Nutritional Determinants of the Timing of Puberty

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Abstract

The timing of puberty has important public health, clinical, and social implications. The plasticity of sexual development onset could be a mechanism that adapts to prevailing environmental conditions. Early-life nutrition may provide cues for the environment's suitability for reproduction. This review focuses on recent developments in our understanding of the role of diet in the timing of sexual maturation. Population-based observational studies consistently indicate that childhood obesity is related to the earlier onset of puberty in girls. Similarly, intake of animal foods has been associated with earlier sexual development, whereas vegetable protein intake is related to delayed maturation. Evidence for prenatal nutrition, infant feeding practices, and childhood intake of fat, carbohydrate, and micronutrients is inconsistent. Secondary analyses of prenatal and early-life randomized nutritional interventions with extended follow-up through peripubertal years would help clarify the role of nutrition in the timing of sexual maturation.

INTRODUCTION

Puberty encompasses a series of physical and psychosocial changes during the transition from childhood to young adulthood that prepare the human body for reproduction. These changes affect body size, shape, and composition and involve the maturation of the reproductive organs and the acquisition of secondary sex characteristics.

From a physiological standpoint, the onset of puberty follows the disinhibition of the hypothalamic-pituitary-gonadal axis, which results in progressive amplifications of the pulsatile secretion of gonadotropin-releasing hormone (GnRH) by hypothalamic neurons. The childhood restraint on the GnRH pulse generator may be caused in part by proteins involved in ubiquitination (e.g., makorin RING-finger protein 3) that are abundantly expressed in the hypothalamic arcuate nucleus during brain development. The release of this restraint toward the end of childhood may be mediated by leptin levels and increased expression of neuropeptides, including neurokinin B and kisspeptin and their receptors (45). GnRH stimulates the pulsatile release of luteinizing hormone (LH) and, to a lesser extent, of follicle-stimulating hormone (FSH) by the pituitary. These two gonadotropins act on different gonadal cells to stimulate production of sex hormones. LH acts on ovarian interstitial (theca) cells to promote synthesis of estradiol's androgenic precursors and on testicular Leydig cells to induce testosterone secretion. FSH acts on ovarian granulosa cells and testicular Sertoli cells to promote gametogenesis (9).

Sex hormones are responsible for the physical manifestations of puberty. These include thelarche, the onset of breast development; pubarche, the appearance of pubic hair; gonadarche, the onset of sex hormone production by the gonads; menarche, the initiation of menses; and spermarche, the appearance of spermatozoa in semen (9). Pubertal changes in pubic hair, characteristics of external genitalia in males, and breast development in females are conventionally described in terms of five progressive physical stages as defined by Tanner (86). Thelarche and pubarche consist of the transition from Tanner stage 1 to Tanner stage 2. Testicular growth is an additional parameter sometimes used in sexual development research; specifically, reaching an estimated volume of 4 mL is conventionally considered the first recognizable enlargement of the testis and an indicator of puberty onset.

The sequence of these events varies substantially at the population level and is seldom the parameter of interest in epidemiologic research. Instead, puberty onset is usually defined in terms of reaching one of these milestones, particularly those that can be measured reliably and at low cost in population studies. In this review, the onset of puberty is used interchangeably with the appearance of any of these measurable physical manifestations.

The timing of puberty has important public health ramifications because it is related to a number of health outcomes (38). Early puberty is associated with adolescent alcohol abuse, smoking, drug use, early sexual debut, sexually transmitted infections, teenage pregnancy, aggressive behavior, and poor academic performance (28, 29, 37). In the long term, the early onset of puberty has been related to breast and endometrial cancers, obesity, type-2 diabetes, cardiovascular disease, and all-cause mortality (16, 21, 27, 43). Timing of puberty is also relevant from a public health perspective because it has been associated with a large number of environmental exposures that may be amenable to intervention.

