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Puberty in girls of the 21st century

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Abstract

Several studies have noted contemporary girls are undergoing pubertal maturation at younger ages. During this same time period many Western nations have experienced an obesity epidemic, prompting investigators and public health officials to consider the association of these two events, and if other exposures might impact this relationship. There are several potential mechanisms that could impact the relationship of pubertal timing in girls with greater body mass, including direct effects of obesity on pubertal timing as well underlying exposures that impact body mass as well as timing of pubertal maturation. These underlying conditions include chemical compounds that could impact synthesis or action of sex hormones, called endocrine disrupting chemicals (EDs). This paper will examine the decline in the age of breast development and potential genetic and environmental influences, the obesity epidemic in the US and other nations, and potential mechanisms to explain the relationship between greater body mass index with earlier puberty in girls.

KEY WORDS / SHORT PHRASES

Obesity; Puberty; Endocrine disrupting chemicals

Introduction

A group of experts in puberty and public health were convened by the Environmental Protection Agency and the National Institute of Environmental Health Sciences, and examined the data over the past several decades regarding timing of puberty. They concluded that girls are experiencing earlier breast development.¹ There appear to be several factors to account for these changes, which include an association between elevated body

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mass index and earlier timing of puberty (vide infra), prompting some to consider the recent changes in adolescent obesity and pubertal timing as the “perfect storm.”² It appears that girls of the 21st century are indeed experiencing a perfect storm, with an evolutionary drive for energy conservation; a mismatch in energy balance through greater consumption of calorically dense foods and decreased energy expenditure, reflecting recent trends in physical activities; and a contemporary chemical cocktail with greater levels of exposure to endocrine-disrupting chemicals and obesogens. This paper will examine the decline in the age of breast development and potential genetic and environmental influences, the obesity epidemic in the US and other nations, and potential mechanisms to explain the relationship between greater body mass index with earlier puberty in girls.

The timing of puberty may serve as a sensitive indicator of environmental factors.³ Onset of puberty and age of menarche dropped in the first half of the 20th century; as noted in Table 1,^{4–12} onset of breast development appears to have declined over the second half of the twentieth century as well. A panel of experts concluded that there were sufficient data to note a trend in earlier onset of breast development in the US over the second half of the 20th century.¹ Similarly, the Copenhagen Puberty Study reported that girls matured one year earlier than a comparable cohort born 15–16 years earlier,⁵ and Caucasian girls at ages 7 and 8 in the Breast Cancer and the Environment Program¹³ were more mature than girls born 15 years earlier from the Pediatric Research in Office Settings (PROS) Study.⁸ Age of menarche has not dropped as much; in examining nationally representative data generated through NHANES, women born in the 1980’s reported age of menarche 0.2–0.4 years earlier than those born in the 1950’s.^{1, 14} Although the correlation between age at onset of breast development and age of menarche was high several decades ago (correlation up to 0.90), it appears that this correlation has decreased among more recent cohorts (correlation around 0.40), suggesting there is less shared variance between onset of breast development and age of menarche.¹⁵ Given a limited opportunity for genetic changes, the change in correlation most likely represents environmental or gene/environment interactions (including epigenetic changes).

As noted earlier, natural selection appears to favor earlier reproductive development and both a thrifty genotype¹⁶ as well as thrifty phenotype.¹⁷ Our genes evolved during times when procurement of food was more difficult, leading to genetic changes which promoted thrifty genotypes and phenotypes in response to harsh times.^{18, 19} This “developmental plasticity”, impacted by environmental exposures during sensitive developmental periods, is associated with greater obesity as well as other metabolic and physiologic consequences.²⁰ Bouchard, examining those genes associated with obesity, as well as observing behavioral and biologic traits which optimized energy storage, proposed five major classes of genotypes that favored energy conservation. These are the thrifty genotype (low basal metabolic rate, low thermogenesis); hyperphagic genotype (poor regulation of appetite and satiety); sedens genotype (propensity to physical inactivity); low lipid oxidation genotype (low lipid oxidizer); and adipogenesis genotype (ability to expand the complement of adipocytes and high lipid storage capacity).²¹ Others have summarized this mismatch between genes and environment as “Stone Age” genes with “Space Age” circumstances.²²

