Puberty: When is it normal?

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Classically, the normal chronological age for pubertal onset is between 8 and 13 years in girls and 9 and 14 years in boys based on data from epidemiological studies from the 60's (1). However, the age limit for pubertal timing is still a challenge (2,3). It is well known that puberty is a complex and multi factorial process that involves genetic, metabolic, socio economic, nutritional and ethnic factors. Moreover, the evidence that initial pubertal signs, mainly in girls, are appearing earlier today than in the last 4 decades has been described by several epidemiological studies (2-4).

In the last years, genetic control of pubertal onset has been demonstrated through the identification of pathogenic mutations. Several loss-of-function mutations of *MKRN3*, a gene encoding the makorin RING-finger protein 3, result in familial central precocious puberty, suggesting a potential inhibitory input to gonadotropin-releasing hormone (GnRH) secretion (5). Interestingly, the mean age of pubertal onset in *MKRN3* affected girls was 6.0 years (ranging from 3.0 yr to 7.0). Notably, pubertal timing, pubertal height growth and age at menarche are strongly associated with adiposity in both epidemiological and genetic studies, since genome-wide association studies revealed genetic *loci* linking pubertal height growth, pubertal timing and childhood adiposity (6). The relationship between pubertal timing and adiposity is stronger in girls. Environmental factors, such as endocrine chemical disruptors (pesticides, phthalates, bisphenol A, and plant-derived phytoestrogens) or low levels of estrogens in the food supply have been influenced the timing of puberty, leading to precocity or delay in this process, specially, in animal models (3).

It is reasonable to suppose that each population has peculiar epidemiological features that influence the age of pubertal onset. To establish the age of initial pubertal signs in the Brazilian population is a big task, not only due to the continental size of the country, but mainly due the population heterogeneity. The data of pubertal onset and its progression in Brazilian population is very scarce. Feibelmann and cols. (7) performed a relevant cross sectional epidemiological survey of age of breast development in girls in a representative population of 665 schoolgirls (aged 5.9 to 18 yr) in Uberaba, Minas Gerais, Brazil. The authors identified that mean chronological age of thelarche was 9.8 ± 1.4 yr (ranging from 7 to 12 yr) and pubarche 10.2 ± 1.4 yr (ranging from 7 to 13 yr). In addition, the mean age of menarche was 11.7 ± 1.3 yr (ranging from 9 to 14 yr). The interval between thelarche and menarche was 1.7 ± 1.3 years. Interestingly, black girls had thelarche and pubarche significantly earlier than white girls, reinforcing the influence of ethnicity.

It is well known that the decline reported for the mean age of thelarche is not accompanied of significant changes in the mean age of menarche (3,4). While in American and European studies, the reported mean age of menarche was 12.5 yr and mean interval between thelarche and menarche of 2.3 yr, in the Brazilian study both indicators were lower (11.7 yr for menarche and 1.7 yr for mean interval between the-

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larche and menarche) (3,7). In addition, the diagnosis of abnormal puberty (non progressive and progressive forms) was established in 4.7% of girls in the Feibelmann' study (7). These findings reinforce the idea that the prevalence of sexual precocity is underestimated. In fact, parent's education regarding the detection of first pubertal signs is essential for prompt recognition of precocious puberty (8,9).

Castilho and cols. (10) evaluated the secular trend of menarche according to body mass index (BMI). It was demonstrated that menarche in Brazilian girls has anticipated 3.24 months in the last 10 years, together with an increase of obesity prevalence. In the study by Feibelmann TC and cols. (7), the prevalence of overweight and obesity was 18.8 and 12.5%, respectively. Other studies have documented that higher BMI is correlated with earlier onset of puberty, implicating leptin, a fat cell-derived protein, and other adipokines required for normal gonadotropin secretion (3,6,9). However, it is not clear if increased adiposity is the cause or the consequence of early pubertal development in girls. Finally, other larger, longitudinal and multicenter epidemiological studies involving the Brazilian population will be necessary for understanding the complexity of normal and abnormal pubertal timing.

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