Long-Term Experience with GnRH Agonist Treatment of Central Precocious Puberty

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Abstract. In the decade that has passed since the introduction of GnRH agonists as investigational and therapeutic agents, much has been learned about their impact in children with central precocious puberty (CPP). This report will review the ongoing experience from a longitudinal study which began 13 years ago as a collaboration among the Massachusetts General Hospital, Boston’s Children’s Hospital, and the University of Virginia Medical Center. Data is reviewed regarding the suppression of pituitary gonadotropin and gonadal sex steroid secretion and regression of puberty clinically during GnRHa administration as well as the patterns of development which ensue once therapy is discontinued. Finally, long-term growth data is summarized, including final height outcomes in the first cohorts of children with CPP who have completed their growth following the reactivation of pubertal gonadal function post-therapy.

Key Words: puberty, precocious puberty, growth, GnRH analogues

Introduction

GnRH agonist-analogues were first reported to be effective in suppressing pituitary-gonadal function in children with central precocious puberty in 1981 (1). However, it is only in recent years that the long-term outcomes regarding final height and reproductive competency after therapy have been documented by several groups from around the world (2-5). During our own ongoing longitudinal studies, some 200 children with early pubertal development have been evaluated, with approximately two-thirds going on to receive GnRH analogue therapy, some for as long as 9 years. More than half of these children have now re-entered puberty following the discontinuation of GnRH analogue administration. This review will address the experience from our longitudinal studies with respect to: suppression of pubertal development during GnRH analogue administration; the reactivation of puberty following the discontinuation of therapy; and the impact of gonadal sex steroid suppression on long-term growth and final height.
Pituitary Gonadotroph Desensitization: Impact on Pubertal Development

Following the discovery and characterization of GnRH, the decade of the 1970s was marked by tremendous advances in our understanding of the physiology of hypothalamic-pituitary regulation as well as in our ability to translate this new information into novel therapeutic approaches. Physiologic studies revealed that hormone secretion from the anterior pituitary occurred in a pulsatile fashion and that the pituitary gonadotroph required intermittent stimulation by GnRH to achieve this physiologic pattern of hormone release (6). Continuous stimulation by GnRH resulted not in high level, ongoing gonadotropin secretion but rather an eventual decline in LH and FSH secretion or desensitization of the pituitary response. On a different front, several laboratories sought to modify the native GnRH decapeptide to create more potent and long-lasting analogues. Employing similar strategies of peptide design, several GnRH agonist analogues were synthesized and subsequently employed in clinical trials (7). It was soon recognized that these GnRH analogues, by virtue of their increased potency and prolonged duration of action were capable of achieving continuous receptor occupancy on the pituitary gonadotrope and thus of inducing pituitary desensitization.

With increased clinical experience with these agents, especially in children with precocious puberty, it became clear that there were important differences among therapeutic regimens of GnRH agonist administration in their ability to induce complete pituitary-gonadal suppression. The potency, dose, and route of administration of the regimen employed must all be considered in designing the appropriate regimen, but more importantly, the impact of that regimen must be monitored in each patient to ensure that the desired degree of suppression has been attained (7,8).

Given that the appropriate consideration is given to issues of potency and pharmacokinetics, the chronic administration of a GnRH agonist results in virtually complete blockade of the reproductive axis at the level of the pituitary (cf. Fig. 1). When this degree of pituitary gonadotropin suppression is achieved, dramatic changes in pubertal development result. The changes in sexual maturation which are induced by suppressing LH, FSH, and estradiol include a return to prepubertal appearances of the uterus and ovaries on ultrasound (9), a halt or regression in breast development (cf. Fig. 2), and the cessation of menses, with the caveat that an initial episode of bleeding may follow the fall in estrogen that comes within the first few weeks of GnRH analogue administration.

Despite consistent suppression of the pituitary-gonadal axis, we and others have shown that adrenarche, as indexed by serum levels of dehydroepiandrosterone-sulfate, progresses during GnRHa administration (10). As shown in Figure 2, the clinical manifestations of this can be dramatic since rising levels of adrenal androgens may result in the new appearance of pubic hair during the same period that breast development undergoes striking regression. We have utilized this ability to block gonadarche selectively to dissect...
the impact of adrenarche in our patients with CPP and have reported a modest but significant impact of adrenarche on the rates of skeletal maturation during GnRHa administration (10). In ongoing studies, the ability to block gonadal steroids selectively allows us to test whether changes in adrenal sex steroid secretion are correlated with the increases in both lean body mass and body fat which accompany normal development in the latter stages of childhood. There are a host of questions which remain to be explored regarding the biologic consequences of adrenarche, many of which are the subject of longitudinal study in our patients in whom gonadal steroids are “clamped” at prepubertal levels.

