmbH, Reutlingen, Germany). The within-run CV% was

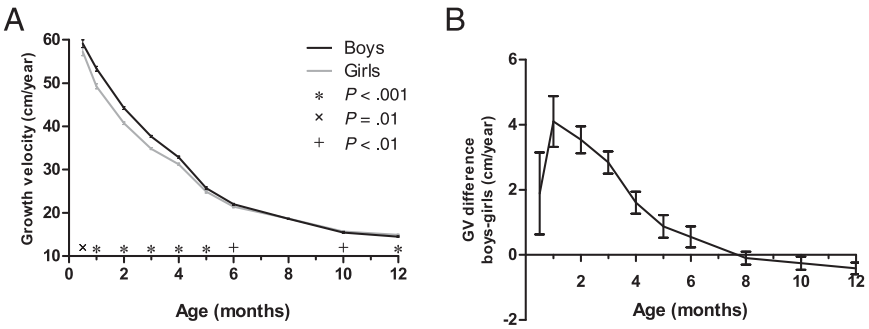

FIGURE 1

A, Growth velocities (95% confidence interval) in 9468 boys and 9102 girls from birth to 12 months of age. First GV is measured at 2 weeks of age, from which boys grow faster than girls until 6 months of age. B, Difference in GV (± 95% confidence interval) between genders reaching its maximum at 1 month of age.

4.7% (mean IGF-1 4.8 nmol/L) and between-run CV% for control serum was 6% (mean IGF-1 13.6 nmol/L) in the range of 0.65 to 65 nmol/L.

Growth Modeling and Statistical Analyses

Linear growth in infancy occurs in an episodic manner,[17] and GV shows major changes during the first months of life.[10] In cohort 1 with 18 570 infants, the periodicity of infantile growth was smoothed based on the large number of subjects. Linear GV (cm/year) was calculated between height measurements of the consecutive scheduled visits by dividing the change in length by the time interval between the measurements. In cohort 1, a total of 162 003 height measurements were made from birth to the 12-month visit, but because of a lack of height data at certain points, it was possible to determine only 123 655 GVs. Because repeated observations from same individuals were included, a linear mixed model was used to evaluate differences in mean GVs between genders at different time points. In the model, patient code identified multiple measurements between scheduled visits at different time points. GV was the dependent variable; the time point of the measurement, infant gender, and interaction between sex and measurement point were included as fixed factors.

To account for the periodicity of growth in the prospectively collected cohort 2 with 84 infants, the linear growth was modeled individually by fitting a second-degree polynomial function to the observed length data, where age was plotted on the x-axis and length on the y-axis. The fitting procedure was done by using the R software (R Foundation for Statistical Computing, Vienna, Austria). The derivative of the growth model function was used to determine the individual GVs from 1 to 6 months of age. Differences in GVs, T, E2, and IGF-1 levels between genders were analyzed using the linear mixed model with birth weight and length SDs as the fixed effects and twinness (ie, family code) as a random effect.

First, for evaluation of possible unadjusted correlations between GV and hormone levels, and GV and birth size or gestational age, Spearman correlations were used. The *t* test was used for comparison of correlation coefficients between boys and girls, and 2-sided *P* values are presented. To evaluate association between GV and hormonal factors independently from confounding factors, 2 linear mixed models were used with different combination of fixed effects. Model 1 included GV as the dependent variable and T and E2 levels (M1–M6) and serum IGF-1 level (M3) as explanatory variables. Model 2 was supplemented with birth weight and length SDs[15] and gestational age at birth as explanatory variables. Urinary T and E2 levels were not normally distributed, and therefore, to achieve normality of the residuals in the linear mixed model, a decadic logarithmic transformation was used. To avoid zero values from dropping out, a constant value of 10 was added to the creatinine corrected T and E2 values before the logarithmic transformation. T, E2, IGF-1, and gestational age values were standardized in each time point to produce parameter estimates from the linear mixed model that are equivalent to partial correlation coefficients. Twinness was included in both models as a random factor to account for interdependencies between twins.

All statistical analyses were performed with IBM SPSS Statistics, Version 19 (IBM Corp, Armonk, NY).

RESULTS

Gender Differences in Linear Growth

GV of 9468 boys and 9102 girls from birth to 12 months is presented in Fig 1A. GV decreases after birth in both genders. In early infancy, until age 6 months, GV in girls was significantly slower than in boys ($P < .01$ for 2 weeks of age, $P < .001$ for M1–M5, $P = .01$ at M6). The GV difference between genders reached its peak at 1 month of age, when GV in boys was 4.1 cm per year faster than in girls (Fig 1B).

