Mini-Puberty and Growth

Kenneth C. Copeland, MD, Steven Chernausek, MD

Within the first few months of life, the human infant experiences a transient activation of the hypothalamo-pituitary-gonadal axis. First described in the 1970s, after the development of assay methodology sufficiently sensitive to detect low levels of hormones in blood,[1] this process has been described as a "mini-puberty." Its purpose remains unclear, but is most commonly thought to be an important developmental event related to subsequent reproductive function.[2,3] Mini-puberty occurs in both sexes, with an increase in testosterone in boys and increase in both estradiol and testosterone in girls (testosterone concentrations in girls are ~30% lower than those in boys at peak). Resultant effects on the reproductive organs include testicular, penile, and prostate growth in boys, uterine and breast enlargement in girls, and sebaceous gland and acne development in both sexes. Effects of this early activation of the hypothalamo-pituitary-gonadal axis are not confined to the reproductive organs, however. Recent evidence suggests that the androgen exposure of mini-puberty also predicts later sex-typed behavior.[4,5]

In this issue of *Pediatrics*, Kiviranti et al[6] describe yet another effect of this neonatal androgen surge: increased skeletal growth. Although sex differences in linear growth in the first year of life have been described previously, this study is the first to link closely the testosterone surge of mini-puberty with the increased growth velocity in boys relative to girls. In this analysis, not only was the testosterone surge temporally linked to increased growth in both sexes, but the magnitude of the maximum growth velocity sex difference mirrors the magnitude of the sex difference in testosterone concentrations. Thus, these data strongly support the notion that it is the rise in testosterone in the infant boy that is directly responsible for the increased skeletal growth.

The magnitude of this effect on growth is not trivial. The 4.1-cm per year sex difference in growth velocity at 1 month of age reasonably explains the 1.9-cm mean difference in lengths between boys and girls at 12 months of age (and constitutes ~15% of the height discrepancies between adult men and women). Although the relationship between sex steroids and skeletal growth is convincing, a few questions remain. If growth velocity and testosterone concentrations are both greater in boys, why is the correlation between growth velocity and testosterone tighter in girls than boys at the peak surge at 1 month of age? Why is there no correlation between growth velocity and estrogen concentrations in girls? Likely the answers according to this study relate to the much smaller subset of subjects in whom hormonal measurements were made, and perhaps the estrogen concentrations were just too low, by using current measurement methods.

Although the current report itself was not meant to be a comparison between mini-puberty and puberty, how do these observations relate to what we know about pubertal growth? There is a tight correlation between the pubertal growth spurt and increased secretion of both growth hormone and insulinlike growth factor-1 (IGF-1), likely mediated primarily by estrogen.[7] In this study, even though circulating IGF-1 correlated with growth rate, no sex differences in IGF-1

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were observed. If IGF-1 is a primary mediator of skeletal growth, is it a problem that no sex difference in IGF-1 concentrations was observed in this report, despite sex differences in growth velocity? Not necessarily, because IGF-1 concentrations do not reflect the sex differences in maximal growth velocity at puberty. Estrogen stimulates both growth hormone and IGF-1, and IGF-1 concentrations at puberty are higher in girls than boys,[8,9] yet peak growth velocity is greater in boys than girls during puberty, suggesting the presence of other sex-specific factors, perhaps direct effects of testosterone and/or Y-chromosome genes on the growth plate independent of hormones. Whereas the paramount importance of estrogen on bone mass and epiphyseal closure is unquestioned,[10,11] the precise role of estrogen on linear growth itself is less clear. It is possible that the link between IGF-1 and growth in this study has little to do with sex steroid secretion, but more closely reflects the role of nutrient (energy) intake on circulation IGF-1, a well-described phenomenon, independent of growth hormone and sex steroids. Thus, children of either sex who had higher levels of IGF-1 may have simply been those who had higher caloric intake and, as a consequence, were growing faster.

Last, are there other ramifications of this mini-puberty, potentially even more important than these modest and transient effects on linear growth velocity? The effects of testosterone on muscle mass and carbohydrate metabolism are well described in adolescents and adults and explain many of the differences in metabolic state, body composition, and cardiovascular function between sexes. Does the infant's exposure to testosterone result in increased muscle mass? Does this persist throughout childhood and influence subsequent health? Does this transient period of androgen exposure result in epigenetic modifications that result in permanent structural or biological changes that, in turn, influence the metabolism, cardiovascular risk, reproductive function, and behavior of the adult? These and many other questions related to mini-puberty remain unanswered but are plausible hypotheses aligned with the fetal/perinatal origins theory of adult health and disease.[12]

ABBREVIATION

IGF-1: insulinlike growth factor-1

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