Puberty and Pediatric-Onset Inflammatory Bowel Disease

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The Pubertal Process in Healthy Children and Adolescents

Puberty is defined as the developmental stage during which sequential biological processes occur that ultimately lead to reproductive capacity [1]. The onset of puberty is initiated following increased synthesis and secretion of gonadotropin releasing hormone (GnRH) in the hypothalamus and its transport to gonadotrophs within the anterior pituitary. In response to pulsatile GnRH, the gonadotrophs secrete luteinizing hormone (LH) and follicle stimulating hormone (FSH), which in turn regulate ovarian and testicular functions. Pituitary sensitivity to GnRH varies throughout life, but increases prior to the onset of puberty. At this time, LH is secreted in a pulsatile manner, primarily during sleep, but subsequently changes to a pulsatile pattern throughout the day as puberty progresses [2]. In females, LH stimulates theca cells in the ovary to produce androgens, which diffuse to granulosa cells for conversion into estrogens. FSH causes growth of granulosa cells in the ovarian follicle and estrogen production (estrone or E1 and estradiol or E2). The estrogen elaborated in large amounts by the ovaries leads to feminization in girls. In males, LH stimulates testosterone production by Leydig cells in the testis. Testosterone subsequently undergoes 5α-reduction to dihydrotestosterone, which induces secondary sex characteristics. FSH acts on Sertoli cells in the seminiferous tubules of the testes to stimulate sperm production and testicular enlargement.

Adrenarche involves maturation of the adrenal gland with increased secretion of 17-ketosteroid and androgen production in response to ACTH. Adrenarche most often occurs between 6 and 9 years of age with elevation of circulating dehydroepiandrosterone sulfate (DHEAS) [3]. This results in the growth of pubic and axillary hair. Adrenarche is typically temporally related to pubertal maturation of the hypothalamic–pituitary–gonadal (HPG) axis, but is not causally related to maturation of this axis. While adrenal androgen production is a minor component of the midpubertal male testosterone level, the adrenal gland contributes about half the total testosterone produced in the female. Since adrenal androgen production is ACTH- dependent, this synthesis is subject to suppression with exogenous glucocorticoid therapy. In normal maturation, DHEAS is the most abundant circulating adrenal steroid after the onset of adrenarche and often reflects endogenous glucocorticoid secretory capacity. Adrenal androgen production has also been shown to be affected by other hormones, such as insulin, growth hormone (GH), and insulin-like growth factor 1 (IGF-1), and indirectly to nutritional status [4].

Since in early puberty increased gonadotropin pulse amplitude increases first during sleep, gonadal steroid secretion at this point of development is maximal in the very early morning hours and may wane to low, prepubertal levels by 0900. Thus, it is important to assay gonadotropin and sex steroid levels in the early morning. In addition, it is important to perform these assays in a specialty laboratory with sensitive pediatric assays to detect the normally low prepubertal and early pubertal levels. The adrenal steroid DHEAS does not follow this pattern because of its long plasma half-life, and a meaningful level may be determined throughout the day. A summary of normal hormone levels in puberty is seen in Table 14.1.

Although puberty typically occurs between the ages of 9–12 in girls and 10–13 in boys, the factors in the brain that trigger the onset of the pulsatile GnRH secretion at the time

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Table 14.1 Hormone levels in puberty

Hormone	Stage/age	Male	Female
Dehydroepiandrosterone	Tanner I	<89	<46
Sulfate (DHAS) (mcg/dl)	Tanner II	<81	15–113
	Tanner III	22–126	42–162
	Tanner IV	33–117	42–241
	Tanner V	110–510	45–320
Luteinizing hormone (LH)	3–7 years	<0.26	<0.26
	8–9 years	<0.46	<0.69
Pediatric – IU/L	10–11 years	<3.31	<4.38
	12–14 years	0.23–4.41	0.04–10.8
	15–17 years	0.29–4.77	0.97–14.7
Follicle stimulating	5–9 years	0.21–4.33	0.72–5.33
hormone (FSH)	10–13 years	0.53–4.92	0.87–9.16
Pediatric (IU/L)	14–17 years	0.85–8.74	0.64–10.98
Estradiol (E2)	Prepubertal	<4	<16
Pediatric (pg/ml)	10–11 years	<12	<65
	12–14 years	<24	<142
	15–17 years	<31	<283
Estrone (E1) (pg/ml)	Prepubertal	<10	<34
	10–11 years	<12	<72
	12–14 years	<28	<75
	15–17 years	<64	<188
Testosterone (Te) (ng/dl)	Tanner I	<5	<8
	Tanner II	<167	<24
	Tanner III	21–719	<28
	Tanner IV	25–912	<31
	Tanner V	110–975	<33
IGF-1 (ng/ml)	Tanner I	96–341	105–359
	Tanner II	101–478	99–451
	Tanner III	101–478	197–642
	Tanner IV	318–765	330–776
	Tanner V	318–765	330–776

