Mini-Review

An Approach to the Evaluation and Management of the Obese Child With Early Puberty

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Abbreviations: BA, bone age; BMI, body mass index; CNS, central nervous system; CPP, central precocious puberty; DHEAS, dehydroepiandrosterone sulfate; GnRH, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone analogue; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone; MPH, mid-parental height; MRI, magnetic resonance imaging; PAH, predicted adult height; SDS, standard deviation score.

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Abstract

With the declining age at onset of puberty and increasing prevalence of childhood obesity, early breast development in young obese girls has become a more frequent occurrence. Here, we examine available literature to answer a series of questions regarding how obesity impacts the evaluation and management of precocious puberty. We focus on girls as the literature is more robust, but include boys where literature permits.

Suggestions include: (1) Age cutoffs for evaluation of precocious puberty should not differ substantially from those used for nonobese children. Obese girls with confirmed thelarche should be evaluated for gonadotropin-dependent, central precocious puberty (CPP) to determine if further investigation or treatment is warranted. (2) Basal luteinizing hormone (LH) levels remain a recommended first-line test. However, if stimulation testing is utilized, there is a theoretical possibility that the lower peak LH responses seen in obesity could lead to a false negative result. (3) Advanced bone age (BA) is common among obese girls even without early puberty; hence its diagnostic utility is limited. (4) Obesity does not eliminate the need for magnetic resonance imaging in girls with true CPP. Age and clinical features should determine who warrants neuroimaging. (5) BA can be used to predict adult height in obese girls with CPP to inform counseling around treatment. (6) Use of gonadotropin-releasing hormone analogues (GnRHa) leads to increased adult height in obese girls. (7) Obesity should not limit GnRHa use as these agents do not worsen weight status in obese girls with CPP.

Key Words: precocious puberty, overweight, obesity, BMI, gonadotropin-releasing hormone analogues
Traditionally, the onset of secondary sexual characteristics prior to age 8 years in girls and 9 years in boys has been considered precocious. However, data over the past 50 years indicate that puberty is occurring at younger ages than previously. This shift is greater in girls, as the age of onset of breast development (thelarche) has shown the most pronounced decline [1-7], leading some to recommend lowering the cutoff for precocity to 7 years in girls [2]. While most girls referred for suspected precocious puberty will represent benign variants of normal growth and physical development, the proportion who prove to have true, gonadotropin-releasing hormone (GnRH)-dependent central puberty is not insignificant (up to 20% in some reports [8]), with underlying disorders identified in up to 18% of cases [9-11]. Thus, controversy remains around what ages should be used as cutoffs for diagnostic evaluations among children with early development of secondary sexual characteristics.

A significant rise in the prevalence of pediatric obesity has paralleled the decreasing age of pubertal onset, and multiple studies have demonstrated that overweight and obesity are associated with earlier timing of puberty in girls [10, 12-18]. Data are less consistent for boys, implying the relationship between adiposity and pubertal timing may be more complex in males, where the overall effects are not as large. Still, the preponderance of studies in boys do support that earlier pubertal timing is associated with increased indices of adiposity [19-24]. The mechanistic link between overweight and obesity and early puberty is not fully understood, but elevated levels of leptin [25-28] and adipokines [29] have been suggested to play a role. So too have insulin resistance leading to increased adrenal androgen production and increased aromatase activity in adipose tissue leading to peripheral conversion of androgens to estrogen [30-32]. Through these or other mechanisms, increased adiposity could contribute to GnRH-dependent but idiopathic central precocious puberty (CPP) and to isolated early development of androgen and/or estrogen-mediated secondary sexual characteristics.