Growth velocities during the first months of life in 84 infants with hormonal measurements (cohort 2) were in line with the normative growth pattern in cohort 1. Also in this small cohort, there was a statistically significant difference in GV between gender, with GV being greater in boys at ages 1, 2, and 3 months (M1: $P = .010$, M2: $P = .009$, and M3: $P = .018$; data not shown).

TABLE 1 Correlation Between T Level and Concurrent GV From 1 to 6 Months of Age in 84 Infants

	1 Month		2 Months		3 Months		4 Months		5 Months		6 Months	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
All ($n = 84$)	0.57	<.001	0.63	<.001	0.47	<.001	0.37	<.001	0.30	.01	0.22	.053
Boys ($n = 38$)	0.32	.054	0.49	.003	0.34	.04	0.37	.02	0.50	.002	0.55	<.001
Girls ($n = 46$)	0.68	<.001	0.69	<.001	0.58	<.001	0.41	.007	0.20	.21	0.02	.92
Comparison of correlations between genders		.03		.17		.18		.82		.13		.008

Correlations between genders differ significantly at 1 and 6 months. *P* values for significance of difference in correlation coefficients between boys and girls are printed in the lowest row.

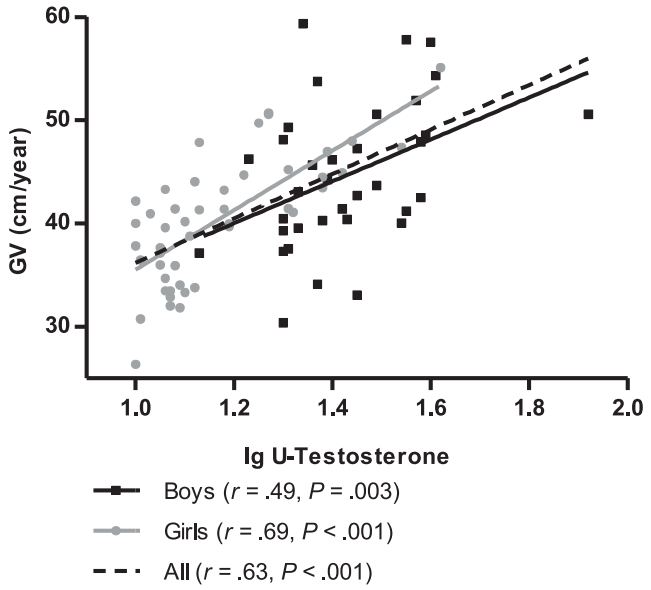

FIGURE 2
Correlation between GV and T level at 2 months of age in girls and boys. A positive correlation between T and concurrent GV was observed both in boys and girls (difference between correlation coefficients of girls and boys is not significant; $P = .18$). Ig U-Testosterone = Ig(urinary T (nmol/L)/U-creatinine (mmol/L) +10).

Associations of Postnatal Sex Steroids and GV

Postnatally, T levels increased between D7 and M1 and were higher in boys than girls from D7 to M6 ($P < .001$ from D7 to M5 and $P < .01$ at M6). E2 levels were generally ~1000 times lower than T levels (picomolar versus nanomolar). Median E2 levels were similar at D7 in boys and girls; thereafter, E2 levels in infant girls were higher than in boys ($P < .01$ at M1 and $P < .001$ from M2 to M6; Supplemental Fig 3). IGF-1 levels did not differ significantly between genders at D7 (81 ng/mL in boys and 85 ng/mL in girls, $P = .49$ for difference) nor at M3 (78 ng/mL in boys and 74 ng/mL in girls, $P = .52$ for difference).

During the first 5 months of life, a significant positive correlation was observed between T level and concurrent GV (Table 1). The strongest correlation was seen at M2 (Spearman ρ 0.63, $P < .001$). The slope of the fit line was similar in both genders at the overlapping area of T levels, indicating similar relationships between T exposure and GV (difference between boys and girls statistically nonsignificant, $P = .18$; Fig 2). At M2, variation in T level attributed to 40% of variance of GV (48% in girls and 24% in boys; Table 1). From M2 to M5, the correlation between T and GV did not differ significantly between genders (*P* from 0.13 to 0.82; Table 1). At M1, the correlation between T and GV was significantly stronger in girls ($P = .03$), whereas at M6, the correlation was stronger in boys ($P = .008$).