Modified from Nakamoto and Mason [82], and Quest Diagnostics Reference Ranges, Quest Diagnostics Inc., San Juan Capistrano CA
Caution is suggested in differentiating puberty from prepuberty, especially with regard to LH, FSH, E2, and Te. The assays must be sufficiently specific as well as sensitive for the normally low prepubertal and early pubertal levels. In addition, these hormones are secreted episodically with short half-lives in the blood. Early morning testing is recommended

of puberty are still not completely understood. Leptin is a peptide hormone expressed predominantly in adipocytes that regulates food intake and energy expenditure at the hypothalamic level [5]. Serum leptin levels have been shown to correlate closely with body fat content. Leptin is thought to be an important link between nutrition and the attainment and maintenance of reproductive function, as patients with leptin deficiency have been shown to not only be obese, but to also have gonadotropin deficiency [6]. However, while leptin levels normally rise throughout childhood and puberty, a rise in leptin is not required to trigger puberty. Thus, leptin likely functions as a permissive factor rather than a trigger in the onset of human puberty. In late 2003, loss of function mutations of GPR54 (a G-protein coupled receptor) were described in patients with hypogonadotropic hypogonadism [7]. This discovery led to the finding that GPR54 and its ligand (kisspeptin) act as a signal for pubertal GnRH release. Further research suggests that kisspeptin influences the timing of puberty and the integration of nutritional and energy status, likely indirectly through leptin expression. However, what controls the regulation of kisspeptin expression at the time of puberty is not completely known.

Neuropeptide Y (NPY), a potent appetite-stimulating agent found in the hypothalamus, may also mediate the effects of leptin on puberty. Based on studies in prepubertal rats, Pralong et al. suggested that NPY may inhibit GnRH secretion and delay sexual maturation [8]. In a limited study, girls with constitutional delay in puberty were found to have higher levels of NPY than those with a normal course of puberty [9].

The onset of puberty is associated with Tanner stage II for breast development in girls and testicular volume of 4 ml or length of 2.6 cm in boys [10, 11]. The current best estimates for the mean age of onset of puberty in healthy children in the United States are 10.2 years for girls and 11.5 years for boys [10]. The mean age of menarche is 12.6 years in Caucasian girls, 12.3 years in Mexican-American girls, and 12.1 years in African-American girls of normal weight [12]. The mean age for spermarche in boys is between 13.5 and 14.5 years [13]. The average duration of puberty in girls is 4 years (range 1.5–8 years) and for boys 3 years (range 2–5 years) [13]. This is important as it reflects the wide range in maturation of normal, healthy individuals as well as the variation in duration to completion [14–16].

The standard deviation for all pubertal milestones is about 1 year [17, 18]. Thus, girls older than 13 years and boys older than 14 years without evidence of Tanner II development are considered to have delayed puberty. The most common cause of delayed puberty in otherwise healthy children is an extreme variant of normal known as constitutional delay of growth and puberty (CDGP). This occurs due to an unexplained delayed activation of the hypothalamic–pituitary–gonadal axis. A family history of delayed puberty can usually be elicited. In a large case series, CDGP was found to be the cause of delayed puberty in 53% of the subjects (approximately 63% of boys and 30% of girls) [19]. The second most common cause of delayed puberty in the case series was functional gonadotropin deficiency, which affected 19% of subjects. Functional gonadotropin deficiency can be seen in chronic illness, especially in conditions that are also associated with decreased body fat. Other less common causes of delayed puberty include primary gonadal failure and gonadotropin deficiency.

