

Effect of Minipuberty on Growth of External Genitalia in Healthy Full Term Male Babies Born in Tertiary Care Hospital Setting of Pakistan

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ABSTRACT

Objective: To observe the increase in penile length, width and testicular volume in healthy term male neonates during the phase of minipuberty born at a tertiary care setup.

Study Design: Prospective observational study.

Place and Duration of Study: Neonatal Unit and Outpatient Department of Fatima Memorial Hospital Lahore, Pakistan from Jan to Dec 2023.

Methodology: We included 300 neonates in the study through purposive sampling, who fulfilled the inclusion-exclusion criteria. Penile length, width and testicular volume were noted down within 48 hours of birth. Data was taken on a specially designed questionnaire. Parents were called along with the infants for follow up visit at the age of 06 months. Penile length was taken by conventional stretch method, width by Vernier calipers and testicular volume by orchidometer by the same researcher.

Results: During the follow up we lost 52 cases. In the remaining 248 neonates, there was significant growth seen in neonatal weight, length and head circumference with p -value <0.001 , each. Similarly, penile length, width and testicular volume were also increased at the end minipuberty phase with p -value <0.001 , each. The correlation among neonatal length, weight, head circumference and penile length was significant with p -value <0.001 .

Conclusion: There is a significant increase in penile length, width and testicular volume in the first 6 months of life during the phase of minipuberty.

Keywords: Minipuberty, Newborn, Stretch Penile length (SPL), Testicular volume.

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INTRODUCTION

Minipuberty is defined as the development of sexual organs brought on by the elevated levels of gonadotropin and sex hormones due to the activation of the newborn Hypothalamic-Pituitary-Gland axis. This phase typically occurs in the first 6 months of life. In boys, this gonadal activation leads to an increase in testosterone (T) levels, which peaks 1-3 months later, resulting in testicular and penile growth.¹

During embryogenesis, the pituitary gland begins synthesizing both Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) at around 9 weeks of gestation.² Due to the negative effect of placental hormones (Estrogens and Progesterone) on gonadotropins, there is a drop in LH and FSH in cord blood at birth in healthy infants of both sexes.³ But after birth, due to lack of negative feedback on the

Gonadotrophin Releasing Hormone pulse generator, there is reactivation of the HPG axis. This postnatal activation that starts in the first few days of life is known as “minipuberty”.⁴

Studies on healthy term neonates show that LH and FSH levels rise around 1 week after birth, peak between 1 to 3 months, and decline by 6 months.⁵ These hormonal changes significantly influence infant growth, behaviour, and urogenital development.⁶

Several studies in the literature shows that there is a significant growth of external genitalia in male infants during the first few months of life. For example, the study of Shima *et al.*⁷ shows that the testicular volume in neonates is increasing from 0.27 to 0.44 cm³ from birth until 5–6 months of age, and then decreasing to 0.31 cm³ at 9 months of age. It is because of a positive correlation between FSH levels and testicular growth and in fact the effect of minipuberty. Similarly, Mohamed *et al.*⁸ and Boas *et al.*⁹ studied the effect of testosterone on penile size and growth rate from birth until 3 years of age and found that the

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endogenous testosterone levels had a significant effect on the growth of external genitalia in male infants.

The initial few months of life are crucial for the development of male reproductive organs. In Pakistan, no data is available on the effect of minipuberty on growth of external genitalia of male infants. Thus, we aimed this study to observe increase in penile length and width along with testicular volume and to see the effect of minipuberty in healthy full-term infants. The rationale of this study is to know the effect of minipuberty on postnatal increase in SPL during the phase of minipuberty to have a fair idea about androgen levels especially when facing a small size penis or XY disorders of sex development (DSD).

METHODOLOGY

The Prospective observational study was conducted at Neonatal unit and outpatient department of Fatima Memorial Hospital Lahore, Pakistan from January 2023 to December 2023. The study was conducted after approval from Institutional Review Board (IRB Certificate No. FMH-19/01/2022-IRB-1003, approved on April 04, 2022). The sample size was calculated using the "Sample Size Calculators for Designing Clinical Research." Assuming a 95% confidence interval, 80% power, a mean penile length of 3.55 ± 0.46 cm at birth and 3.75 ± 0.54 cm at 1 year,¹⁰ the estimated sample size was 3 pairs. To address normality concerns, 30 pairs were included in the study. Since the data readily available, and considering potential attrition affect during the 6-month follow-up, the sample size was increased to 300. Data was collected through Consecutive, Purposive sampling technique.

Inclusion Criteria: All the healthy male infants born at term (37 - 42 weeks of gestation) having normal male type genitalia were included in the study. Data was collected through Consecutive, Purposive sampling technique.

Exclusion Criteria: All the babies large for gestation at birth, born premature or had evidence of intrauterine growth restriction. Babies born to mothers with history of hormonal use or any signs of virilization and babies with family history of DSD, Congenital Adrenal Hyperplasia, or any disorder of puberty were excluded from the study.