To evaluate the possible independent association of T and concurrent GV, 2 linear mixed models were constructed (Table 2). In model 1, including T, E2, and IGF-1 levels, a significant positive association between T and GV was observed from M1 to M5 (parameter estimates 0.34–0.62, $P < .05$). The relationship between T and GV remained significant after including IGF-1 level in model 1 at M3 (parameter estimate 0.51, $P < .001$). Significant negative correlations were observed between both T level or GV and gestational age at birth and birth size (birth weight or length SDs). Therefore, model 2 was complemented with gestational age at birth, birth weight and length SDs, in addition to sex steroids and IGF-1. In model 2, the association between T and GV from M1 to M3 remained significant (parameter estimates 0.21–0.36, $P < .05$; Table 2). According to both models, the strongest association between T and GV was observed at M2. In addition to T level, IGF1 was positively associated with GV at M3 (in model 1, parameter estimate 0.30, $P < .001$; in Model 2, 0.28, $P < .001$). E2 level was not associated in GV at any time point.

DISCUSSION

We conducted a longitudinal cohort study to clarify 2 questions. First, we characterized in detail the magnitude and timing of sexual dimorphism in human growth during the first

TABLE 2 Association of Hormone Levels With GV in 84 Infant Boys and Girls During the Transient Postnatal Gonadal Activation From 1 to 6 Months of Age in 2 Linear Mixed Models

	1 Month		2 Months		3 Months		4 Months		5 Months		6 Months	
	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Model 1 factors												
T	0.51 (0.33 to 0.69)	<.001	0.62 (0.44 to 0.81)	<.001	0.51 (0.31 to 0.71)	<.001	0.40 (0.20 to 0.61)	<.001	0.34 (0.1 to 0.56)	.002	0.09 (−0.14 to 0.32)	.23
E2	0.13 (−0.05 to 0.32)	.16	0.06 (−0.10 to 0.23)	.44	0.12 (−0.05 to 0.28)	.16	0.01 (−0.14 to 0.16)	.84	0.10 (−0.12 to 0.33)	.37	−0.02 (−0.24 to 0.20)	.79
IGF-1	—	—	—	—	0.30 (0.14 to 0.45)	<.001	—	—	—	—	—	—
Model 2 factors												
T	0.32 (0.15 to 0.50)	<.001	0.37 (0.18 to 0.55)	<.001	0.21 (0.03 to 0.39)	.02	0.19 (−0.01 to 0.38)	.06	0.15 (−0.07 to 0.38)	.18	−0.03 (−0.19 to 0.14)	.68
E2	0.11 (−0.06 to 0.27)	.20	0.02 (−0.12 to 0.17)	.75	−0.01 (−0.16 to 0.13)	.87	−0.02 (−0.19 to 0.14)	.73	0.06 (−0.16 to 0.28)	.58	−0.03 (−0.24 to 0.18)	.70
IGF-1	—	—	—	—	0.29 (0.16 to 0.42)	<.001	—	—	—	—	—	—
GA at birth	−0.39 (−0.58 to −0.20)	<.001	−0.44 (−0.62 to −0.26)	<.001	−0.50 (−0.68 to −0.33)	<.001	−0.58 (−0.77 to −0.39)	<.001	−0.47 (−0.71 to −0.23)	<.001	−0.38 (−0.61 to −0.16)	<.001
Birth wt SDs[a]	−0.18 (−0.42 to 0.06)	.13	−0.19 (−0.40 to 0.02)	.07	−0.24 (−0.44 to −0.04)	.02	−0.08 (−0.31 to −0.15)	.48	−0.03 (−0.31 to 0.25)	.81	−0.23 (−0.57 to 0.11)	.14
Birth length SDs[a]	0.04 (−0.19 to 0.26)	.73	0.08 (−0.12 to 0.29)	.42	0.12 (−0.05 to 0.32)	.16	0.07 (−0.14 to 0.29)	.48	0.10 (−0.16 to 0.36)	.43	0.24 (−0.05 to 0.53)	.10

Values are expressed as parameter estimates and 95% confidence intervals (CIs). GA, gestational age. — indicates data not available.

[a] SDS, SD score, according to Finnish growth reference for birth size.[11]

months of life. Second, we looked for evidence for the transient postnatal HPG activation ("minipuberty") being involved in the regulation of linear growth during infancy.

