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CLINICAL STUDY

Postnatal penile length and growth rate correlate to serum testosterone levels: a longitudinal study of 1962 normal boys

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Abstract

Objective: Infant boys show a brief activation of their hypothalamic–pituitary–gonadal axis shortly after birth, the physiological significance of which is poorly understood. The objective of the study was to investigate the correlation between endogenous testosterone levels and penile size and growth.
Design: Prospective, longitudinal population-based study taking place at two large primary obstetric centres at the University Hospitals of Copenhagen, Denmark, and Turku, Finland.
Methods: Infant boys, 728 Danish and 1234 Finnish, underwent clinical examinations at 0, 3, 18 and 36 months in Denmark and at 0, 3 and 18 months in Finland with blood samples taken at 3 months ($n = 630$). Penile length and growth were registered and reproductive hormones (testosterone, sex hormone binding globulin, oestradiol) were analysed.
Results: Penile length increased from birth (3.49±0.4 cm) to 3 years of age (4.53±0.51 cm) with the highest growth velocity from birth to 3 months (1.0 mm/month). Penile length and growth were significantly, positively correlated to serum testosterone ($r = 0.31$ and 0.076, $P = 0.006$ and 0.001 respectively) and to free testosterone index ($r = 0.385$ and 0.094, $P = 0.0001$ and 0.0001 respectively).
Conclusions: We found that endogenous testosterone was significantly associated with penile size and growth rate in infant boys. Thus, the postnatal surge in reproductive hormones appears to be important for genital growth. Our data may serve as an updated reference for normal penile length in Caucasian boys up to 3 years of age.

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Introduction

The hypothalamic–pituitary–gonadal axis is activated during the first months of life (1, 2), but the physiological significance of this is not completely clear. Whereas the efficacy of testosterone treatment for micropenis is well established (3), the correlation between endogenous levels of testosterone and infant penile growth has not previously been studied. In a large prospective longitudinal cohort study we measured penile length in healthy newborns until 3 years of age and assessed its association to reproductive hormones at 3 months of age.

Materials and methods

All children were examined as part of a prospective population-based study at the University Hospitals of Copenhagen and Turku between 1997 and 2003. This cohort has previously been described in detail (4). Infant boys, 1073 Danish and 1494 Finnish, were recruited prenatally. Here only healthy boys (without chronic disease, cryptorchidism or hypospadias), born at term (gestational age 37–42 weeks) with a normal weight-for-gestational age defined as a birth weight within ±2 S.D. of the mean birthweight were studied; 728 Danish boys were examined longitudinally at birth, and at 3, 18 and 36 months of age while 1234 Finnish boys were examined longitudinally at birth and at 3 months. Only a subgroup (n=270) of the included Finnish children was examined at 18 months. These boys were selected numerically (every 10th healthy boy) or as a matched control for a boy with cryptorchidism (matched by parity, smoking, diabetes mellitus, gestational age and date of birth). Recumbent length was measured with a portable infantometer (Kiddimeter, Raven Equipment Ltd, Essex, UK) to the nearest 0.1 cm. Weight was measured on a digital scale (Solotop Oy, Baby scale model, Helsinki, Finland) to the nearest 0.005 kg. The study was performed according to the Helsinki II declaration. Written informed consent was obtained from the parents. The study was approved by the local ethical committees and the Danish Data Protection Agency. At each examination penile length was

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measured as flaccid penile length, avoiding erection. The penis was slightly straightened and the distance between the lower edge of the pubic bone and the tip of the glans penis (excluding foreskin) was measured using a small slide gauge (Baty International, Burgess Hill, West Sussex, UK) in the Danish or a ruler in the Finnish boys. All examinations were carried out in warm conditions with the child supine. In order to secure standardisation and reproducibility, repetitive workshops were performed and one Finnish doctor worked in Denmark for one year. All measurements included here were obtained from observers that performed ≥ 250 examinations each. In order to assess measurement variation two different observers measured penile length in 91 boys. The standard deviation for inter-observer variation was 0.34 cm, i.e. 95% of paired measurements were within ± 0.67 cm. In 20 boys, three blinded consecutive measurements of penile length were performed. The standard deviation for intra-observer variation was 0.18 cm, i.e. 95% of measurements were within ± 0.36 cm.