This cross-sectional analytical study was done on the male infants from 0 to 6 months of age who were successfully fulfill the study inclusion criteria. Initially

penile length, width and testicular volume was noted down within 48 hours of birth by a single researcher.

Written informed consent was taken from all the parents who agreed to have their neonates included in the study after clearly explaining the study objectives and design to them. They were also assured that the data would be kept confidential and analyzed in an anonymous manner. A detailed interview of the parents of male infants was conducted to rule out the history of Congenital Hypogonadism, CAH, Hormonal Disorders, Genetic Syndromes, Familial Traits, Placental Insufficiency, history of diabetes, hypertension, or infections during pregnancy, history of Exposure to chemicals like phthalates, bisphenol A (BPA which are present in plastic containers canned foods, toiletries and menstrual products .and other endocrine disruptors, history of malnutrition or vitamin D deficiency, history of any type of Infection like maternal infection, toxoplasmosis, rubella, cytomegalovirus, and herpes, and history of usage of drugs, smoking or alcohol were taken before inclusion of infant in the study. Parents were called along with infants for follow up in outpatient department of Fatima Memorial Hospital at the age of 06 months. Informed consent was taken from the parents. The demographic data and measurements were collected on a pre-designed proforma. Penile length was measured using the conventional stretch method from the pubic ramus to the tip of the glans penis by applying gentle traction until resistance was felt. Penile width was determined at the widest point along the shaft using Vernier calipers. Testicular volume was assessed by comparing the testicle to beads on Prader's orchidometer, with the closest matching bead indicating the volume. All measurements were conducted by the same researcher to ensure consistency.

All the data was entered and analyzed in Statistical package for social sciences (SPSS) version 25. Frequency and percentage were calculated for all qualitative variables. Quantitative variables were presented in the form of mean with SD or Median ((IQR). Bivariate correlation was used to test the relation between penile length, penile width and testicular volume with infant length, infant weight and head circumference. A one sample - one tailed t-test was used to calculate the penile growth at the end of minipuberty phase. p -value ≤ 0.05 was considered statistically significant.

RESULTS

We recorded detailed information for 300 parents of 300 neonates included in the study. During the follow-up, 52 cases were lost to contact and did not attend the final checkup at the end of the minipuberty phase. The mean maternal age of 248 neonates was 30.456 ± 5.977 years with a minimum and maximum age was 18 and 42 years. The ratio of high risk pregnancies was 0.290 (72 out of 248). Deliveries through cesarean section were 25.40% (63 out of 248).

The effect of minipuberty on infant length, weight, head circumference, penile length, penile width and testicular volume is mentioned in Table-I.

Table-I: Neonatal Growth During the Phase of Minipuberty (n=248)

Somatic growth parameters	At initial stage (n=248)	At the end of minipuberty phase (n=248)	p value
Neonatal weight (kg)	3.16 ± 0.74	6.94 ± 0.52	<0.001
Neonatal Length (cm)	49.65 ± 3.47	68.21 ± 2.85	<0.001
Neonatal Head circumference (cm)	34.49 ± 1.98	43.92 ± 1.68	<0.001
Penile Length (cm)	3.15 ± 0.38	5.37 ± 0.36	<0.001
Penile width (cm)	0.83 ± 0.16	1.47 ± 0.17	<0.001
Testicular volume (ml)	1.00 ± 0.00	3.00 ± 0.11	<0.001

The neonatal somatic growth parameters showed significant change at the end of minipuberty phase (Table-I). The relation between neonatal length, weight, head circumference, penile length, penile width and testicular volume at initial stage after birth as well as the end of the minipuberty phase is mentioned in Table-II.

The table shows bivariate correlation analysis between neonatal characteristics. Neonatal length had strong relation with penile length before and after the phase of Minipuberty. Neonatal weight had strong relation with penile length at initial stage but not after the phase of minipuberty. Both neonatal length and weight not related to penile width before and after the phase of minipuberty. Testicular volume at initial stage was constant at "1". So, correlation coefficient doesn't exist.

DISCUSSION

The present study shows a significant increase in the growth of external genitalia in male infants. The findings of our study correlate with the study of Boas M9, whose research showed that penile length increases from birth (with a mean $3.49 \text{ cm} \pm 0.4 \text{ cm SD}$) to three years of age. The most significant growth rate occurs from birth to initial months, averaging 1 mm per month. Several studies from different

countries in Asia have reported varying results. Results of an Indian study,¹¹ showed mean penile length of $30.20 \pm 3.30 \text{ mm}$ in term infants which coincides with the present study. Several reports from other country like singapore,¹² also showed results comparable to our study While a Turkish study,¹³ and a Chinese study,¹⁴ both found the mean stretched penile length (SPL) of term newborns to be 30 mm (3cm), and an Indonesian study,¹⁵ reported a mean SPL of 23.5 mm (2.35cm). These studies clearly indicate that SPL values differ significantly among various races and ethnicities. Thus, it is essential for neonatologists and healthcare staff in each country to refer to the values relevant to their specific population. This ensures accurate assessment and diagnosis for their particular racial or ethnic group.¹⁶