A hypothesized increase in age at menarche from the Neolithic period to the Industrial Revolution (36) and its well-documented decline during the past two centuries (30, 46) indicate that the onset of puberty is responsive to changes in the environment. Although the exact nature of those changes remains uncertain, population-based studies have linked variability in the timing of puberty with socioeconomic conditions, psychological factors, environmental toxicants, physical activity patterns, and nutritional exposures (17, 94). Of these environmental influences, nutritional

factors are among the most relevant. From an evolutionary perspective, the age at initiation of reproductive capacity may have been subjected to selective forces that tended to maximize chances for reproduction and offspring survival. Environmental availability of energy, protein, and nutrients, which are necessary for sustaining pregnancy, lactation, and offspring's physical and cognitive development, could have driven this selection. Early-life nutrition could provide organisms with cues to the suitability of the environment for successful reproduction. The plasticity of age at onset of puberty, evidenced in its high variability across human populations and through recent secular trends, could be a mechanism that has adapted to favor the initiation of reproductive capacity when its probability of success is maximized. This review emphasizes recent developments in the study of nutritional influences on the timing of puberty from an epidemiological perspective.

PRENATAL NUTRITION

The intrauterine nutritional environment may have long-term effects on human development and health. Nutritional-related endocrine abnormalities during pregnancy could affect the hormonal milieu of the developing fetus and, in theory, affect its tempo of maturation later in life. Nevertheless, epidemiologic evidence suggesting that nutrition plays a causal role during pregnancy in the offspring's timing of sexual maturation is insufficient. Maternal height, an indicator of women's early socioeconomic status, nutrition, and exposure to infections, has been associated with later age at menarche in daughters in some (1) but not all (50) studies. Maternal obesity around the time of conception is related to altered secretion of adipokines, insulin resistance during pregnancy, and obesity in the offspring (6, 20). Whether these factors could alter the onset of puberty is uncertain. Prepregnant overweight and obesity have been related to younger age at menarche in some cohort investigations (23, 50); nevertheless, this association may not necessarily represent a causal effect but could instead be a result of shared genetic or environmental factors. One study reported a weak, U-shaped association between gestational weight gain and the risk of early menarche in the offspring (10), but this relation was not independent of prepregnancy weight in another investigation (23).

Studies of obesity-related obstetric complications and timing of puberty in the offspring are few and inconclusive. Preeclampsia has not been related to timing of puberty (71, 74), whereas the potential effects of gestational diabetes have not been addressed. Indicators of intrauterine growth are crude measures of the maternal nutritional status. Early studies suggested that intrauterine growth retardation may be related to earlier onset of sexual development (1), but more recent evidence does not support this view (5).

From copregnancy controlled investigations in which siblings with discordant timing of puberty onset are compared in relation to maternal exposure status during each pregnancy, one could infer whether maternal energy balance plays a causal role on offspring's age at maturation. Follow-up of offspring from participants beyond puberty in randomized interventions during pregnancy would also offer opportunities to estimate the causal effects of maternal nutrition on timing of sexual development. Nutriomics studies of maternal or cord blood samples stored in biological repositories of long-term birth cohorts could similarly shed light on the role of intrauterine nutrition on the onset of puberty.

INFANT FEEDING

The effect of breastfeeding on child growth is a matter of debate. Early studies showed inverse associations between breastfeeding duration and later development of adiposity. Nonetheless, an emerging body of evidence suggests that breastfeeding may not have a causal effect on childhood obesity (84). Its role on the timing of sexual development remains uncertain.

A few longitudinal studies have examined the association between breastfeeding and the onset of puberty, with inconsistent results. In an investigation of Hong Kong Chinese children, breastfeeding (defined as never, partial, or exclusive ≥3 months) was not associated with age at pubertal onset (57). Similarly, among 215 German children, no relation was found between exclusive breastfeeding ≥4 months and age at pubertal growth spurt, an outcome closely related to the timing of puberty (49). Prospective studies in Germany (40), Great Britain (8), and the midwestern United States (85) found no independent relation between breastfeeding and menarcheal age. In a study of 101 5-year-old girls and boys from the United States who were either predominantly breastfed or predominantly formula fed, investigators found no difference in reproductive organ volumes or characteristics (4). However, these children were too young to have undergone puberty.