Childhood Obesity

Over the span of four decades there has been an alarming increase in childhood obesity in both industrialized and developing countries. In general, body mass index (BMI) is the most commonly used metric to classify (over)weight status, given availability of age, gender, height and weight in national datasets, as contrasted to other measures which are not typically available, such as percent body fat and waist circumference. Data from NHANES 2005–2008 reveal an estimated 17% of US children ages 2–19 years are obese (BMI >95th

percentile for age and gender), compared with 6.5% during 1971–74.²³ Although there was no significant increase in obesity prevalence for any age group between the years 1999 through 2008, data on adolescents reveal that 17% of girls and 19% of boys ages 12–19 years had a BMI at or above the 95th percentile for age and gender compared to 5% during 1971–74 (see Figure 1). Of concern, obese children and adolescents are more likely to become obese adults, and are subsequently at high risk for a host of obesity related conditions including type 2 diabetes, osteoarthritis, cardiovascular disease, and cancer.^{24, 25}

Although many have concluded that the underlying etiology of the current obesity epidemic is the result of an imbalance between dietary intake and caloric expenditure, comprehensive reviews have encouraged more attention to other factors contributing to the obesity epidemic, including exposure to infectious agents, epigenetic modifications, increasing maternal age, sleep deprivation, exposure to endocrine disrupting agents as well as selected pharmacologic agents, and the intrauterine environment.²⁶ Data from the 2009 Youth Risk Behavior Surveillance reveal that 78% of students in grades 9–12 had not eaten fruits and vegetables five or more times per day and nearly 82% were not physically active for at least 60 minutes per day.²⁷ More adolescent males (45.6%) than females (27.7%) met basic recommendations for 60 minutes of activity 5 out of 7 days, and only one-third of high school students attended physical education daily.

The national goal for Healthy People 2020 is to reduce the percentage of obese children and adolescents by 10%.²⁸ Interventions targeting dietary and physical activity level alone have met with limited success. Comprehensive behavioral interventions combined with community level approaches have been recommended to tackle the obesity epidemic. Research on the “built” or neighborhood environment highlights the need to consider the contextual influences on childhood obesity encompassing the family, school, as well as community at large.²⁹ These data lend themselves to the development of community level interventions that either promote or act as barriers to healthy lifestyles, e.g., availability of walking and biking trails and easily accessible high fat, high calorie “junk” foods. Disparities in availability of healthy food and physical activity resources is increasingly acknowledged to play a role in underlying disparities in obesity and obesity related health outcomes as seen in low income and predominantly minority communities.

Emerging research is now examining the role of endocrine disrupting chemicals, especially the group known as “obesogens,” and their role in the obesity epidemic.^{2, 30–32} It is postulated that certain environmental chemicals, including diethylstilbestrol (DES), bisphenol A (BPA), phthalates, perfluorooctanoic acid (PFOA), and organotins. Because of the potential of obesogens to disrupt the endocrine system, these chemicals fall under the larger classification of endocrine disruptors, but all endocrine disruptors do not act as obesogens. The major pathway by which obesogens contribute to the etiology of obesity is by directly promoting adipogenesis, that is, promotion of either adipocyte number or size³⁰ with activation of nuclear receptors (e.g., RXR and PPAR gamma), promotion of adipose cell lines at the expense of other cell lines, regulation of signaling pathways that commit adipose cell lines over other cell lines, enhanced differentiation of pre-adipose to adipose tissue through activation of PPAR gamma, promotion of increased storage of fat, and finally, potential epigenetic mechanisms which promote factor transcription activation of adipogenic genes.^{31, 32} Proposed indirect effects of obesogens include promoting change in the basal metabolic rate, shifting energy balance in favor of storage of calories and altering hormonal control of appetite and satiety.

While this remains an emerging area of human research, the animal studies are compelling. As an example, Newbold et al. hypothesized that the developing organism is extremely sensitive to perturbation by chemicals with endocrine disrupting activity.^{33, 34} Using a

prenatal diethylstilbestrol (DES) animal model, Newbold et al. found that low dose prenatal and neonatal DES caused an increase in body weight of mice and this effect was seen by 6 weeks of age. The increase in body weight was significantly associated with an increasing percentage of body fat. Mice treated neonatally with DES had a significant increase in body weight, estimated fat weight, and percent body fat as compared to controls. This effect was also seen when alternate estrogen sources were used. The authors thus conclude that even brief exposure to low levels of environmental estrogens early in life increases body weight as mice age.