Non-fasting venous blood samples were obtained at 3 months (mean age 3.05 months, range 2.07–4.57 months) in 630 children (340 Danish/290 Finnish). Serum was stored at $-20\,^{\circ}C$. Serum sex hormone binding globulin (SHBG) was measured by a time-resolved immunofluorometric assay (Delfia; Wallac Inc., Turku, Finland) with a detection limit of 0.23 nmol/l and intra- and interassay coefficients of variation (CV) of $<6\%$. Serum testosterone was measured with a radioimmunoassay (Coat-a-count; Diagnostic Products, Los Angeles, CA, USA) with a detection limit of 0.23 nmol/l and intra- and interassay CV of $<10\%$. Free testosterone index was calculated as total testosterone/SHBG * 100. Oestradiol was measured by radioimmunoassay (Pantex Corp., Immunodiagnostic Systems Ltd, Santa Monica, CA, USA). The detection limit was 18 pmol/l, inter- and intra-assay CV were $<13\%$ and $<7.5\%$ respectively. Fifty-four percent ($n = 181$) of oestradiol analyses were below the detection limit.

Descriptive statistics were used for anthropometrical measurements, penile length and growth rate and reproductive hormones. Body mass index (BMI) was calculated as weight (kg)/length^2 (m^2). Measurements of penile length showed a statistically significant difference between countries, with Denmark having slightly larger values than Finland (mean difference: 0.7 mm at birth, 1.7 mm at 3 and 18 months). This difference was half the intra-observer variation and 20% of the inter-observer variation and therefore considered clinically irrelevant. Thus, the two populations were pooled for analysis.

Serum testosterone and free testosterone were transformed by square root to achieve normal distribution. The association between reproductive hormones at three months and penile length as well as penile growth rate was analysed by stepwise multiple linear regression including length, weight and age as covariates. Ninety-five percent confidence intervals (CI) were calculated for estimates (SPSS for Windows 11.0, Chicago, IL, USA). Spearman correlation coefficients are given for the associations between penile length and anthropometric measurements.

Reference curves were estimated by local linear regression. The 2.5 and 97.5 percentiles were estimated by the mean± 1.96 times the square root of the variance. The variance was estimated as a function of age, length and weight by local linear regression of the squared residuals (5).

Results

Mean (S.D.) age, length, body weight, BMI and penile length and median (minimum/maximum) penile growth rate at all ages are given in Table 1. The lower limits of the normal range (-2.5 S.D.) for age were 2.49, 2.67, 3.05 and 3.26 cm for 0, 3, 18 and 36 months respectively.

Median (2.5 and 97.5 percentiles) serum hormone values were: testosterone 3.23 nmol/l (0.60–7.79), SHBG 141 nmol/l (71–266), free testosterone index 2.32 (0.46–4.89) and oestradiol 18 pmol/l (<18–40) at 3 months of age.

Fig. 1A–C shows smoothed growth curves for penile length in relation to chronological age, length and

Table 1 Age, length, body weight, BMI and penile length measurements in 1962 healthy boys from Denmark and Finland. Data are given as means (standard deviation) unless otherwise stated.

	Examination (months)			
	0	3	18	36
Exact age at examination (months)	0.03 (0/1.6)[a]	3.1 (0.3)	18.4 (1.0)	36.6 (0.9)
Weight (kg)	3.69 (0.44)	6.62 (0.71)	11.87 (1.29)	15.05 (1.63)
Length (cm)	51.8 (2.1)	62.2 (2.0)	83.9 (2.8)	97.4 (3.5)
BMI (kg/m^2)	13.6 (1.4)	17.1 (1.4)	16.8 (1.4)	15.9 (1.1)
Number of penis measurements	1702	1706	808	406
Penile length (cm)	3.49 (0.40)	3.77 (0.44)	4.17 (0.45)	4.53 (0.51)
Penile growth rate (mm/month) since last examination[a]	—	1.0 (-5.7/7.5)	0.2 (-0.7/1.5)	0.2 (-0.7/1.2)

[a] Results expressed as median (minimum/maximum).

weight. Penile length according to age showed a curvilinear relationship with a rapid increase during the first 3 months of life. Penile growth according to body size (length and weight) showed a more linear relationship. Penile length was at all ages significantly and positively correlated to body length (0 months: $r = 0.244$, $P = 0.0001$; 3 months: $r = 0.076$, $P = 0.002$; 18 months: $r = 0.185$, $P = 0.0001$; 36 months: $r = 0.19$, $P = 0.0001$). Penile length was negatively correlated to BMI at 3 and 18 months of age, but not at any other time point (0 months: $r = 0.08$, $P = 0.052$; 3 months: $r = -0.16$, $P = 0.0001$; 18 months: $r = -0.087$, $P = 0.014$; 36 months: $r = 0.013$, $P = 0.80$); similarly penile length was negatively correlated to weight at 3 months of age, but not at any other time point (0 months: $r = 0.208$, $P = 0.0001$; 3 months: $r = -0.088$, $P = 0.0001$; 18 months: $r = 0.051$, $P = 0.15$; 36 months: $r = 0.14$, $P = 0.005$).