The effects of overweight and obesity on pubertal development raise the question of how weight status affects evaluation and management of children with early signs of puberty. The general approach to children with early development of secondary sexual characteristics has been reviewed recently [33-35]. The differential diagnosis of early secondary sexual characteristics includes peripheral precocities (such as congenital adrenal hyperplasia, McCune Albright syndrome, and ovarian tumors), benign variants (such as premature thelarche and adrenarche), environmental exposures (such as lavender or tea tree oil), and true, progressive CPP. Depending on the clinical features, all these entities may need to be considered during evaluation, especially if progression is rapid or development is contrasexual [33-35]. In this review, we specifically focus on our approach to the overweight or obese child whose presentation raises concern for CPP, with suggestions summarized in Fig. 1. We address the following questions, as they pertain to the most common scenario—a young girl presenting with early breast development:

Does obesity:

1. Affect age cutoffs for the initial evaluation of such patients?
2. Affect results of diagnostic testing?
3. Affect criteria for evaluation with magnetic resonance imaging (MRI) in the case of true CPP?
4. Impact consideration of GnRH analogue (GnRHa) therapy?
5. Worsen due to GnRHa therapy?

We close with discussion of areas of uncertainty, including whether responses to these questions differ for boys.

**Methods**

Medline, Embase, and Cochrane databases were searched using the following MeSH terms: precocious puberty AND (overweight or obese or obesity). Search limits included publications from January 1, 2000, to May 21, 2021, and English language. The initial search resulted in 345 publications. Redundant or irrelevant material was eliminated, as were articles focusing primarily on other forms of sexual precocity, such as premature adrenarche. Additional references were identified from the reference lists of the selected articles.

The terms overweight and obesity are defined in most of the cited literature as body mass index (BMI) between the 85th and 94th percentiles and ≥ 95th percentiles, respectively, although not all articles adhered to these distinctions. Moreover, available literature does not support different conclusions for these 2 categories in girls. Thus, for simplicity, from here on in this review, the term obesity is used to refer to BMI ≥ 85th percentile.

**Questions Addressed and Suggestions**

How Does Obesity Affect Age Cutoffs for the Evaluation of the Young Girl with Early Breast Development?

In the general approach to evaluating a girl with early breast development, the main goal is to differentiate true GnRH-dependent CPP from benign variants, such as premature thelarche. Progressive CPP can lead to early onset of menses and reduced adult height, and more importantly,
it may be a sign of an undiagnosed underlying hypothalamic/pituitary lesion. Therefore, initial evaluation is aimed at identifying those girls who warrant further investigations (such as brain imaging) and pubertal suppression with GnRH analogues (for height preservation and psychosocial concerns) [15, 16, 34-37].
Several studies have demonstrated that age of breast development is strongly associated with body weight [1, 14-17, 37, 38]. The Pediatric Research in Office Settings (PROS) study was one of the first large studies to show that breast development was occurring at younger ages than the previously used norms, and that younger age of development was correlated with higher BMI Z-scores [1]. Subsequent studies using both inspection and palpation to minimize any impact of lipomastia have yielded similar results and demonstrated a progressive relationship between increased BMI and earlier breast development. In fact, elevated BMI has been reported as the strongest predictor of earlier age of thelarche [14, 17, 37].

However, this weight-related decrease in age of breast development is not always associated with evidence of early “true” central puberty. Akssglaede et al compared pubertal development in cohorts of girls from 1991 and 2008. Although mean age of thelarche had declined by a full year in the 2006-2008 cohort, population-based gonadotropin levels had not changed significantly, suggesting that earlier breast development was not necessarily associated with earlier activation of the hypothalamic-pituitary-gonadal (HPG) axis [5]. This lack of uniform HPG axis activation may explain, in part, why the average age of breast development has decreased more substantially than the average age of menarche in recent population studies [5, 39, 40].

On the other hand, although less marked, there is a correlation between increasing BMI and declining age of menarche, suggesting that obesity is not only a risk factor for early breast development, but also early central puberty in some cases [39-43]. Those obese girls with early breast development who have initiated true puberty may be at risk of early menarche and compromised adult height. Confirming HPG activation in these cases will inform the counseling and anticipatory guidance provided to the patient and family/caregiver regarding likely progression of pubertal development and allow for consideration of treatment. Furthermore, given the lack of data demonstrating that obesity is an independent predictor of normal central nervous system (CNS) imaging in those with CPP (see “Does Obesity Affect Age Cutoffs for Evaluation With MRI in the Case of CPP?” below), it seems prudent to identify those girls with HPG axis activation so they can be assessed for pathologic/neurogenic causes if warranted.