A growing body of human studies, while limited and typically cross sectional in nature, are now beginning to corroborate the extant animal studies which initially demonstrated the potential obesogenic role of environmental chemicals.^{35–38} Data gaps remain, however. In addition to examining exposures cross-sectionally, longitudinal studies examining endocrine disrupting chemical (ED) exposures throughout the lifespan (from pre-conception to in utero to early childhood exposures and beyond) in addition to studies examining multiple concurrent ED exposures are needed. These studies will address better the complex mixtures of every day exposures that one encounters in life throughout various windows of vulnerability. Still, if EDs play even a small role in the obesity epidemic, exposure reduction and legislation supporting such efforts has a potential role in future obesity related public health interventions.

Relationship of obesity and timing of puberty in girls

Multiple studies have noted a relationship between body mass index (BMI) and timing of pubertal onset in girls, as reviewed by Kaplowitz,³⁹ among others.^{2, 40, 41} His review noted an association between body fat and earlier timing of puberty,³⁹ and that the data supported but did not establish causality. Although many of the studies examined this relationship through crosssectional analyses, for example, studies with BCERC,¹³ PROS⁴² and NHANES,⁴³ several studies utilized longitudinal data. For example, this relationship has been demonstrated with BMI z-scores as early as 3 years of age with earlier breast development as well as earlier age of menarche⁴⁴ and percent adiposity at 5 years of age with breast development,⁴⁵ as well as BMI at age 7 with breast development⁴; BMI at age 8 with menarche⁴⁶; and BMI two years prior to puberty with onset of the growth spurt.⁴⁷ Of note, a recent study noted the linkage of a gene that was associated with pubertal timing (a polymorphism of LIN28B) with increased BMI at ages 15–43 in women, but not associated with BMI at younger ages⁴⁸; this suggests a genetic association between earlier puberty and adult obesity, but not with greater BMI and timing of puberty. Several of the more recent studies have suggested that the earlier onset of breast development noted both in the US and Europe may occur independent of activation of the hypothalamic-pituitary-gonadal axis,⁵ perhaps through endocrine disrupting chemicals acting on adipocytes or on other hormonally responsive tissues.^{1, 3, 49, 50}

Proposed mechanisms for obesity to impact timing of puberty

The observed association between obesity and early puberty leads to speculation that there may be a mechanism by which obesity directly leads to early puberty, or that obesity is part of a pathway that also leads to early puberty, with another common cause. The Frisch hypothesis suggested that menarche occurred at a critical weight (originally defined as 48kg), and that early and late maturers had similar weight at menarche.⁵¹ This weight, later modified to be critical fat mass, is theorized to be associated with a decrease in metabolic rate and achievement of a characteristic body composition, allowing the establishment of cyclic menstruation. This hypothesis has been examined by several investigators, and is now felt to be less plausible. Garn examined skin fold thickness in 2251 girls at ages 11–15 years, and found that higher skin fold thickness and body fat percentage were associated

with earlier menarche, but there was significant overlap, and thus no “critical” threshold that could predict menarche.⁵²

There are several potential mechanisms by which body fat stores might influence onset of pubertal development as well as tempo of puberty. One is through the direct action of adipokines, such as leptin, signaling energy reserves as well as having other direct metabolic effects. In addition, adipose tissue has aromatase action, which increases androgen conversion to estrogens. Adipose tissue is also related to increasing insulin resistance, which lowers sex hormone binding globulin (SHBG) levels and leads to increased bioavailability of sex steroids.

Adipose tissue is not simply a dormant supplier of energy, but acts as a potent organ involved in metabolic regulation. In addition to leptin, adipose tissue secretes other adipokines including adiponectin, resistin, retinol binding protein-4 (RBP-4), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6).⁵³ Adiponectin is inversely correlated to fat mass and may be involved in insulin sensitivity and suppression of hepatic glucose production, as well as having a central effect on the hypothalamus.⁵³ Resistin, TNF- α , RBP-4 and IL-6 are produced from adipose tissue macrophages and may all play differing roles in increasing insulin resistance.⁵³ Obesity is related to chronic low grade inflammation, likely due to release of inflammatory mediators such as those noted above, by macrophages and other non-adipose cells located in adipose tissue.