For distinguishing different phases of pubertal development, most reports in the pediatric gastroenterology literature

have used Tanner stages which rely on visual observation of the progression of pubic hair character and distribution, breast size and contour, and testicular size [20]. Schall et al. studied the validity of self-assessment of sexual maturity in 100 patients, age 8–18 years, with Crohn's disease [21]. The instrument included drawings and written description of Tanner stages. Patients' self-assessments were compared with those of a designated pediatrician. Agreement varied between 74% and 85%, depending on the sex and sexual maturity status with younger children and overweight boys tending to overestimate their sexual maturity status (SMS). Rapkin et al. also noted that self-staging of Tanner stage was as accurate as circulating estradiol and FSH measurements in 124 healthy girls, aged 8–18 years [22]. However, one needs to be cautious with Tanner staging of breasts in overweight girls by self-report, as adipose tissue in the chest can be mistaken for early breasts. This emphasizes the necessity of palpation to identify true breast bud tissue in girls.

Thus, puberty involves a change in the balance of inhibitory and stimulatory signals that impact the GnRH neuron. Genetic factors, ethnicity, nutrition, and environmental chemicals are important in the pubertal process. However, the mechanisms by which neuroendocrine and genetic factors control pubertal development are yet to be fully elucidated.

The Influence of Inflammatory Bowel Disease on Puberty

Delayed puberty and poor growth often complicate the clinical course of children diagnosed with IBD, especially children diagnosed with Crohn disease (CD). As progression through puberty and increased growth velocity are intricately linked, most studies that look at the effects of IBD on puberty examine both growth and pubertal progress. Normal prepubertal growth velocity after 3 years of age averages about 5–6.5 cm/year. The pubertal growth spurt provides an additional 15–25 cm of growth [9, 12–14]. Delayed puberty is often associated with lower peak height velocity. Midparental target heights can be calculated with the following formulas: for boys, add 13 cm to the mother's height and average it with the father's height; for girls, subtract 13 cm from the father's height and average it with the mother's height. Most children will fall within ±8.5 cm of this prediction.

From the viewpoint of the authors, one of the most interesting studies which assessed the effect of IBD on puberty is that of Hildebrand et al. [23]. This study obtained height and weight data collected from birth through final adult height in 46 patients with childhood-onset Crohn disease (CD) and 60 patients with childhood-onset ulcerative colitis (UC) from a defined area in Sweden. In this study, the age at peak height velocity (PHV) was stated to represent the middle of puberty. Individual values for height were converted into standard deviation scores (SDS) using the infancy–childhood–puberty growth standard of Karlberg et al. [24]. The PHV for healthy children in Sweden was reported to be 12.05 ± 0.88 years for girls and 14.15 ± 0.98 for boys. Delayed puberty was defined as a delayed age at PHV of >2.0 SDS. No significant delay was noted in children with UC with age at PHV 11.9 ± 1.1 years for girls and 14.0 ± 1.2 years for boys. However, mean age at PHV was later in patients with CD: 12.7 ± 1.4 years for girls and 14.9 ± 1.2 years for boys, and 23% of these children with CD had a delayed age of PHV of >2.0 SDS.

Brain et al. also observed several alterations in the pattern of puberty among pediatric patients with IBD [11]. The mean age of onset of puberty was delayed for both female and male patients when compared to healthy controls: 12.6 years versus 11.1 years in girls and 13.2 years versus 12.4 years in boys. In addition, the duration of puberty was prolonged, especially in adolescents with frequent relapses during puberty [11]. Some patients with IBD took up to 4 years to progress from Tanner stage II to stage IV. Peak height velocities during puberty reached rates >12 cm/year in patients who remained in remission in contrast to as little as 1–2 cm/year in those with relapsing disease. When surgical resection was performed in 11 prepubertal children with CD, puberty started within 1 year of resection. The authors postulated that if the onset of puberty was delayed beyond 14 years, then the final height may be "irreparably compromised." Our data would confirm that statement, as we observed that there was a strong correlation between age at menarche and height gain [25]. When menarche occurred at <13 years of age, the mean increment in height was 10 cm compared with only 3.0 cm in those aged >15 years. Homer et al. also noted that catch-up growth, even in prepubertal patients, occurred only in those with sustained clinical remission [26].