**Suggestion.** Age cutoffs for the evaluation of the obese girl with early breast development should not differ substantially from the nonobese girl. These girls should have a complete history and physical examination. If needed, palpation should be carefully performed to distinguish between lipomastia and true breast tissue. Presence of firm glandular tissue under the areolae (Tanner stage 2) or extending beyond (Tanner stage 3+), best palpated with the patient in the supine position indicates thelarche [9]. For those with confirmed thelarche, we recommend evaluation include assessment of the HPG axis to identify those with CPP.

**Does Obesity Affect Results of Diagnostic Testing When Performed?**

**Gonadotropins**

GnRH-dependent central precocious puberty is distinguished from other causes of precocity by pubertal levels of LH. A basal LH value of ≥ 0.3 mIU/L is commonly used to diagnose CPP (although cutoff is specific to local assay) and obviates the need for GnRH stimulation testing. Baseline LH levels, however, do lack sensitivity below these thresholds and do not definitively rule out CPP [44-47]. Therefore, GnRH stimulation testing can be performed if clinical presentation/progression continues to suggest CPP. Following administration of GnRH or a GnRHα, a peak LH level outside the normal range for the assay (> 5.0 mIU/L for most assays) indicates an activated HPG axis [36, 48, 49].

Given that our goal is to identify those obese children with HPG axis activation, we must consider whether obesity affects the results of diagnostic testing. This question has been addressed in children indirectly through physiologic studies of the effects of BMI on LH levels. For example, Bordini et al compared sleep-related LH levels in prepubertal and pubertal girls with and without obesity and noted that obese pubertal girls had a significantly blunted sleep-related LH rise compared with nonobese girls, including some profiles that overlapped with those of prepubertal girls [50]. Another study showed reduced LH pulse frequency during overnight sampling in prepubertal and early pubertal (Tanner stage 2) obese girls; however, the pulse frequency normalized by Tanner stage 3 [51]. These data are interesting and speak to how obesity may influence the HPG axis.

However, these concepts have shown variable translation to clinical studies of early puberty. The available data show that basal, nonstimulated LH values do not differ between obese and nonobese girls with CPP [52-54]; however, other studies have shown that responses to GnRH stimulation testing may be impacted by BMI, with obese girls having significantly lower LH peaks and LH/FSH (follicle-stimulating hormone) ratios than nonobese girls [53-55]. This observation, again, seems to only apply during early stages of puberty (Tanner 2-3), as LH levels after GnRH stimulation in Tanner stage 4-5 showed no correlation with BMI [52, 55]. These clinical studies, therefore, raise the possibility of false negative GnRH stimulation tests and missed diagnoses of CPP in obese girls. We note,
though, that this possibility is only theoretical, as all girls in these studies who had been diagnosed clinically with CPP also already had stimulated LH values above assay cutoffs for diagnosis of CPP.

**Suggestion.** Basal LH values remain an effective first-line test for identification of CPP, followed by stimulation testing when warranted. Obesity is associated with lower peak LH responses to GnRH stimulation testing in early puberty. This effect could theoretically lead to false negative tests; thus, it is important to continue to consider CPP if other clinical features are consistent with this diagnosis.

### Bone age

Advanced skeletal maturation is among the clinical features used to diagnose CPP, and significant bone age (BA) advancement is typically more suspicious for true CPP than benign entities such as premature thelarche or slowly progressive/intermittent CPP [34, 35]. However, advanced BA, along with increased growth velocity, is often observed among obese children even without early puberty, potentially confounding diagnostic/discriminatory utility [9, 36].

Studies have shown a strong correlation between BA standard deviation score (SDS) and BMI SDS even at young ages within the general population [56-58]. In a study of 167 children (age 3-18 years), those with obesity had more advanced BA compared with those without obesity. BA was advanced more than 2 years in 33% of obese children compared with only 1% of nonobese children [57]. Another study also observed the effect of obesity on BA advancement, specifically among preschool children (age 3-6 years) [59].