Our study confirmed earlier observations that boys grow faster than girls in infancy during the first 6 months of life. Maximal difference in GV between genders was seen during the first 2 months of life. The difference in GV between genders is of the same magnitude as in puberty, that is, GV in infant boys is up to 4 cm per year faster than in girls. According to Finnish growth standards, the gender difference in GV during the first 6 months of life results in a 1.8-cm difference in median length between genders at 6 months of age (girls 67.6 cm, boys 69.4 cm), and this difference remains almost constant until age 12 months (girls 75.7 cm; boys 77.4 cm).[13]

Our longitudinal study, using serial urine samples, confirmed the earlier observations of a T peak during the first months of life in boys, which occurs at the same postnatal age in term and near-term infants.[5] In addition, we observed higher levels of T in male than in female infants. The higher T levels in boys reflect the biological activity of testes, whereas T measured in girls originates from the adrenal glands and from peripheral conversion of adrenal androgen precursors such as dehydroepiandrosterone produced in large amounts by the involuting fetal adrenal cortex during the early postnatal life.[18] In contrast to elevated postnatal T levels in both genders, E2 surge was seen only in girls. We have previously shown that the postnatal sex steroid surge has biological effects on hormone-sensitive target tissues.[5,16] In the postnatal period, elevated T levels associate with simultaneous prostate-specific antigen rise from the prostate and growth in penile length.[5] In addition, postnatal urinary androgens are

associated with androgen-mediated cutaneous manifestations, such as sebaceous gland hypertrophy and acne in both infant girls and boys.[18] In girls, the subtle E2 surge in infancy is associated with the growth of E2 sensitive tissues, such as the uterus and mammary glands.[16] Taken together, these data indicate that the transient sex steroid surge during minipuberty has biological effects on sensitive target tissues expressing androgen receptor (AR) and estrogen receptors. The current study shows evidence, for the first time, that the growth plates of long bones are also sensitive and influenced by the postnatal sex steroid surge.

The timing of the maximal GV difference between genders at 1 to 2 months of age observed in the present data matches perfectly with our observations of the timing of maximum postnatal HPG axis activation.[5] This finding indirectly supports our hypothesis that differences in sex steroid levels contribute to differences in GV between infant boys and girls. Direct support for the role of sex steroids on infantile growth was provided by the positive associations between postnatal T levels with GV during the first months of life. In general, the strongest correlation was seen at 2 months of age, when variation of measured T level explained as much as 40% of the variance of GV. Even though boys had higher T levels than girls during the minipuberty, the relationship between T levels and GV seems to be aligned in the partially overlapping areas of T levels in boys and girls. This probably indicates that both sexes may respond similarly to T exposure during infancy. This is also supported by the observation that from M2 to M5, the strength of the correlation between T and GV did not differ significantly between boys and girls. However, we observed a stronger correlation in girls at M1 and in boys at M6. These temporal differences between genders might be due to differences in timing of the androgen surge during the first months of life or to type 1 error in our relatively small study cohort.

After birth, the majority of length gain is achieved in the metaphyses of long bones through proliferation, differentiation, hypertrophy, and subsequent calcification of the growth plate chondrocytes.[19,20] During infancy, GH is the primary regulator of circulating IGF-1, and GH and IGF-1 are the 2 key hormones regulating linear growth. Sex steroids influence growth through the GH-IGF-1 system but probably have direct effects on the growth plate as well via AR and especially estrogen receptors.[21] In the growth plate of both girls and boys, C19 androgens such as T are aromatized into estrogens, which are probably more important than androgens of the regulation of growth. Thus, the measurable T level is probably not a good surrogate of estrogen exposure in peripheral tissues such as the growth plate. In addition to the T level indicating availability of aromatizable androgens, gonadal estrogen production in girls (with much lower circulating levels than T) and the local aromatase activity in the growth plate, among other factors, contribute to the observed differences in GV.

Data from various experiments have provided some additional insight on the role of sex steroids in linear growth in infancy. Some,[22,23] but not all,[24] studies have shown increased birth size and a lack of typical sexual dimorphism in birth weight in patients with congenital adrenal hyperplasia exposed to androgen excess already in utero. Infants with a delayed diagnosis of this disorder and continuous androgen excess after birth grow faster than healthy children during the first year of life,[22] supporting a role for adrenal steroids in linear growth. Boys with congenital hypogonadotrophic hypogonadism who completely lack the postnatal T surge show stunted linear growth during minipuberty.[25] A temporary increase in GV has been reported in infants and prepubertal boys exposed to repeated doses of intramuscular T for treatment of micropenis.[26] These findings further support the view that androgens have a potential to enhance growth, either directly or through aromatization, also during infancy.