Ferguson and Sedgwick described delayed puberty in IBD based on a retrospective survey of adults with a history of pediatric-onset UC and CD [27]. Their results were different from other published reports in several ways. Adult stature achieved by 67 of 70 patients was similar to normal adults, and no difference was seen whether the patients had CD or UC. Delayed puberty was based on patients' recall many years later. Pubertal delay was reported as follows: Crohn disease, 11/28 (39%) of men and 13/22 (59%) of women compared with 2/9 (22%) of men and 3/11 (27%) of women with UC. These numbers were not statistically different. Age at menarche was reported to be >16 years in 8 of 11 (73%) women whose menarche occurred after the diagnosis of CD.

More recently, Gupta et al. compared the age at menarche in 34 patients with CD with that for 545 controls, using data from the National Health and Nutrition Examination Survey (NHANES) [28]. They found that the median chronological

age at menarche (13.9 years) in CD was older than that in the NHANES sample (12.0 years). In CD patients, the cumulative incidence of menarche was 10% at chronological age 12 years, 51% at chronological age 14 years, and 100% at chronological age 16 years. Sixty-eight percent reached menarche by bone age 13.5 years and 100% by bone age >14 years. Menarche occurred earliest in South Asians, followed by East Asians, and then Caucasians. They suggested if menarche has not occurred by bone age >14 years, endocrinology referral should be considered.

Other studies also show that onset of IBD during the prepubertal period is frequently associated with subnormal growth. In the Hildebrand et al. study, growth velocity in children diagnosed with IBD during the prepubertal period was −2.0 SDS in 24% of children with UC and 40% of children with CD [23]. Kanoff et al. and Kirschner also reported impaired growth in 68–88% of prepubertal children with CD [29, 30]. In addition, within a group of prepubertal patients, Saha et al. noted the poorest growth in those with severe CD when compared with UC [31]. In this study, no difference was seen between patients with and without corticosteroid treatment. In contrast, Motil et al. and Sentongo et al. reported that the prevalence of growth failure was equal regardless of the stage of pubertal development [32, 33]. Sawczenko et al. studied the effect of CD on final height in 123 patients who were designated "prepubertal" based on age at onset of symptoms: <13 years for boys and <11 years for girls [34]. Nineteen percent had a final height 8.0 cm or more below the targeted or midparental height. Those children who received steroid therapy were not found to be significantly shorter than other children at final height, suggesting that the judicious use of systemic steroids should not lead to significant long-term growth delay. However, of the shorter children in their study, boys were overrepresented with an OR of 3.70.

Several additional studies have suggested that boys with CD are more likely to have abnormalities of growth, especially while their disease is active. In an earlier report, Griffiths et al. had also observed less catch-up growth in boys than girls [35]. More recently, Gupta et al. reported that serum IGF-1 levels were reduced in males with IBD for both chronological and skeletal age when compared with female patients with IBD, and this may explain, at least in part, why male children with CD achieve less catch-up growth and have lower ultimate height Z-scores than females [36]. Gupta et al. subsequently reported that mean bone age Z-scores were lower in females, perhaps providing an opportunity for greater catch-up growth for females, once they are in remission [37]. To determine if some of the newer therapies in use for CD lead to improvements in growth and normal advancement in puberty, Pfefferkorn et al. analyzed growth outcomes in children with newly diagnosed CD [38]. They found that despite improvements in disease activity, mean height SDS scores did not change significantly, and pubertal progression remained slow. Children diagnosed with CD prior to 9 years of age had a higher mean growth velocity 2 years after diagnosis, as compared to children diagnosed after 9 years of age. Children who required prolonged corticosteroid therapy (longer than 6 months) had poorer growth outcomes. These data suggest that despite advances in nutritional and anti-inflammatory therapies for CD, growth and pubertal delays continue to persist in these children with CD.