In the assessment of children with early puberty, significantly (> 2 years) advanced BA typically favors CPP over benign variants, although such advancement can occasionally be seen in girls with both isolated premature thelarche [60] and premature adrenarche [61, 62]. In these benign variants, as in the population studies discussed above, higher BMI Z-scores are associated with more advanced BA [60-62]. Thus, perhaps not surprisingly, obesity not only blurs the distinction between bone ages seen among prepubertal vs pubertal children, but it can also confound the distinction of CPP from benign variants of early development.

**Suggestion.** Advanced BA is common in obese girls and should be used with caution to distinguish CPP from other forms of sexual precocity.

### Does Obesity Affect Age Cutoffs for Evaluation With MRI in the Case of CPP?

Although most cases of CPP in girls will be idiopathic, the differential diagnosis does include potentially serious and treatable CNS lesions. In a systematic review and meta-analysis, the prevalence of abnormal MRI findings within the overall CPP population was 9% for girls younger than 8 years, with the prevalence in individual studies ranging from 0% to 27% [8, 11, 63-65]. When stratifying based on age, prevalence was much higher for the girls younger than 6 years compared with those aged 6 to 8 years (19%-25% vs 2%-11%) [66-68]. Indeed, younger age is the strongest predictor of CNS pathology, and MRI is routinely recommended in all girls younger than 6 years [69, 70]. The benefit of neuroimaging in girls with CPP older than 6 years of age remains controversial, with some studies in support [11, 67, 71] and other studies against routine MRI [63, 65, 70, 72, 73].

Chalumeau et al aimed to identify clinical features that could predict CNS abnormalities and the need for MRI among a group of 197 children, 11 (5.6%) of whom had CNS findings. Using a BMI Z-score cutoff of > 0.5, they found no significant association (positive or negative) between BMI and risk of CNS abnormalities [68]. Although the number of individuals with CNS findings in this study was small, similar studies have also found no difference in BMI SDS between girls with CPP and normal vs abnormal imaging [67, 71, 74]. In fact, none of these studies identified any strong clinical or biochemical predictors of CNS abnormalities and therefore continued to recommend routine imaging in girls younger than 8 years. It has been suggested that obesity is a strong enough basis for early puberty that MRI can be deferred [9], but data from the above studies indicate that presence of obesity does not fully mitigate the risk of underlying pathology when the early puberty is secondary to true CPP.

**Suggestion.** MRI should be performed for all girls younger than 6 years with CPP, regardless of weight status. For girls aged 6 to 8 years, decision around MRI should be individualized and based on the same factors as in children without obesity, such as medical history, racial/ethnic population group, family history of pubertal timing and neurologic risk factors.

### How Does Obesity Impact Consideration of GnRHa Therapy?

#### Bone age and prediction of adult height outcomes

As discussed above, BA may have limited discriminatory value in the diagnosis of CPP in obese girls; however, it remains an important tool for predicting height outcomes, which may impact counseling and treatment decisions [9, 36]. BA advancement can be significant in obese girls, which raises concern around the possibility of compromised adult height [60, 61]. However, differences in prepubertal growth between obese and nonobese children may mitigate this risk. Studies show that although children with obesity early
on in life already show BA advancement, this is often associated with early growth acceleration and tall stature for chronological age. This increased height gain in childhood is then followed by earlier slowing of linear growth—a pattern that results in adult height approximating calculated mid-parental height (MPH) [38, 75-78].

In the setting of CPP and early puberty, some [79, 80] but not all [81-84] studies have reported that obese girls display more exaggerated BA advancement compared with nonobese girls. In one study by Park et al, in which BA was similarly advanced (2 years) in obese and nonobese girls, predicted adult height (PAH) was significantly lower than MPH in the nonobese group, while PAH and MPH were not significantly different in the obese group. This suggests that not all BA advancement in obese girls will lead to compromised predicted height, again, likely due to the differences in prepubertal growth patterns. Both groups of girls were treated in this study and use of GnRHa was associated with increased PAH at the end of treatment in both the obese and nonobese girls. As studies evaluating height outcomes in obese girls with untreated CPP are lacking, it is not clear what PAH/near adult height the obese girls would have attained without intervention. It is possible that obese girls without concerning PAHs may not warrant therapy. Regardless, this study implies that BA led to accurate prediction of adult height in the obese girls, and that these heights were then increased by GnRHa therapy. Studies are limited, but no data suggest that use of BA for height prediction in obese children is less accurate than in nonobese children. Thus, it is likely that BA may still be used to determine PAH in obese girls and that those with compromised PAH may benefit from consideration of GnRHa therapy.