The complete androgen insensitivity syndrome (CAIS) constitutes a model to study the role of estrogens and androgens in the regulation of linear growth. Individuals with CAIS have 46,XY genotype, and, despite normal or high T levels, absent androgen action due to abnormal AR. However, a growth spurt during puberty can be normal in CAIS.[27] This suggests that pubertal growth is primarily mediated by estrogens, which can be originated from local aromatization of androgens. Our data show no connection with E2 and GV in infancy, but it is probable that the concentration of E2 in urine does not reflect the concentration in the growth plate. It has been suggested that patients with CAIS do not have a postnatal sex steroid surge, and therefore this condition does not serve as a model to study the role of sex steroids postnatally.[28]

CAIS also constitutes a model to assess the nonhormonal factors that contribute to linear growth. The nonhormonal factors include growth promoting genes of the Y chromosome that may influence longitudinal growth independently of sex steroids.[29] The 46,XY CAIS women have mean adult heights intermediate between average females and males.[27] The shorter adult height compared with healthy men may indicate the impaired androgen action due to mutations in the AR gene, whereas the taller height compared with healthy women implies androgen-independent effects of

genes in the Y chromosome. Thus, both hormonal and nonhormonal factors seem to contribute to these sex-specific patterns of linear growth.

The limitation of the study was that we did not have population-based urinary hormone data from the large population in which the sexually dimorphic growth was described. Instead, we tested the hypothesis in the cohort of 84 infants recruited for the prospective longitudinal study on the mechanisms, characteristics, and roles of minipuberty, the postnatal HPG axis activation. However, the sexually dimorphic growth pattern during the first months of life was visible also in the prospective cohort.

CONCLUSIONS

Results from this study clarify differences in GV between genders in infancy, when boys grow faster than girls until age 6 months. The maximum difference in GV was observed at 1 month of age, simultaneously with the maximum postnatal T surge of the transient gonadal activation. Furthermore, a positive association between GV and postnatal T surge was demonstrated. The positive association between T and GV in infancy is evident even after adjustments for multiple confounding factors. Thus, the study suggests a new role for the postnatal gonadal activation in the regulation of growth.

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ABBREVIATIONS

AR: androgen receptor
CAIS: complete androgen insensitivity syndrome
E2: estradiol
GH: growth hormone
GV: growth velocity
HPG: hypothalamic-pituitary-gonadal
IGF-1: insulin-like growth factor 1
T: testosterone

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REFERENCES

1. van der Eerden BC, Karperien M, Wit JM. Systemic and local regulation of the growth plate. *Endocr Rev*. 2003;24(6):782–801
2. Perry RJ, Farquharson C, Ahmed SF. The role of sex steroids in controlling pubertal growth. *Clin Endocrinol (Oxf)*. 2008;68(1):4–15
3. Keenan BS, Richards GE, Ponder SW, Dallas JS, Nagamani M, Smith ER. Androgen-stimulated pubertal growth: the effects of testosterone and dihydrotestosterone on growth hormone and insulin-like growth factor-I in the treatment of short stature and delayed puberty. *J Clin Endocrinol Metab*. 1993;76(4):996–1001
4. Forest MG, Cathiard AM, Bertrand JA. Evidence of testicular activity in early infancy. *J Clin Endocrinol Metab*. 1973;37(1):148–151
5. Kuiri-Hänninen T, Seuri R, Tyrväinen E, et al. Increased activity of the hypothalamic-pituitary-testicular axis in infancy results in increased androgen action in premature boys. *J Clin Endocrinol Metab*. 2011;96(1):98–105
6. Andersson AM, Toppari J, Haavisto AM, et al. Longitudinal reproductive hormone profiles in infants: peak of inhibin B levels in infant boys exceeds levels in adult men. *J Clin Endocrinol Metab*. 1998;83(2):675–681
7. Chellakooty M, Schmidt IM, Haavisto AM, et al. Inhibin A, inhibin B, follicle-stimulating hormone, luteinizing hormone, estradiol, and sex hormone-binding globulin levels in 473 healthy infant girls. *J Clin Endocrinol Metab*. 2003;88(8):3515–3520
8. Kuiri-Hänninen T, Kallio S, Seuri R, et al. Postnatal developmental changes in the pituitary-ovarian axis in preterm and term infant girls. *J Clin Endocrinol Metab*. 2011;96(11):3432–3439
9. Lamminmäki A, Hines M, Kuiri-Hänninen T, Kilpeläinen L, Dunkel L, Sankilampi U. Testosterone measured in infancy predicts subsequent sex-typed behavior in boys and in girls. *Horm Behav*. 2012;61(4):611–616
10. Roche AF, Guo S, Moore WM. Weight and recumbent length from 1 to 12 mo of age: reference data for 1-mo increments. *Am J Clin Nutr*. 1989;49(4):599–607
11. Rosen O, Cohen A. Analysis of growth curves via mixtures. *Stat Med*. 2003;22(23):3641–3654
12. Gasser T, Sheehy A, Molinari L, Largo RH; T. Gasser, A. Sheehy, L. Molinari. Sex dimorphism in growth. *Ann Hum Biol*. 2000;27(2):187–197
13. Saari A, Sankilampi U, Hannila ML, Kiviniemi V, Kesseli K, Dunkel L. New Finnish growth references for children and adolescents aged 0 to 20 years: length/height-for-age, weight-for-length/height, and body mass index-for-age. *Ann Med*. 2011;43(3):235–248