In contrast, a study by Malik et al. suggested that children who had a clinical response to infliximab therapy had improvement in their linear growth that was independent of their pubertal progression [39]. In addition, children who had not been exposed to exogenous glucocorticoids also exhibited better growth with infliximab therapy, suggesting that the effect on growth was not simply related to a decrease in glucocorticoid use. In a more recent study, Mason et al. followed 63 adolescents with IBD (CD, n = 45 [23 males] and UC, n = 18 [12 males]), median age 13.4 years (range 10–16.6 years) over 12 months [40]. Interestingly, they reported no significant delay in puberty in their subjects. However, attenuation of the pubertal growth spurt was evident in these subjects. In the adolescents with IBD, the median IGF-1 SDS score was lower and IGFBP-3 higher than the control group, suggesting an abnormality of IGF-1 bioavailability.

Pubertal Arrest

Pubertal delay in IBD can have many etiologies, and poor nutritional status is often thought to be the major cause, as optimal nutrition is necessary for the initiation and maintenance of reproductive function. GnRH secretion is blunted in the malnourished state which leads to pubertal arrest, and secretion of GnRH normalizes with weight gain [41]. However, the delay of puberty in IBD presents a more complex issue, with weight not the sole independent variable. Stress and inflammation likely also have important roles. In addition to delays in the onset of puberty, slowing or cessation of sexual maturation may occur in patients with IBD. For example, secondary amenorrhea is a well-recognized complication of weight loss.

Potential Causes of Pubertal Delay in Patients with IBD

The complex interactions between severity of disease, fluctuations in inflammatory cytokines, and their effect on nutritional status and hormonal profile make it difficult to determine how individual factors influence the onset and progression of puberty in pediatric patients with IBD. As a

consequence, while nutritional deficits are well described in patients, other aspects such as the potential role of inflammatory cytokines on puberty are often extrapolated from animal models [42].

Nutritional Causes of Pubertal Delay

In otherwise healthy children, undernutrition may cause a delay in sexual maturation and menarche. Important studies done by Frisch and colleagues demonstrated that the age of pubertal growth and menarche in girls correlated more closely to weight than to chronological age [43–45]. During the adolescent growth spurt prior to menarche, girls had a continuous decline in the percent body water and increase in body fat, resulting in a change in the ratio of lean body weight from 5:1 to 3:1 and a mean percent body fat at menarche of 22% [43–45]. The investigators noted that the mean weight at menarche in girls in the United States was 47.8 ± 0.5 kg [43–45]. A possible relationship between body fat and menarche was suggested by adipose tissue being a significant extragonadal site of estrogen production through conversion of androgen into estrogen. She postulated that the decrease in age at menarche (approximately 3–4 months each decade over the past 100 years) is due to girls reaching the "critical" weight earlier, secondary to improved nutrition. In girls with primary amenorrhea due to undernutrition, a minimal equivalent of 17% body fat may be necessary for menarche to occur [43–45]. For girls experiencing secondary amenorrhea, resumption of menses usually occurred when weight gain was 10% higher than the weight at menarche.

Dreizen et al. compared the age at menarche of 30 girls with "chronic undernutrition" with 30 "well-nourished" girls living in north central Alabama [46]. The average age at menarche was 14.5 years in the former group and 12.4 years in the latter group. Interestingly, standing heights that had differed by 9.2 cm at 12.5 years decreased to a difference of only 3.5 cm at 14.5 years and were not significantly different (1.1 cm) at 17 years. Similarly, skeletal age was delayed in the undernourished group, but at the time of menarche, the bone age in the undernourished girls was only 3.8 months more advanced than the well-nourished group. Complete fusion of the epiphyses was delayed in the malnourished group to 17.6 years versus 15.9 years for healthy controls. Therefore, although the timing of the adolescent growth spurt was delayed by undernutrition, final height (in the absence of underlying disease) was not significantly reduced. An earlier study by the same authors in undernourished boys also showed delayed epiphyseal fusion to 18.7 years versus 17.0 years and a mean difference in height between the groups of 2.68 inches at 16 years [47]. Unfortunately, final adult heights were not reported.