In other studies, breastfeeding was related to the later onset of puberty. A study of 1,237 girls in the United States found that, compared with those fed formula, girls who had been predominantly breastfed had a significantly lower probability of initiating breast development at 6–8 years of age (48). Although the study estimates were adjusted for potential confounding by maternal and family characteristics, the interpretability of the results is limited because adjustment also included body mass index (BMI) in childhood, a variable that could be a mediator in the causal pathway. In a study of 219 Korean children, after adjusting for age and sex, those who were breastfed for ≥6 months had lower odds of reaching a Tanner stage ≥2 at 9 years of age compared with children who were breastfed for <6 months (58). In a prospective investigation of 994 Filipino girls, every month of exclusive breastfeeding was associated with a 6% lower probability of menarche over the follow-up period after adjusting for socioeconomic, maternal, and birth characteristics (3). Contrary to these studies, an investigation of 770 Filipino boys found that those who were breastfed as infants had a faster height velocity from birth to 6 months, which was inversely associated with pubertal maturation, than did boys who were not breastfed (56).

Drawing causal inference from these studies is hampered for several reasons. First, the definition of breastfeeding was highly heterogeneous with respect to type and/or duration. The measurement of breastfeeding could have been subject to recall bias because it was assessed retrospectively in most studies. Second, many of the studies had large losses to follow-up, which could result in selection bias if both infant feeding practices and pubertal stage affected retention. Third, most studies were restricted to girls, which hinders the generalizability of findings; in addition, some of the investigations that included both girls and boys did not present results stratified by sex (58). Fourth, observational studies are subject to residual confounding, and some of the analyses (48) may have incurred overadjustment bias. Finally, publication bias might partly explain a preponderance of published studies showing apparent breastfeeding effects that may be considered beneficial. Secondary analyses of randomized breastfeeding interventions in which follow-up has been extended throughout puberty (65) are warranted to clarify the effect of infant feeding on the timing of sexual development.

EARLY LINEAR GROWTH

Childhood nutrition affects linear growth patterns, and some evidence suggests that these patterns may be related to the timing of sexual maturation. A prospective study of 2,083 Brazilian girls showed that those with rapid growth from ages 19 to 43 months were 42% significantly more likely to experience menarche before age 12 years than were girls with slower growth, after adjusting for sociodemographic factors and maternal characteristics (68). In that study, rapid growth was defined as a change in height-for-age z-score ≥0.67. Similarly, British girls with the highest growth rates from 2 to 7 years of age had the earliest menarche (26). Few studies have examined this association in boys. Among 770 Filipino boys, those in the highest tertile of height growth velocity from birth

to age 6 months reached puberty earlier, according to pubic hair Tanner staging, and had higher testosterone levels at 15–16 years of age than did those in the lowest tertile (56). These results could nonetheless be biased by overadjusting for height velocities from 6 to 24 months of age.

From these studies we cannot determine whether early linear growth per se is causally related to the timing of sexual maturation. High linear growth velocity encompasses several heterogeneous mechanisms (e.g., catch-up growth versus rapid growth) and can be the result of many different environmental influences. Growth in height could lie on a causal path from early growth retardation or could be a proxy for different exposures (e.g., diet, infections) with varying distributions across populations. In addition, an association between the tempo of linear growth and the timing of sexual development could be the result of genetic common causes.

CHILDHOOD OBESITY

The potential effect of early-life energy balance on the timing of sexual development was first observed in animal experiments conducted in the 1960s (51). In the 1970s, Frisch et al. noted that whereas age at menarche was highly variable across human populations, attained weight at menarche seemed relatively homogeneous (31, 33). Further research led them to hypothesize that the onset of puberty in girls was triggered only when total body fat reached about 17% (32). Although this hypothesis generated controversy (89), further epidemiologic studies supported the role of energy balance, as reflected on body size during childhood, on the timing of sexual development.

In girls, studies have shown a consistent link between higher adiposity during childhood and earlier puberty (59, 63, 81, 91). For example, Wang et al. (91) followed 856 infants from the North Carolina Infant Feeding Study and found that higher weight gains in intervals from 0 to 2 years were associated with earlier menarche, compared with lower weight gains. Similarly, Lee and colleagues (59) showed that BMI z-scores and changes in BMI z-scores from 36 months to 6–7 years of age in girls from the United States were positively associated with early puberty, according to Tanner staging and menarcheal age. Childhood obesity may also be related to the rapid progression of sexual development, but current evidence is circumscribed to a relatively small study (13).