**Suggestion.** Despite significant BA advancement in obese girls with CPP, PAH may be preserved due to early accelerated growth. BA can be used to predict adult height in obese girls with CPP, and the resulting PAH can be used to inform counseling around GnRHa treatment.

**Effectiveness of GnRHa therapy**

GnRH analogues have been the standard of care in the treatment of CPP since the 1980s [85]. They act by providing a continuous source of GnRH stimulation to the pituitary gonadotrophs leading to their desensitization and subsequent suppression of LH, follicle-stimulating hormone, and sex steroid production. The use of these agents prevents further pubertal development and ideally slows BA advancement, thereby extending the period of growth and preserving/increasing adult height [36, 86].

In our context, it is important to consider if obesity affects the degree of GnRHa-induced pituitary-gonadal suppression and whether GnRHa therapy is as effective in obese as nonobese girls. The answer to the first of these 2 questions appears to be no. Sinthuprasith et al directly compared suppression of gonadotropins during GnRHa treatment among obese and nonobese children and demonstrated that all subjects in both groups displayed mean peak-stimulated LH levels of < 4 IU/L. Similar dosing of either leuprolide or triptorelin was used in obese and nonobese children [87].

In terms of height outcomes, available data indicate that use of GnRHa in obese girls with precocious puberty can slow BA advancement and allow them to achieve adult heights within their expected mid-parental target ranges, as is observed among nonobese girls [82-84, 87, 88]. Kim et al directly compared the effect of GnRHa therapy in obese children (N = 74) with that in nonobese children (N = 108). BA advancement decreased similarly in both groups in response to therapy. Both groups also showed significant improvement in PAH and height SDS for BA while on therapy, attaining near adult heights comparable to their MPH [89]. As noted above, Park et al also found that obese children improved their PAH while on GnRHa therapy and reached near final heights exceeding their MPH [81].

**Suggestion.** GnRH analogues are effective in increasing/preserving adult height in obese children with CPP.

**Does GnRHa Therapy Worsen Obesity?**

The safety and efficacy of GnRH analogues is well-established [36, 86], but the long-term impact on body weight has been the interest of much research. A small number of studies have reported increases [88, 90-93] or decreases [94] in BMI SDS associated with use of GnRHa to treat girls with CPP. However, the majority of studies have shown no significant change [95, 96], or transient increases [81, 87, 97-99] during treatment that decrease after termination of therapy. These studies and others have been reviewed by 2 different writing groups [36, 86] with the overall conclusion being that BMI SDS before treatment and BMI after treatment at near adult height are not significantly different from each other [94, 100-102]; that is, GnRHa therapy is not associated with long-term worsening of obesity among girls with CPP.

It is noted that many girls with CPP are obese at the start of therapy. Thus, even if GnRHa use is not associated with increases in BMI SDS, there is a need for counseling and intervention regarding healthy diet and lifestyle for many children with CPP and their families. Given data indicating that some nonobese girls may also experience a transient increase in BMI SDS with initiation of GnRHa therapy, the need for lifestyle counseling may also be relevant to nonobese children with CPP to help ensure any increases do not persist posttreatment [81, 84, 89, 95, 101-104]. Long-term studies of treated girls with CPP provide reassurance
that treatment is not associated with increased risk of obesity or poor metabolic outcomes [95, 104]. Lazar et al, for example, followed a historical cohort of former CPP girls into the third to fifth decades of life and found that the mean BMI and BMI distribution of both treated and untreated girls with CPP were similar to the normal population [95].