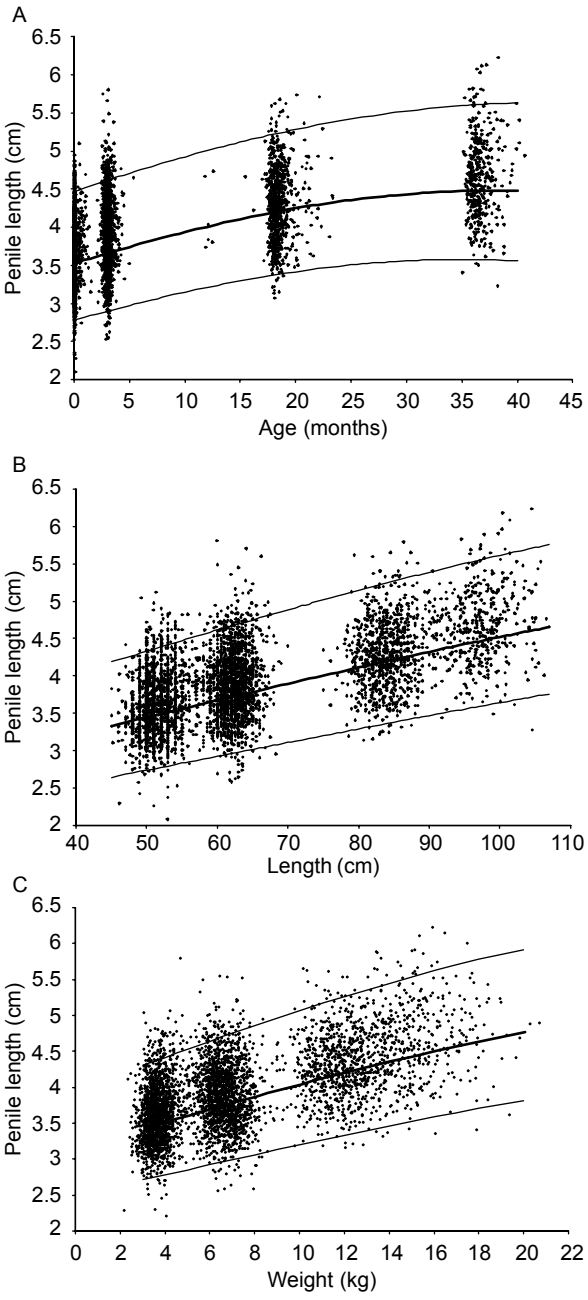

Figure 1 Penile length (cm) in 1962 healthy boys versus (A) chronological age (months), (B) length (cm) and (C) weight (kg). Dots represent individual measurements, the lines describe the estimated mean with the 2.5 and 97.5 percentiles.

Penile length at 3 months of age showed a significant positive correlation with both testosterone ($r = 0.31$ (CI: 0.194–0.426), $P = 0.006$) (Fig. 2) and free testosterone index ($r = 0.385$ (CI: 0.259–0.511), $P = 0.0001$). Penile growth rate between birth and 3 months was significantly positively correlated to both testosterone ($r = 0.076$ (CI: 0.031–0.121), $P = 0.001$) and free testosterone index ($r = 0.094$ (CI: 0.045–0.143), $P = 0.0001$).

In the multivariate analysis, penile length was significantly ($P < 0.0001$) correlated to serum testosterone ($r = 0.16$), height ($r = 0.05$), and weight ($r = 0.14$). In an analysis including free testosterone, penile length was significantly ($P < 0.0001$) correlated to free testosterone ($r = 0.25$), height ($r = 0.06$), and weight ($r = -0.15$). Penile growth rate was significantly correlated to serum testosterone ($P < 0.005$, $r = 0.41$), height ($P < 0.05$, $r = 0.01$), and weight ($P < 0.005$, $r = -0.44$). In an analysis including free testosterone, penile growth rate correlated to free testosterone ($P < 0.005$, $r = 0.06$), height ($P < 0.05$, $r = 0.01$) and weight ($P < 0.0001$, $r = -0.05$).