Among boys, the relation between adiposity in childhood and sexual maturation is controversial. Whereas some studies found a positive association between early-life BMI and the onset of puberty, others showed the opposite. A population-representative longitudinal study of Swedish children found that every unit of BMI was related to a 0.6-year earlier age at peak height velocity (APHV) in boys (44). However, a study of 705 boys from the United States showed that those with the fastest BMI trajectory from ages 2 to 11.5 years were less likely to have reached puberty during follow-up, according to objectively staged genital development, than were boys in the lowest BMI trajectory (60). One potential explanation for these discrepancies is that the relation between BMI and puberty could be nonlinear; i.e., overweight may be associated with early puberty, whereas more severe obesity may be related to late puberty (88). Information bias could also explain these inconsistencies because assessment of puberty onset in boys is less reliable than it is in girls, especially when the measures are self-reported (79). A potential effect could be related to the development of obesity during specific periods of childhood that may not have been examined in all studies. Finally, the definitions of early-life overweight, obesity, and adiposity have been highly variable.

The Frisch hypothesis could also be considered in the context of low levels of adiposity. Girls and boys who undergo intensive physical training have lower body fat percentages and BMI (12) and have a later pubertal onset than do children with more body fat. Elite gymnasts and ballet

dancers tend to experience menarche later than the general population (34, 35, 64). Although studies among males are lacking, the relation between body fat and pubertal timing may be different in boys than in girls. One investigation showed that, while body fat percentages were lower among male gymnasts compared with age-matched nongymnasts, there was no difference in genital or pubic hair Tanner staging (41). In that study, however, body fat percentage at the time of assessment did not necessarily correspond with the prepubertal body fat percentage.

One potential mechanism to explain the triggering of puberty by accruing a critical amount of fat could be related to leptin. Leptin, an adipokine produced by adipose tissue, could induce expression of kisspeptin (83), a neuropeptide involved in releasing the prepubertal restraint on the GnRH pulse generator. Another potential mechanism is seen when adipose-related signals involving insulin-like growth factor (IGF)-1, insulin, leptin, adiponectin, and C-reactive protein act aggregately to alter the expression of sex hormone binding globulin, a protein associated with the initiation of puberty (76). Long-term follow-up of children participating in randomized interventions to prevent excessive weight gain or to promote weight loss could provide critical evidence on the causal effect of early-life adiposity on the timing of sexual maturation.

CHILDHOOD PROTEIN INTAKE

Early studies of total protein intake in relation to the onset of puberty were null (22, 55). However, further studies of specific sources of protein provided insights into the potential effects of this macronutrient on the timing of sexual maturation. The effects may vary according to protein sources.

Some evidence indicates that animal protein intake during childhood may be related to the earlier onset of puberty. In a small study of girls from the United States, total animal protein intake at 3–8 years of age was related to earlier menarche and APHV (7), whereas among German boys and girls, intakes of total and animal protein at 5–6 years of age were related to early APHV, menarche in girls, and voice break in boys (40).

Specific animal food groups that have been examined in relation to the timing of sexual maturation include dairy products and meat. Gunther and colleagues (40) reported that protein intake from cow milk and other dairy was related to earlier pubertal growth spurts and APHV among 112 German boys and girls. Similarly, in a prospective study of 134 Iranian girls, those with milk intake at ≥34 g per day at 9 years of age had higher odds of early menarche at or before age 12 years than did girls with milk intake at <34 g per day (78). Using data from the National Health and Nutrition Examination Survey, Wiley et al. (93) found that higher milk consumption at ages 5–12 years among 2,057 girls from the United States was associated with an earlier age at menarche. In other studies, dairy intake has not been related to the onset of puberty (15).