Leptin was discovered in 1995 as the product of the *ob* gene and serves a permissive function in most of its varied roles. It is produced primarily in adipocyte. The leptin receptor, a class 1 cytokine receptor, is involved with appetite regulation and located in and around the hypothalamus, as well as in the periphery. Leptin levels vary in a circadian rhythm possibly related to food intake,⁵³ and women and obese individuals have higher levels. Obesity may be viewed as a consequence of leptin resistance. Leptin plays a role in all the hypothalamic-pituitary axes, including gonadal, thyroid, adrenal, and growth hormone. With food deprivation, leptin levels fall and lead to other neuroendocrine changes to maintain energy homeostasis. As adipocyte mass decreases, leptin-induced changes decrease energy expenditure, thus preventing further weight loss. Replacement of leptin during caloric deprivation is associated with prevention of the down regulation seen in the hypothalamic-pituitary-gonadal axis. Leptin also appears to play a role in the control of insulin sensitivity through a variety of mechanisms.⁵⁴

The discovery of leptin led to speculation regarding its apparent role in puberty and obesity. Leptin is related to growth and pubertal development, as well as regulation of appetite, adipose tissue stores, energy balance, and fertility in animals.⁴¹ Leptin levels rise before onset of puberty, although in boys the levels fall in mid-puberty.^{2, 55} Leptin is a marker of adiposity and part of a feedback loop of energy metabolism, and thus may be the mechanism underlying the Frisch hypothesis. Matkovic, et al⁵⁶ examined 343 healthy white girls, and found a direct correlation between leptin levels and timing of menarche. Every increase of 1 ng/mL in serum leptin was associated with a lowering of the age at menarche by 1 month, and a gain in body fat of 1 kg was associated with a lowering of the timing of menarche by 13 days. The authors speculate that there may be a “critical” threshold of leptin for regular menses to be established, recalling the Frisch hypothesis. The critical threshold might not be total body mass or fat mass, although leptin may represent this fat mass. Other data suggest that leptin seems to have a facilitative role in pubertal onset, but does not seem to be the indispensable trigger, as noted by Ahmed, et al.⁴⁰ Once adequate energy stores are achieved in the form of adipose tissue, particularly subcutaneous fat, leptin may allow activation of the GnRH pulse generator.^{55, 57} Leptin appears to serve as the signal to the hypothalamus GnRH pulse generator that there are sufficient energy stores in the adipose tissue for fertility

to commence,⁴¹ which is necessary but not sufficient for the initiation of puberty.⁵⁸ Leptin thus seems to be the link between energy storage and the hypothalamic-pituitary-gonadal axis, although it seems to act as a permissive factor rather than the critical threshold as Frisch proposed. Teleologically, it makes sense that reproductive function is tied to energy supplies, in order to ensure that mother and baby have adequate energy supplies.³⁹ In our modern society, the abundance of over-nutrition may have led to perturbations in this evolved system.

Aromatase activity within the adipocyte is dependent on fat mass, and thus obesity may result in greater peripheral conversion of androstenedione to estrone and testosterone to estradiol.^{2, 59} The higher estrogen levels could promote earlier onset of breast development and menarche in girls. In addition, obesity-mediated insulin resistance leads to decreased SHBG and thus increased bio-availability of sex steroids.^{41, 59} This may change the tempo of puberty, potentially resulting in lengthened time to menarche (see Figure 2).⁶⁰

An analysis of a large population-based cohort of 135,000 girls demonstrated that pre-pubertal BMI (at age 7) was associated with earlier age of puberty (determined by age of onset of growth spurt and age at peak height velocity) in a cohort born 1930–1969,⁴ although there was a general earlier trend across BMI categories during the time periods studied, suggesting other causes in addition to BMI. Endocrine disrupting chemicals (EDs) may exert their action through adipocytes or other hormonally responsive tissues, impacting time of maturation. Studies of various potential EDs show differing effects depending on the developmental period of exposure.³ There may be a ‘critical window’ of susceptibility for each ED, which could interact with other EDs, and impact the total body burden for an individual, depending on timing and dose of each exposure. Exposure to these chemicals may change adipocyte metabolism,^{3, 31, 32} thus potentiating the combination of obesity and environmental exposures.⁴⁹ Preliminary cross-sectional results from an ongoing longitudinal investigation showed weak correlations between urinary levels of several EDs, some with earlier and some with later pubertal timing.⁵⁰ The mechanisms of these changes will require additional investigation of this and similar cohorts.