Table-II: Correlation analysis between Neonatal Measurements at Birth and at the end of Minipuberty Phase (n=248)

	At Initial stage		At the end of minipuberty phase	
	r	p-value	r	p-value
Neonatal length - Neonatal weight	0.545	<0.001	0.108	0.089
Neonatal length - Neonatal head circumference	0.487	<0.001	0.962	<0.001
Neonatal length - Penile length	0.366	<0.001	0.404	<0.001
Neonatal length - Penile width	0.087	0.174	-0.218	0.001
Neonatal length - Testicular volume	Not Applicable		-0.128	0.043
Neonatal weight - Neonatal head circumference	0.498	<0.001	0.177	0.005
Neonatal weight - Penile length	0.434	<0.001	-0.018	0.777
Neonatal weight - Penile width	0.188	0.003	-0.038	0.554
Neonatal weight - Testicular volume	Not Applicable		-0.351	<0.001
Neonatal head circumference - Penile length	0.415	<0.001	0.379	<0.001
Neonatal head circumference - Penile width	0.018	0.781	-0.187	0.003
Neonatal head circumference - Testicular volume	Not Applicable		-0.103	0.105
Penile length - Penile width	-0.01	0.874	-0.260	<0.001
Penile length - Testicular volume	Not Applicable		-0.287	<0.001
Penile width - Testicular volume	Not Applicable		0.019	0.765

Similarly, minipuberty is linked to testicular growth,¹⁷ and testicular volume serves as a key indicator of external genitalia androgenization and reflects the proper function and activity of the HPG axis.¹⁸ And it is observed by the researchers that testicular volume significantly increases during the first 5-6 months of life.^{7,17} In the present study we also

measured testicular volume during minipuberty phase and the volume increased from mean 1 ± 0 ml ($\approx 0.83 \pm 0.16 \text{ cm}^3$) at birth to 3 ± 0.11 ml ($\approx 1.47 \pm 0.17 \text{ cm}^3$) with p -value < 0.001 at 6 months of age. Atalabi *et al.*¹⁹ and Hu S *et al.*²⁰ reported mean testicular volume of $0.28 \pm 0.09 \text{ cm}^3$ and $0.38 \pm 0.14 \text{ cm}^3$ respectively, at birth in healthy newborn born at term. These values are lower compared to our findings at birth. Additionally, they did not measure testicular volume at the end of minipuberty phase. We approximated our measured values of testicular volume in ml to cm^3 to compare with the international data. Our study stands out because we followed infants through the end of the minipuberty phase to assess its effect on the penile length, width and testicular volume.

Another key finding of our study is the correlation between penile length, width and testicular volume with the birth weight, head circumference and body length of neonates. Researchers from various countries have also confirmed the association between penile length and anthropometric measurements.^{14,21} This linear relationship between birth weight and penile length as demonstrated in numerous studies,^{22,23} can be explained by the concurrent growth mechanisms of fetal body size (including birth weight, head circumference and body length) and penile length and width, driven by hormonal regulation.^{23,24}

This study is the first of its kind in Pakistan to evaluate the increase in penile length, width, and testicular volume in healthy term male neonates, as well as to assess the effect of minipuberty on the growth of external genitalia and anthropometric measurements. The findings provide valuable insights into male genital development and play an essential role in disease diagnosis and follow-up. A key strength of our research is the large sample size, with measurements conducted by a single observer to minimize bias and ensure accuracy. However, a limitation of this study is the absence of serum testosterone, LH, and FSH levels, which could have verified correlations with our observed results.

Male external genitalia growth is most significant during the first six months of life, and observations of penile growth during this period may reflect underlying activation of the HPG axis, increased serum testosterone levels, and the influence of gonadotropins (LH and FSH). Understanding this physiological process suggests avoiding exogenous testosterone in cases of suspected micropenis or DSD during minipuberty to better evaluate the effect of

endogenous androgens. Future research may explore the clinical significance of minipuberty in specific patient groups, such as premature infants and those small for gestational age, while incorporating serum hormone levels to strengthen correlations and provide deeper insights.

CONCLUSION

This study demonstrates a significant increase in penile length, penile width, and testicular volume during the first six months of life, correlating with the minipuberty phase in healthy full-term male neonates. The observed correlation between somatic growth parameters and external genital measurements highlights the intricate interplay of hormonal and physical development. These results provide valuable baseline data for clinical assessment in the Pakistani population and offer insights into the diagnosis and management of conditions like micropenis and DSD.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

HA & MU & AM: Conception, study design, drafting the manuscript, approval of the final version to be published.

SA & ZA & IH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

ZN & HA & FIH: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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