Meat intake has also been implicated in the timing of puberty. Among 3,298 girls from Southwest England participating in the Avon Longitudinal Study of Parents and Children (ALSPAC), those with the highest meat intake at 3 and 7 years of age had greater odds of menarche at age 12.5 years as compared with girls in the lowest meat intake category (80). Of note, intake at age 10 years was not related to menarche, which could indicate an age-specific effect. In the Bogotá School Children Cohort, red meat intake at 8 years of age, on average, was inversely related to age at menarche among 456 girls (47). Girls who consumed red meat at least twice daily had a statistically significant, adjusted 64% higher probability of menarche during follow-up compared with girls with red meat intake frequency at <4 times per week. Similarly, in a cross-sectional study of 422 Korean children, adherence to a "shellfish and processed meat" dietary pattern was significantly, positively related to breast development staging after adjusting for age, body fat, and bone mineral content (61). Another investigation found that girls who consumed meat at ages

9–15 years reached menarche an average of 6 months earlier than did girls with a vegetarian diet in childhood (53), although the estimates were not adjusted for potential confounding. Carwile et al. (15) reported no association between peri-pubertal meat intake and age at menarche in 5,583 girls from the United States, after adjusting for sociodemographic and nutritional potential confounders.

Many reasons could explain the discrepancies across studies. One potential reason is the age at assessment of exposure. Some researchers have proposed that animal protein intake in early childhood may predict an early onset of puberty, whereas prepubertal intake may be less relevant (80); however, the mechanisms to explain these potential age-specific exposure effects are unknown. Differences in the dietary assessment methods used may be another explanation. Assessment of intake with a single-day measure (e.g., 24-h recall) (53, 78, 93) may induce attenuation of the associations. Adjustment for body composition (7, 61), a potential intermediate variable, could also impact the results. And finally, differences in exposure variability across populations may explain discrepancies between studies.

The potential effects of animal foods, especially dairy, on the timing of puberty have been attributed to a protein-mediated stimulation of IGF-1 secretion (52). Higher circulating levels of this hormone during childhood have been related in some studies to an earlier onset of puberty (87). Nonetheless, animal foods are also sources of other nutrients, notably some micronutrients and fatty acids, that may also play a role in the timing of sexual maturation. Available evidence is reviewed in the sections below.

In contrast with the studies suggesting a role for animal protein sources in early sexual development, intake of vegetable protein sources during childhood has been related to the delayed onset of puberty. For example, analyses of the Dortmund Nutritional and Anthropometric Longitudinally Designed Study showed that children in the lowest tertile of vegetable protein intake at 3–4 years of age had an earlier APHV than did children in the highest tertile (40). Similarly, Berkey et al. (7) showed that levels of vegetable protein intake were positively correlated with age at menarche and APHV. In another investigation, girls in the upper quartile of nuts, grains, and beans intake at baseline had a later menarcheal age than did girls in the lowest quartile of intake (53).

Despite the consistency of results across studies, we cannot conclude that the associations between vegetable protein intake and the onset of puberty are causal. Confounding by fiber intake (22, 54) or other nutrients, including isoflavones, could also explain the findings. Soy isoflavones exert weak estrogenic effects that could influence pubertal development. Cheng et al. (18) reported that childhood isoflavone intake was related to a later age at menarche in German girls, although estimates were adjusted for baseline body composition, a potential intermediate. In contrast, a longitudinal study of 2,920 British girls found an inverse association between soy infant formula intake and age at menarche (2). In one cross-sectional investigation of 339 Seventh-Day Adventist girls, intake of total soy, soy-containing meat alternatives, tofu/traditional foods, or soy beverages was not related to age at menarche, but estimates were adjusted for BMI (82).

DIETARY FAT

Results of studies to determine the association of total fat intake during childhood and the onset of puberty are inconsistent. Whereas some studies have reported inverse associations between total fat intake at ages 1–2 years or 8–12 years and the age at onset of puberty (67), others have found a lack of an association (22, 55, 80) or a positive association (54). In a randomized controlled trial of 663 children ages 8–10 years with elevated low-density lipoprotein cholesterol, limiting total fat intake to 28% of total calories did not result in differences in age at menarche (24). However, girls in the intervention group had lower concentrations of estradiol during the follicular phase of the

menstrual cycle and higher testosterone during the luteal phase of the menstrual cycle than did girls in the control group. These results were restricted to the postmenarcheal period, which could suggest an effect of total fat on slowing the maturation of the hypothalamic-pituitary-ovarian axis. Among boys, no differences were noted in testicular volume or Tanner stage progression, and sex hormones as well as binding protein concentrations were similar between treatment groups (25).

From the biological and public health standpoints, it is more relevant to identify the potential effects of fat quality than to identify those of total fat. The relations between types of fat and the onset of puberty have been examined in a few investigations, with varying results. They are summarized below.

