INVITED COMMENTARY

Minipuberty in Full-term and Preterm Asian Indian Infants: The First Glance

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Minipuberty is a transient postnatal hypothalamic-pituitary-gonadal (HPG) axis reactivation following withdrawal of the maternal estrogens. Minipuberty in male infants, promotes early penile growth, an increase in testicular size, completion of testicular descent (if not already completed at birth), and increase in growth velocity. The increased testicular size results from the lengthening of seminiferous tubules with a concomitant increase in the total numbers of germ cells and Sertoli cells. Absent or diminished minipuberty in male infants with congenital hypogonadotropic hypogonadism (CHH) is associated with reduced reproductive function during adulthood. Hence, priming of the testis during minipuberty seems crucial for future fertility [1].

Minipuberty provides a window of opportunity for the evaluation of gonadal disorders and disorders of sex development (DSD) without the need for dynamic testing [2]. In male infants with cryptorchidism, and/or micropenis, evaluation during minipuberty facilitates early diagnosis. Serum gonadotropins and testosterone levels are lower in CHH during minipuberty whereas gonadotropins are elevated in anorchia and Klinefelter syndrome [2]. Diagnosis of these disorders during infancy provides early therapeutic opportunities. In CHH, induction of minipuberty with gonadotropin therapy during infancy increases the potential for future fertility [3]. In Klinefelter syndrome, though not encouraged for routine use, testosterone therapy during infancy has positive benefits on body composition, phallic enlargement, and linear growth [4].

Interestingly, the minipubertal pattern may completely differ from the pubertal one in some conditions. For example, in complete androgen insensitivity syndrome, minipuberty is absent in contrast to elevated androgen and luteinizing hormone levels seen during puberty [2]. Besides, some common factors like prematurity may also alter minipuberty. Earlier and exaggerated minipuberty in preterm (PT) than full term (FT) infants have been well-described in Caucasians [5]. However, the data on minipuberty in Asians especially Indians, a unique and ethnically diverse population, is lacking.

In this issue of *Indian Pediatrics*, Danda et al described the patterns of minipuberty in FT and PT south-Indian infants by assessing the urinary hormonal profile and genital examination [6]. They noted an earlier and exaggerated minipuberty with faster phallic and testicular enlargement in Indian PT infants compared to those born at term gestation. Lower urinary follicle-stimulating hormone (FSH) on day 7 of life and higher luteinizing hormone (LH) and total testosterone (TT) throughout the first 4-6 months of life in PT infants were also observed [5,6]. All these observations are in a close agreement with Finnish data [5] indicating no/minimal ethnic differences in minipubertal patterns of the two populations. However, the increment in phallic length during the first month of life was noticeably different between the Indian and Finnish PT infants [5,6]. The increase in nonstretched penile length in Finnish FT infants was maximum during the first month of life with subsequent plateauing whereas it was gradually progressive till 5 months of life in PT infants. A slower increase in penile length during the first month in Finnish PT infants was associated with lower levels of urinary free prostate-specific antigen indicating an impeded androgen action [5]. In contrast, the increase in penile length in Indian PT infants was maximum during the first month of life [6]. PT infants showed a significant mean percentage increase in SPL (20% vs 13.3%; $P < 0.001$) at one month in comparison with FT infants. This observation needs further validation to verify whether this represents an ethnic-specific difference.

A study from Japan reported higher LH but lower FSH urinary concentrations in PT small for gestational age (SGA) infants than their appropriate e for gestational age (AGA) counterparts [7]. Another study from Sweden also

reported higher total testosterone at birth and 0-month corrected age in moderate and late preterm infants with birth weight < 2500 g than those with birth weight ≥ 2500 g [8]. These two studies suggest an effect of intrauterine growth retardation on minipuberty. As demonstrated in recent studies from Poland, maternal factors such as vitamin D deficiency (exaggeration) and hypothyroidism (dampening) may also affect minipuberty [9,10]. Hence, further exploration of the common factors that may alter minipuberty is warranted.

Pubertal/minipubertal testosterone level is usually noted on the first 1-2 days of postnatal life, the usual time when DSD neonates are identified with atypical genitalia [11]. This period may offer the earliest opportunity for hormonal evaluation of 46, XY DSD. However, the studies by Danda et al [6] and Kuiri-Hunninen et al [5] have not evaluated urinary gonadotropins during this period of life. A recent study from Italy has reported urinary gonadotropins and testosterone during <72 hours of life [12]. Interestingly, testosterone was higher during this period than any other period of minipuberty and this was despite relatively lower gonadotropins. More interestingly, urinary testosterone was higher in FT infants than PT infants during this period, but it reversed at ≥ 30 days of life [12]. This interesting phenomenon of contrasting trends in testosterone levels between PT and FT infants also needs further exploration.

Measurement of gonadotropins in urine, a more convenient sampling method, has been used not only to predict, diagnose, and monitor precocious puberty but also to evaluate delayed puberty [13,14]. Danda et al used the measurement of gonadotropins and testosterone in urine to evaluate minipuberty, which suggests its potential utility in the interpretation of minipuberty [6]. Most of the previous studies have used immunofluorometric or immune chemiluminescence assays whereas Danda et al have used enzyme-linked immunosorbent assay (ELISA) which is not a commonly used method for measurement of gonadotropins and testosterone [6]. Hence, future studies evaluating minipuberty in Asian Indian infants using the commonly used immunoassays with the establishment of reference ranges for urinary gonadotropins and testosterone are warranted.

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