There are some chemical exposures which are associated in children with higher body burdens than adults similarly exposed; for example, levels of perfluorochemicals were found to be greater in children than adults, given similar environmental exposures.⁶¹ Additionally, underlying obesity can increase the body burden of lipophilic compounds. The ‘perfect storm’ may be that EDs directly worsen obesity as well as directly impact endocrine function. The resultant obesity and change in the hormonal milieu feedback may act additively or synergistically to disrupt normal pubertal development.

Relationship of obesity and timing of puberty in boys

Although the literature is consistent regarding the relationship of BMI and timing of puberty in girls, the literature is not consistent about this relationship in boys. There are several groups who noted that boys with greater BMI^{62, 63} or fat mass⁶⁴ enter puberty earlier. In part, greater BMI may represent adequate caloric reserves rather than obesity; for example, in the study by Boyne, et al., there was a positive association between body fat and greater pubic hair maturation up to 18 kg body fat, at which point maturation decreased.⁶⁴ Several published studies did not note a consistent relationship between BMI and timing of puberty.^{65, 66} Additionally, there are several studies that have noted that boys with greater BMI entered puberty later.^{15, 67–70} There are also several studies that suggest a more complex relationship between BMI and timing of pubertal parameters. For example, boys born more recently were noted to have earlier maturation in the Copenhagen Puberty Study, but BMI explained only a portion of the variance.⁶³ In other European studies, BMI was not associated with onset of the pubertal growth spurt (an early pubertal event), but was

associated with age of peak height velocity (a relatively late pubertal event in boys).⁴⁷ and age of voice break (another late pubertal event).⁷¹ Although it appears there are inconsistencies in these observations, the studies might reflect accurately the changes in peri-pubertal boys and relationship to obesity. As in girls, greater obesity might contribute to greater conversion of adrenal androgens to estrone with stimulation of growth plates, but suppression of the hypothalamic-pituitary-testicular axis and gonadal and pubic hair development, or EDs might impact adipocytes and aromatase activity and/or act on estrogen receptors directly.

Closing

This paper examined the decline in the age of breast development and potential mechanisms to explain the relationship between greater body mass index with earlier puberty in girls. As noted earlier, the epidemiologic studies have documented earlier breast maturation, the typical biologic landmark of pubertal maturation. Several recent investigators have suggested that these changes may reflect pubertal changes rather than reactivation of the hypothalamic-pituitary-ovarian axis, and several mechanisms have been proposed, including the action of endocrine disrupting chemicals, or peripheral aromatization of adrenal androgens through adipocytes. Although the relationship between obesity and timing of pubertal maturation appears to be less consistent in boys than girls, endogenous estrone or endocrine disrupting chemicals could stimulate growth plates but suppress the hypothalamic-pituitary-testicular axis.

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Figure 1.

Figure 2. Proposed mechanism of contemporary factors impacting onset of pubertal changes in girls

Footnotes: EDs = Endocrine disrupting chemicals

SHBG = sex hormone binding globulin

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Table 1

Contemporary studies of the onset of puberty (breast development) in girls.

AUTHORS	Estimated years of birth	Mean age breast stage 2	Mean age of menarche
Reynolds & Wines Reynolds & Wines (1948)	1930–35	10.8	12.9
Marshall & Tanner Marshall & Tanner (1969)	1959	11.2	13.5
Harlan; MacMahon (NHES) (Harlan et al 1980; MacMahon 1974)	1960–65	12.8	12.5 / 12.8
Herman-Giddens (PROS) (Herman-Giddens et al 1997)	1979–85	8.9 / 10.0	12.2 / 12.9
Sun (NHANES III) (Sun et al 2002)	1978–85	9.5 / 10.4	12.1 / 12.6
Biro (NGHS) (Biro et al 2001)	1978–79	9.8 / 10.4	12.0 / 12.6
Aksglaede (Copenhagen) (Aksglaede, Sorenson et al 2009)	1991	10.9	13.4
Aksglaede (Copenhagen) (Aksglaede, Sorenson et al 2009)	2006	10.0	13.1

Studies by Herman-Giddens, Sun, and Biro reflect ages of African-American girls, followed by Caucasian girls. Study by Aksglaede reflects two cohorts of girls from the Copenhagen Puberty Study, born 15–16 years apart.