Saturated Fat

Longitudinal studies in girls from the United States (22, 62), Canada (70), and Greece (75) have not found an association between saturated fat intake and age at pubertal onset. However, in most of these studies (22, 62, 75), estimates were adjusted for child anthropometric measures, which could be mediators on the causal pathway.

Monounsaturated Fat

In cohort (54) and case-control (70) studies of Canadian girls, prepubertal intake of monounsaturated fatty acids was inversely associated with age at menarche. In one of the studies (54), the association was attenuated after adjusting for covariates including baseline body weight. Conversely, in a study of 213 girls from the United States, Maclure et al. (62) found a positive relation between oleic acid intake at age 10 years and age at menarche, although these estimates were also adjusted for height and weight at the time of dietary assessment.

Polyunsaturated Fat

In the ALSPAC study, total polyunsaturated fatty acid intake at age 3 years was related to earlier age at menarche (80). One cross-sectional study also reported an inverse association between total polyunsaturated fatty acid intake and age at menarche among 200 girls from the United States after adjusting for total calories, age, ethnicity, height, and weight (11), whereas Petridou et al. (75) found that total polyunsaturated fatty acid intake was positively related to age at menarche in Greek girls. There is scant evidence on specific polyunsaturated fatty acids in relation to the onset of pubertal timing. Maclure and colleagues (62) found that omega-3 fatty acid intake was inversely associated with age at menarche, whereas linolenic acid was unrelated. A common limitation of these studies is the adjustment of estimates for child anthropometric measures (11, 62, 75).

CARBOHYDRATES

Energy intake from carbohydrates during childhood has not been related to markers of pubertal development in cohort studies (22, 55, 69). However, in a prospective study conducted in the United States, intake of sugar-sweetened beverages (SSBs) was associated with early sexual development in 5,583 girls (14). Premenarcheal girls who consumed >1.5 servings of SSBs per day at ages 9–14 years had a statistically significant 24% higher probability of menarche during follow-up than did girls who consumed ≤2 servings of SSBs weekly after adjusting for sociodemographic and maternal characteristics, physical activity, and total caloric intake. This association could not be necessarily attributed to sugar but may be related instead to other compounds present in these

beverages, including caffeine. In another prospective study of girls from the United States, every standard deviation of caffeine intake at 10 years of age was related to a 22% higher risk of early menarche (<11 years of age) after adjusting for potential confounding variables (72). In the same study, every SD of aspartame intake was related to a 20% higher risk of early menarche, whereas neither fructose nor sucrose intake was related to the timing of puberty.

MICRONUTRIENTS

Micronutrient requirements increase during puberty; thus, prepubertal micronutrient status may influence the timing of sexual maturation. One study of 134 Iranian girls provided evidence that calcium, magnesium, and phosphorus from dairy may be related to age at menarche (78). Girls in the upper median intakes of each of these nutrients had higher odds of experiencing menarche before 12 years of age compared with those in the lower median intakes. Similarly, in a randomized controlled trial among 160 Gambian boys, those supplemented with calcium for 12 months had an earlier APHV and shorter adult stature than did boys in the control group (77). In another randomized study among 144 Swiss girls, those supplemented with calcium from ages 7.9 to 8.9 years reached menarche earlier than did girls who received the placebo (19).

The apparent effects of animal protein intake on the timing of sexual maturation may be related to nutrients other than protein. Micronutrients, including iron and zinc, are found in animal food sources in highly bioavailable forms. Given the key roles these nutrients play in reproductive functions and offspring development, the status of these nutrients during childhood may be related to the timing of sexual maturation. Evolutionary theory would predict that deficiencies in these nutrients would be related to a delayed onset of reproductive maturity, whereas children who reach adequate stores earlier in life would develop sooner. In a small randomized trial of 17 Iranian children, those supplemented with zinc had an earlier initiation of puberty compared with children assigned to the placebo group (42). In the ALSPAC observational study, zinc intake at seven years of age was inversely related to age at menarche; however, this association was not statistically significant (80). Kissinger & Sanchez (53) reported a statistically significant, positive association between iron intake and age at menarche among 230 girls from the United States. Nevertheless, estimates were not adjusted for potential confounding. Also, in a randomized controlled trial of 102 boys ages 13.6 to 15.5 years with short stature and delayed puberty, supplementation with iron and vitamin A resulted in faster testicular growth (95), but the results could be attributed to vitamin A rather than to iron. In the study by Maclure and colleagues, vitamin A intake was strongly associated with earlier menarche (62), although the opposite was observed in a case-control investigation of Canadian girls after adjusting for total energy intake (70).