Discussion

In our three-year longitudinal study of a large cohort of newborn boys we found a significant association

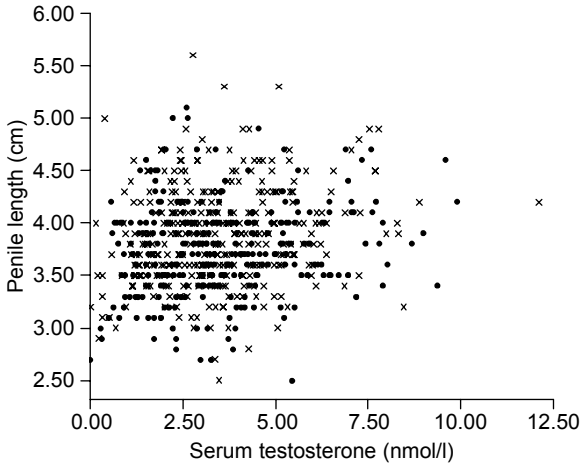

Figure 2 Penile length (cm) versus serum testosterone (nmol/l) at the age of 3 months in 630 Danish (crosses) and Finnish (solid circles) boys.

between serum testosterone levels at three months and penile growth. This association was found for both total testosterone and free testosterone index, which approximates the biologically active fraction of testosterone. Penile growth was not linear, as we found a significantly higher growth rate during the first 3 months of life (coinciding with high testosterone levels) compared with the rest of the observation period. We assume that the postnatal surge in endogenous testosterone plays a physiological role in this growth pattern. However, this correlation was weak, indicating that factors other than testosterone contribute to penile growth at this age. We have previously shown that postnatal involution of normal external genitalia may occur in boys who lack the 3 months' testosterone peak. This period of infancy can be used as a diagnostic window to establish the diagnosis of hypogonadotrophic hypogonadism or testicular failure (6, 7). The testosterone therapy of micropenis in infancy or early childhood has been found to increase penile length up to the normal range for age (3, 8, 9).

Our study also provides new normal longitudinal reference curves for penile growth in Caucasian children. Normal values of penile length are important for determining abnormal penile sizes and monitoring treatment of underlying diseases. During the longitudinal follow-up we observed children who were below −2.5 S.D. for the normal range at a single measurement but they all had measurements within the normal range (±2 S.D.) at consecutive measurements. Such fluctuations in penis size may be due to differences in room temperature and variations in measurement. Therefore, we recommend that in borderline cases, or in cases where measurements have been technically difficult to obtain, the measurement should be repeated after comforting the child and securing warm and relaxed conditions. Despite great efforts to train and standardise the measurement of penile length, our study showed that the inter-observer variation for trained observers is of similar magnitude as one standard deviation of the reference range (0.5 cm). Not all previous studies include information on measurement variation, and there are various techniques available. Many studies have used 'stretched' penile length (10), which has also been reported to have a considerable inter-observer variation (11). We found that the method used in our study was highly acceptable to both children and parents. In the present age group, the flaccid penis is supported by the scrotum, and the pubic bone can be precisely located avoiding measurement bias due to the prepubic fat. With this technique, the penis is stimulated as little as possible, avoiding erection in most cases. In adults, the flaccid penile length has been found to be shorter than the stretched penile length, which was most closely correlated to erect penile length (12). In order to assess whether there were any systematic differences between our method and the method of 'stretched' penile length in the present age group we performed both measurements in 10 boys. There was no systematic difference, the standard deviation between the two methods was ±0.36 cm, i.e. comparable to the inter-observer variation found in our study.

Our reference range corresponds well with previous studies on white Caucasian boys (10, 13, 14) that showed an average penile length in newborns between 3.11 cm and 3.75 cm. There may be ethnic differences between populations, and study population sizes and selection of participants as well as methodological variation may explain differences seen in penile length (15). Thus, two studies of South Indian populations showed great differences in penile length at birth ranging from 2.31 to 3.57 cm (16, 17). A recent large study of Chinese newborns in Hong Kong found the mean penile length at birth to be 3.0 cm (18), in accordance with some studies in Asian populations (16, 19), but not all (17, 20). Thus, our reference data may not be representative for populations other than Nordic ones.

Interestingly, body mass index was negatively correlated to penis size. One explanation may be that increased BMI is often associated with increased subcutaneous fat in the pubic region, making the clear distinction of the pubic bone, essential for accurate measurement, difficult. On the other hand, increased body fat may via aromatase activity lead to an increased endogenous oestradiol synthesis from testosterone, thereby altering the oestrogen-androgen balance. Our oestradiol assay does not have sufficient sensitivity to detect the lowest endogenous oestradiol levels in newborns, as the median was at the detection limit. Thus, we were not able to corroborate this hypothesis.

In conclusion, the longitudinal design of our project allowed us to establish an association between postnatal serum testosterone levels and length as well as growth of the penis. Our study also established new normal reference ranges for penile length and growth in infant Nordic Caucasian boys.

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