**Resumption of Puberty following Discontinuation of Therapy**

Following the discontinuation of chronic GnRHa administration, pubertal secretion of LH and FSH is restored. In patients whom we have monitored as outpatients, urinary gonadotropin excretion has increased after years of virtually complete suppression within weeks following the discontinuation of daily GnRHa injections. Evaluations performed six months following the discontinuation of pituitary desensitization have consistently shown a return of pubertal gonadotropin secretion which has been accompanied by increases in gonadal size and serum levels of gonadal sex steroids in both sexes.

In adolescent girls with idiopathic CPP, menarche has followed the discontinuation of GnRHa therapy by approximately one year,
although the range has extended from a few months to more than three years (2,11). Menstrual cycles lengths became increasingly regular and have been associated with higher rates of ovulation as girls were evaluated for longer periods post-menarche. In our follow-up study of girls with CPP following the discontinuation of therapy, ovulatory rates were comparable to those previously documented in adolescent controls whose onset of pubertal development had been normally timed (11,12). While the patient numbers are far smaller, it is important to note that pubertal maturation in the male also appears to proceed normally when GnRHa is discontinued. However, there has been one patient in our study who has failed to resume puberty following GnRHa therapy and his case makes some important points, for his was not a problem with irreversibility of GnRHa-induced suppression. Rather, he had precocious puberty in the setting of an optic tract tumor for which he received a full course of cranial irradiation. In the ensuing years, he developed growth hormone deficiency and his failure to resume puberty almost certainly represents the additional development of GnRH deficiency. While a unique case in our experience, pediatric endocrinologists are likely to encounter such cases as survivors of childhood malignancies, particularly those who have undergone cranial irradiation, present with complicated and disordered patterns of growth and development. Barring these considerations in patients with neurogenic precocious puberty, the completion of pubertal development following the discontinuation of GnRHa therapy in our male patients, like the female patients, appears to be appropriate and in keeping with expectations for normal adolescents.

Thus, the progression through the final stages of pubertal development appears to be normal in patients with CPP evaluated following chronic GnRHa therapy. Nevertheless, ongoing surveillance with respect to eventual fertility, bone density, and other issues must continue to characterize fully the impact of long-term pituitary-gonadal suppression in childhood.

Impact of Gonadal Suppression on Long-term Growth and Final Height

Left untreated, pubertal levels of sex steroids in young children with CPP result in dramatic growth spurts and tall stature in childhood, but premature fusion of the epiphyses shortens the growth period resulting in final height which fall short of genetic expectations. Figure 3, an individual patient's height and height velocity chart, underscores these points as well as demonstrating the impact of suppressing gonadal sex steroids with GnRHa. While growth velocities decrease with the withdrawal of sex steroids, the delay in epiphysial fusion which also accompanies gonadal suppression results in a prolonged period of growth. Thus, predicted final heights have increased in most patients with CPP, averaging 2-3cm for each year of therapy in our study and others (13,14). However, the changes in predicted height have been quite variable among patients. Some patients have gained up to 20cm while others' have exhibited either no change or small decreases in predicted heights during long-term therapy. This variability comes, at least in part, from the wide range of chronological ages and bone ages with which patients have initiated gonadal steroid suppression. In very young patients with precocity, growth rates have returned to and remained in the normal prepubertal range over many years of GnRHa administration while gonadal suppression begun in patients at older CAs and BAs exhibit growth rates that often are well below prepubertal norms (ie. <4cm/year) (15). While worrisome to the clinician/investigator, these slow growth rates are not unexpected in many such patients given their advanced skeletal maturation (eg. girls with TW BA ≥ 13 years). In fact, predicted heights characteristically increase in this group of patients, since sustained, albeit slow, growth exceeds expectations based on bone age. While, patients with
Fig 3. Height and height velocity charts of a girl with CPP treated with GnRHa from chronological age (CA) 4 to 11 years. During gonadal suppression, the rate of skeletal maturation slowed and epiphyseal fusion was delayed which resulted in a prolonged period of growth at prepubertal rates. The result was an increase in predicted height during therapy such that this patient’s adult stature will be appropriate for genetic expectations. The shaded areas represent mean ±2 SD for CA and the box on the righthand y-axis of the Height vs. Age plot represents mean ±2 residual SD for target height.