Similar delays in menarche (with onset averaging 15.1 ± 0.5 years) are seen in ballet dancers, swimmers, and runners whose training and low calorie intakes begin prior to menarche [44, 45]. Frisch postulated that these females have a raised lean/fat ratio. Both increased nutrition and reduction in the intensity of training may restore menses. Athletic amenorrhea is a hypothalamic reversion to a more immature pattern in GnRH response. Normalization may occur with reduction in exercise and/or other stress without the weight change estimated by Frisch.

Reduction in calorie intake has been documented in many studies of pediatric-onset IBD, especially CD [48–50]. Thus, undernutrition is likely to be one of the contributing factors leading to delay in the onset and progression of puberty. Similarly, secondary amenorrhea seen in female patients with IBD may be caused by weight loss, a frequent complication of IBD in adolescents.

Sentongo et al. used dual energy x-ray absorptiometry (DEXA) and anthropometric measures to compare fat mass (FM) and fat-free mass (FFM) in 132 pediatric patients with IBD and 66 healthy controls [33]. They found that patients had normal fat stores but reduced FFM, consistent with "inflammatory cachexia" [33]. They cited data suggesting that proinflammatory muscle-active cytokines may impair accretion of lean tissue.

Burnham et al. compared 104 North American patients with CD to 233 healthy control subjects and documented delayed sexual maturation in the CD group [51]. Patients within Tanner stages II–IV averaged 1.4–1.5 years older than control subjects at the same pubertal stages. Lean mass was reduced by 8% in the patient CD group. It is the opinion of the authors that the role of undernutrition in both growth failure and sexual maturation may be underestimated if these complications are compared only with documented weight loss. Failure to gain weight (without a history of weight loss) may also adversely affect the timing of menarche and the progression of puberty.

Advancement in puberty may also be related to excess weight gain [12, 52]. Early adrenarche appears to be related to excess weight gain and may be accompanied by skeletal advancement and possibly earlier true puberty. This may be related to peripheral aromatization of adrenal androgens to estrogens in fat.

Endocrine Aspects of Pubertal Delay

Most studies of endocrine function in children and adolescents with IBD have been performed to investigate the causes of growth failure rather than the onset and progression of puberty [48–50, 53–57]. An intact growth hormone/insulin-like growth factor I (IGF-I) axis is necessary for normal postnatal growth. Thyroid hormone and cortisol are also

important, as are the sex steroids at the time of puberty. IGF-I is produced in the liver under the stimulation of GH, and is thought to be the key mediator of the growth-promoting effects of GH. Reports in growth-impaired patients with IBD have generally demonstrated normal GH secretion, thyroid function, cortisol response to hypoglycemia, and gonadotropin response to GnRH. What changes were observed such as reduced amplitude of the GH pulse or increase in reverse triiodothyronine (rT3) were not associated with reduced growth velocity [55]. We observed that weight loss could be associated with prepubertal levels of circulating sex hormones despite previous physical signs of pubertal progression [56]. IGF-1 levels have been shown to be reduced in children and adolescents with IBD [42, 56, 58, 59]. This usually occurs despite the presence of adequate circulating levels of GH and is known as "growth hormone resistance." Since IGF-1 is modulated by both GH and nutritional status, it is not clear whether the reduction of IGF-1 seen in this population is secondary to active disease or to the decrease in calorie intake (or both) [42, 56]. An increase in IGF-1 occurs following nutritional restitution in children with IBD. Some have suggested that the IGF-1 rise following enteral nutrition or surgical resection in children with active IBD precedes improvement in nutritional status (based on anthropometric measures); however, more rapid indices of nutritional restitution such as prealbumin were not measured in those studies. Corkins et al. noted the major binding protein for IGF-1 (IGFBP-3) was also reduced at diagnosis in children with IBD which would result in a reduced half-life for circulating IGF-1 [58]. Evidence using a knockout mouse lacking only liver-derived IGF-1 demonstrated normal growth and development, suggesting an important role for paracrine or autocrine production of IGF-1 by nonhepatic tissues [60]. The use of IGF-1 as a potential therapeutic agent to enhance growth in childhood IBD is hampered by concerns regarding a potential increased risk for colon cancer and other malignancies in this population [61].