**Suggestion.** Obesity should not be a barrier to GnRHα treatment among girls with CPP.

**Areas of Uncertainty and Future Directions**

For all the questions discussed above, additional direct evidence would allow conclusions and suggestions to be strengthened; the currently available literature leaves room for areas of uncertainty and future study. Perhaps the most pertinent unresolved issue is whether the answers to the questions posed above differ for obese males with CPP. Overall, data do suggest a secular trend toward earlier age of testicular enlargement in boys; however, this effect has not been seen in all studies and its magnitude is smaller than that observed in girls [19-21]. Obesity is likely a contributor to earlier puberty in boys, but here too, the effect is smaller and less consistent than that seen in girls [22-24, 37], with some reports of boys with the highest BMI cohorts even experiencing delayed pubertal onset [19, 105]. Given these data, we would not advocate for changing age cutoffs or initial evaluations for obese compared to nonobese boys with CPP. Data around the other questions posed here are quite limited and demonstrate the need for more research regarding boys with CPP. One paper [106] did assess the effect of obesity on basal and stimulated LH values. As in girls, there was an observed effect in boys, in this case with both basal and stimulated LH values being lower in obese compared with nonobese boys, again, raising the theoretical concern of possible false negative results. Another paper also examined the effect of GnRHa therapy on BMI in boys with CPP and did not note any significant change over the course of therapy [107]. Without more robust data, there is no reason to suggest answers to the questions posed in this review differ for boys compared to girls.

Regarding the mechanism for BA advancement in obesity, dehydroepiandrosterone sulfate (DHEAS) may play a role as higher DHEAS levels are often found in obese children. Increased adrenal androgen production, with subsequent aromatization to estrogens, may be a key driver of bone maturation and as such, a strong predictor of BA advancement [60, 61, 108, 109]. Therefore, some have recommended measuring DHEAS as an additional part of assessment for accelerated growth and BA advancement in obese individuals with early puberty [110]. While this consideration is mechanically interesting, it is unclear how the results would impact clinical care.

Another management-related area for future research is whether weight loss could have a role in slowing the rate of pubertal progression among children with CPP. This possibility has not been addressed directly, but BMI trajectory during childhood appears to influence pubertal timing. In a study of 160 obese prepubertal children followed for 1 year in a lifestyle program, girls who had a BMI reduction were less likely to have pubertal onset within the follow-up period [111]. Another study showed that children whose BMI decreased during childhood achieved peak height velocity at older ages, suggesting later onset of puberty [75]. A corollary to these data is the need for studies designed to assess whether lifestyle interventions and weight management in obese children with CPP could impact progression of puberty once it has started.

Finally, understanding of the genetic regulation of pubertal timing is expanding, both from the perspective of quantitative traits and disease-causing mutations. To date, several monogenic causes of CPP have been identified, resulting in identification of the etiology of an increasing number of cases of previously classified as “idiopathic” [112]. Researchers have investigated the inter-relationship among obesity, CPP, and some of these genetic causes. Obesity has not been shown to be associated (positively or negatively) with MKRN3 mutations, the most common monogenic cause of CPP [113, 114]. However, obesity is a common finding among children with DLK1 mutations [115-118]. Although genetic testing is not currently standard in clinical practice, future research may help establish yield and cost-effectiveness in the workup of CPP, and particularly in the presence of obesity (especially central obesity) and other syndromic features [118].

**Conclusion**

Obese children presenting with early signs of puberty are becoming increasingly common. The mechanistic link between weight and early puberty is not fully understood, but some of these children appear to have full activation of the HPG axis while others do not. We believe available data support identifying those with HPG axis activation (true GnRH-dependent precocious puberty) and thus suggest that evaluation through measurement of LH levels remains an important first step among obese girls with early puberty. For the obese girl with early thelarche who is shown to have CPP, subsequent clinical approach should not deviate significantly from that of a girl without obesity (Fig. 1). Full clinical picture, and not weight status alone, should determine the decision for or against additional investigations, such as neuroimaging. Bone age advancement has less diagnostic value among obese girls with early puberty but can still be used to estimate adult height and to inform
counseling around potential use of GnRHa therapy; such therapy can increase predicted adult height in these children and is not necessarily associated with worsening of long-term weight status. It is noted that early puberty may be what brings the obese child to medical attention and hence such presentations may present an important opportunity for lifestyle counseling.

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Additional Information

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