14. Mäki P, Wikström K, Hakulinen-Viitanen T, Laatikainen T; Terveyden ja hyvinvoinnin laitosTerveystarkastukset lastenneuvolassa ja kouluterveydenhuollossa: Menetelmäkäsikirja. Available at: http://urn.fi/URN:NBN:fi-fe201205085455. Accessed May 1, 2016

15. Sankilampi U, Hannila ML, Saari A, Gissler M, Dunkel L. New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. *Ann Med*. 2013;45(5-6):446–454

16. Kuiri-Hänninen T, Haanpää M, Turpeinen U, et al. Postnatal ovarian activation has effects in estrogen target tissues in infant girls. *J Clin Endocrinol Metab*. 2013;98(12):4709–4716

17. Lampl M, Veldhuis JD, Johnson ML. Saltation and stasis: a model of human growth. *Science*. 1992;258(5083):801–803

18. Kuiri-Hänninen T, Haanpää M, Turpeinen U, Hämäläinen E, Dunkel L, Sankilampi U. Transient postnatal secretion of androgen hormones is associated with acne and sebaceous gland hypertrophy in early infancy. *J Clin Endocrinol Metab*. 2013;98(1):199–206

19. Ballock RT, O'Keefe RJ. The biology of the growth plate. *J Bone Joint Surg Am*. 2003;85-A(4):715–726

20. Stevens DA, Williams GR. Hormone regulation of chondrocyte differentiation and endochondral bone formation. *Mol Cell Endocrinol*. 1999;151(1–2):195–204

21. Veldhuis JD, Roemmich JN, Richmond EJ, Bowers CY. Somatotropic and gonadotropic axes linkages in infancy, childhood, and the puberty-adult transition. *Endocr Rev*. 2006;27(2):101–140

22. Jääskeläinen J, Voutilainen R. Growth of patients with 21-hydroxylase deficiency: an analysis of the factors influencing adult height. *Pediatr Res*. 1997;41(1):30–33

23. Balsamo A, Wasniewska M, Di Pasquale G, et al. Birth length and weight in congenital adrenal hyperplasia according to the different phenotypes. *Eur J Pediatr*. 2006;165(6):380–383

24. Chalmers LJ, Doherty P, Migeon CJ, Copeland KC, Bright BC, Wisniewski AB. Normal sex differences in prenatal growth and abnormal prenatal growth retardation associated with 46,XY disorders of sex development are absent in newborns with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Biol Sex Differ*. 2011;2(1):5

25. Varimo T, Hero M, Laitinen EM, et al. Childhood growth in boys with congenital hypogonadotropic hypogonadism. *Pediatr Res*. 2015;36(suppl 2):LBS-026

26. Guthrie RD, Smith DW, Graham CB. Testosterone treatment for micropenis during early childhood. *J Pediatr*. 1973;83(2):247–252

27. Zachmann M, Prader A, Sobel EH, et al. Pubertal growth in patients with androgen insensitivity: indirect evidence for the importance of estrogens in pubertal growth of girls. *J Pediatr*. 1986;108(5 pt 1):694–697

28. Bouvattier C, Carel JC, Lecointre C, et al. Postnatal changes of T, LH, and FSH in 46,XY infants with mutations in the AR gene. *J Clin Endocrinol Metab*. 2002;87(1):29–32

29. Ogata T, Tomita K, Hida A, Matsuo N, Nakahori Y, Nakagome Y. Chromosomal localisation of a Y specific growth gene(s). *J Med Genet*. 1995;32(7):572–575

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