Although the best known functions of vitamin D are related to calcium metabolism and musculoskeletal health, this nutrient and hormone likely plays an important role in reproduction. Vitamin D receptors are present in the ovary, uterus, placenta, testis, and pituitary gland (39). In the Bogotá School Children Cohort, we found that girls who were deficient in vitamin D at the time of recruitment were twice as likely to reach menarche during follow-up as were those who were not deficient in vitamin D, independent of baseline BMI and socioeconomic status (90). By contrast, in a randomized trial among Chinese girls 10 years of age, supplementation of milk fortified with vitamin D and calcium compared with calcium only for 2 years did not have an effect on age at menarche over an extended 5-year follow-up period (97). The vitamin D dosage in this trial, however, was very low.

Information on the potential effects of other vitamins or minerals on the timing of sexual development is scarce. Future studies could address the effects of other micronutrients that are essential for reproduction and child development, including folate and vitamin B-12. Some of

these nutrients play important roles on methylation reactions, and their long-term effects could be explained through epigenetic mechanisms.

TOXICANTS PRESENT IN FOODS

The pubertal timing effects of unnatural compounds that contaminate food through preparation, storage, or preservation are worth a brief commentary because they can act as endocrine disruptive chemicals (EDC). Animal studies indicate a plausible link between EDC and the timing of pubertal maturation, but epidemiologic evidence is scant and/or conflicting, as recently reviewed elsewhere (73). Polychlorinated biphenyls (PCBs) are found in fish from contaminated waters. PCBs have been related to both earlier and later timing of sexual development. Lead blood concentrations have been related to delayed maturation in cross-sectional analyses, but data from longitudinal studies are lacking. Bisphenol A, an estrogenic compound used in food and beverage packaging, has been related to delayed maturation in some (66) but not all (92) investigations. Phthalates, used in food packaging and wrapping, have been related to earlier menarche in girls (96). The sources of these contaminants are not exclusively dietary. Although they may disrupt the timing of sexual maturation at high doses, the effects attributable to their ingestion from contaminated foods seem uncertain. Their adverse effects on other health outcomes may warrant stricter control of their presence in the environment.

CONCLUSIONS

Evidence supporting the role of early nutrition on the timing of sexual development is consistent with regard to the effects of childhood obesity among girls. Most adequately conducted observational studies indicate that obesity and rapid weight gain during childhood are related to an early age at menarche and other markers of puberty. Examining the pubertal effect of preventing excessive weight gain during childhood in secondary analyses of randomized intervention studies could lend support to causality.

Intake of animal foods has been related to an earlier onset of puberty in numerous investigations, but the mechanisms to explain a potential causal effect remain unknown. Although these mechanisms could involve a protein-mediated enhancement of growth factor expression, the roles of other nutrients present in animal foods, including micronutrients and specific fatty acids, are understudied. Investigations of the effects of different types of animal sources (e.g., red meat versus poultry, fatty fish, or freshwater fish), forms of preparation, and level of processing could aid in the process of generating hypotheses about specific dietary factors mediating these effects. Some studies suggest that childhood intake of vegetable protein sources is associated with delayed pubertal development.

Evidence on the effects of fats, carbohydrates, and micronutrients on the timing of puberty is insufficient and inconsistent. Intriguing results from recent studies relating intake of SSBs and vitamin D deficiency to early puberty in girls are noteworthy and require confirmation in other populations. The potential effects of prenatal nutrition and infant feeding practices on the timing of sexual maturation would be best ascertained in analyses of randomized interventions with extended follow-up of the offspring.

Research on the nutritional determinants of the timing of puberty in boys is scant owing to the lack of valid, easily measurable indicators of sexual maturation at the population level. Some of the available evidence indicates that the effects of the environment on the timing of puberty may differ between sexes. Additional investments in research involving boys are required to close this gap.

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