In a trinitrobenzene sulfonate (TNBS) model of experimental colitis in rats, Azooz et al. noted that puberty was delayed but plasma concentrations of gonadotropins were similar to healthy controls [62]. Interestingly, delayed puberty and reduced levels of plasma testosterone and 17β-estriol levels were present in both colitic and noncolitic pair-fed rats, compared to healthy controls, emphasizing the importance of caloric sufficiency. However, the frequency of delayed puberty was less in the food-restricted rats (28%) versus the colitis rats (57%), suggesting an independent role for inflammation in this process. The authors demonstrated that the administration of testosterone subcutaneously on a daily basis to the colitis rats normalized the onset of puberty. Similar results were recently reported by DeBoer and colleagues comparing pubertal progression in dextran sodium sulfate (DSS) induced colitis, food-restricted mice, and free-feeding control mice. Pubertal progression in male mice was measured by separation of the prepuce from the glans penis and in female mice by the timing of the vaginal opening. For both sexes, puberty was more delayed in the colitis model than the food-restricted animals, despite similar leptin levels [63, 64].

Proinflammatory Cytokines–Endocrine Interactions

Several in vitro studies have elucidated ways in which proinflammatory cytokines (such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1 β)), elevated in patients with IBD, affect endocrine function. Elevations of these cytokines have been shown to lead to altered gonadal function and reduced sex steroid synthesis [65]. Several of these findings may be applicable to explaining pubertal delay in patients with chronic inflammatory bowel disease.

TNF-α has inhibitory effects on GH and sex hormone function. Transgenic mice overexpressing TNF-α (or IL-6) are growth-impaired and have low IGF-1 levels despite normal GH because of inhibition of GH signaling within hepatocytes [66]. Denson et al. showed that TNF-α suppressed GH receptor expression by inhibiting Sp1/Sp3 transactivators [67]. IL-6 inhibits hepatic GH signaling by inducing a suppressor of cytokine-inducible signaling (SOCS-3) and reduces the half-life of IGF-1 by increasing the catabolism of its binding protein, IGFBP-3. TNF-α and IL-6 also reduce IGF-1 action by inhibiting insulin receptor substrate 1 which influences IGF-1 binding to its receptors and interleukin-1β (IL-1 β). TNF-α and IL-1β have also been shown to induce anorexia. It has been suggested that GH therapy may overcome hepatic GH resistance induced by IL-6 [68].

TNF-α has also been shown to decrease androgen receptor protein as well as dihydrotestosterone activation. TNF-α, IL-6, and IL-1 β reduce testosterone synthesis in Leydig cells and steroidogenesis in cells in the ovary. DeBoer et al. recently reported partial normalization of puberty in female mice with dextran sodium sulfate (DSS) colitis treated with anti-TNF-α, when compared to a placebo-treated group. The authors utilized the day of life of the vaginal opening as the validated measure of puberty in female mice: day 30 in controls, day 31 in DSS colitis with anti-TNF-α, and day 33 or later in DSS and placebo. The DSS colitis mice controls and those treated with anti-TNF-α maintained similar weights throughout the study, but the DSS–placebo mice had higher IL-6 levels [69].

Psychosocial Issues and Puberty

There is extensive literature describing dynamic changes in the psychosocial interests and concerns of adolescents. Shafer and Irwin addressed these issues and emphasized how

they develop and are different among adolescents during early adolescence (ages 10–13 years), middle adolescence (ages 14–16 years), and late adolescence (ages 17–21 years) [13]. Nottelmann et al. studied the relationship between adolescent psychosocial adjustment and chronological age, pubertal status, and serum hormone levels [70]. In boys, adjustment problems were associated with low sex hormones or lower pubertal stage in conjunction with higher chronological age. These included sadness/anxiety and problems with body and self-image. In girls, adjustment problems in social relationships were also associated with lower pubertal stage and higher age. Both groups had elevated levels of androstenedione, an adrenal hormone responsive to stress, which the authors suggested may be due to self-comparison with same-age peers. They speculated that boys may be more sensitive to hormonal influences and girls to environmental influences.

Delayed sexual maturation may have significant adverse effects on self-esteem and socialization, as the child with delayed puberty looks younger than their chronological age, and often are treated as such [71]. Thus, an adolescent with IBD must cope not only with the impact of having a chronic disease, but also with the psychological issues of delayed puberty.

In addition to the psychological response to pubertal delay, stress itself may interfere with the functioning of the brain–pituitary–gonadal axis. Evidence suggests that this may be mediated by elevated cortisol levels over a protracted period of time. Consten et al. noted that cortisol administration to male carp caused delayed testicular development, reduced testosterone levels, and impaired maturation of pituitary gonadotrophs [72].

Therapeutic Approach to Addressing Pubertal Issues in IBD

The observations and studies described above suggest that prolonged control of active inflammation and providing adequate nutrient intake are both essential in promoting normal puberty. Alperstein et al. reported that it took 2.5–10 years for five of nine children with growth delay who were in Tanner stage I to attain their pre-illness height percentile following surgery [73]. Thus, optimal control of IBD and optimization of nutritional status are paramount in adolescents with IBD and delayed puberty.

Although experience with GH treatment in pediatric patients with IBD is limited, improvement of growth velocity may be observed when there is reasonable disease control with reduced corticosteroid exposure. Furthermore, steroid-related growth effects may be in part ameliorated with GH treatment [74–76]. In one recent study, a trend was observed that improved growth velocity was greater in Tanner stage I and II patients who received GH as compared to those who were in the later stages of puberty [76].

Often, final height preservation is at odds with the child's desire to proceed through puberty. Artificial induction of puberty with estrogen or testosterone runs the risk of skeletal advancement without commensurate growth. An anabolic steroid such as oxandrolone (Anavar®), which does not advance bone maturation as much as testosterone in modest dose, might be of some small value. Mason et al. described a retrospective study of eight boys with IBD (seven of whom were prepubertal at 13.6–15.6 years of age) who received testosterone therapy for pubertal induction [77]. Testosterone dose and route of administration were either monthly injections of testosterone enanthate 50 mg (five patients) or transdermal testosterone patch 2.5 mg daily (two patients) or 5.0 mg daily (one patient). Following 6 months of treatment, seven out of eight boys progressed in puberty to Tanner stage II–IV, and the median height velocity increased from 1.6 to 6.9 cm/year. There was a significant correlation between C-reactive protein levels and height velocity.

Ballinger et al. describe their approach to "young patients with IBD" as including a 3 to 6 month course of 100–125 mg/month of intramuscular testosterone ester (enanthate or cypionate) in boys and ethynyl estradiol 4–6 mcg/day orally for the same length of time in girls [78]. Our current therapy for pubertal induction in selected male patients with delayed puberty consists of a 6-month course of 50 mg/m^2 intramuscular testosterone ester. For girls with either functional gonadotropin deficiency or constitutional delay of puberty, it is reasonable to offer a 6-month course of either a low dose of IM depot estradiol (0.2–0.4 mg monthly), or a low dose estrogen patch (applying a 25 mcg patch twice weekly for 1 week out of the month) for pubertal induction. As opposed to boys, there are few studies that report the outcome of a brief exposure to sex steroid therapy for girls with delayed puberty. The response to this approach in pediatric patients with IBD has not been studied.

The relationship between puberty and its effects on bone density in children with IBD has not been addressed in this chapter as the topic is discussed in depth elsewhere in this text. Although pubertal delay has been associated with reduced BMD in adult men, its impact on peak bone mass in pediatric patients with IBD has not been determined [79, 80]. Bernstein et al. compared BMD T scores of the lumbar spine, femoral neck, total hip, and total body in a series of 70 adult women with IBD, who were <45 years of age. They observed no significant differences between 12 patients with disease onset before puberty compared with 58 whose disease was diagnosed after puberty [81]. More long-range data is needed on the relationship between pubertal delay and bone mineralization in adulthood.

For the reasons stated above, assessment of pubertal staging should be an integral part of the monitoring of pediatric

patients with inflammatory bowel disease. Referral to a pediatric endocrinologist should be considered in boys who have reached 14 years and girls who have reached 13 years without evidence of any physical changes of puberty. Patients who are delayed in puberty, but showing evidence of pubertal progression on physical examination, need not be referred, unless the puberty appears to stall.

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