Circles: Height/Height Velocity vs. CA; Triangles: Height/Height Velocity vs. Bone Age (BA); Squares: Predicted Height vs. CA; Open Symbols: Pre/Post GnRHa; Closed symbols: During GnRHa.

younger bone ages tend to grow at greater rates than older patients despite uniform gonadal suppression in both groups, gains in predicted height in younger patients during GnRHa therapy do not uniformly exceed those of older patients since the rate of bone age advancement, like growth velocity, correlates negatively with age in the absence of sex steroids. It is not unusually for the ratio ∆BA/∆CA to approximate unity if patients begin GnRHa therapy with “prepubertal” BAs. In very young children with CPP, it is likely that the modest changes in predicted height should be viewed relative to the expectation that predictions would have decreased significantly without suppression of pubertal sex steroid secretion.

Children with CPP who begin therapy with “early pubertal” bone ages (eg. girls with TWBA 10-12 years) have exhibited the most variable changes in predicted heights early on. However, these patients often display consistent increases after 1-2 years of therapy and thus typically exceed their pretherapy prediction with long-term therapy (16).

Given these variable patterns of growth and skeletal maturation, long-term longitudinal follow-up has been a necessity to the comprehensive understanding of the impact of GnRHa therapy on growth. In our study and others around the world, data is now being reported about the final height outcomes in CPP.

Mean growth velocities have not changed significantly in the first year following the discontinuation of GnRHa administration,
despite the return of gonadal sex steroid secretion. The lack of a “second” growth spurt may once again be understood if one recalls that the residual growth potential at the relevant BAs (≥13 years in most girls finishing therapy) is quite limited. In some patients, the first year or two post therapy has been associated with a modest fall in the predicted height calculated at the end of treatment. At appears that at least in some settings, the Bayley-Pinneau tables overestimate the residual growth in such patients resuming puberty (4). Thus caution should be exercised when talking with families about height outcomes as their children re-enter puberty.

To date, final heights reported in CPP patients following GnRHa therapy have represented patients who entered therapy at older chronological ages and bone ages and who were therefore likely to show the smallest changes in final height outcomes (3-5). The final heights of a small number of patients with neurogenic CPP, like those of patients with idiopathic precocity described below, significantly exceeded pretherapy predictions (increase of 7cm, n=6 girls). However, their final heights remained more than 2 SD below their genetic targets by virtue of the large deficit resulting from the combination of CPP and their primary diagnoses. Thus, we have looked to our patients with idiopathic CPP to provide us with the most clear insights into the impact of long-term gonadal suppression on growth. In the idiopathic CPP girls now off therapy for a year or longer, measured heights significantly exceed pretherapy predictions by an average of 4cm. In those very close to final height (growth velocity <2cm/year, TWBA=16 years), heights now average 154.1cm vs pretherapy predictions of 150.4cm (p=0.002, n=23). These near final heights remain 1 SD below their genetic targets. On the other hand, girls still growing>2cm/year post-GnRHa are currently projected to exceed their pretherapy prediction by 9cm and attain heights within 0.5SD of their genetic target. The latter group, in whom the impact of therapy resulted in more complete restoration of growth potential, was significantly younger upon starting therapy than those patients whose growth is completed and whose height deficit was only partially erased with therapy. Whether the actual final heights in this younger group now being followed during the return of active puberty will reach current predictions must await ongoing studies.

In addition, a group of patients who began GnRHa therapy at even younger ages is just approaching the discontinuation of treatment at this time. The natural history of CPP would suggest that these patients would exhibit the greatest deficit in adult stature if sex steroid secretion was left unchecked. If their current predictions prove accurate, they also will attain final heights in keeping with their genetic potential. Thus a comprehensive understanding of the impact of long-term gonadal sex steroid suppression on final height across a broad developmental spec-

<table>
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<tr>
<th>Pubertal/Treatment Milestone in CPP Girls</th>
<th>Chron. Age (years)</th>
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<tbody>
<tr>
<td>Thelarche</td>
<td>4 (0-7.5)</td>
</tr>
<tr>
<td>3 mo - 2 years</td>
<td></td>
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<tr>
<td>GnRHa Therapy Initiated</td>
<td>7 (1.5-9.0)</td>
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<tr>
<td>Pituitary-gonadal Suppression Established within 1-4 weeks</td>
<td>11 (9.0-13.0)</td>
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<tr>
<td>GnRHa Therapy Discontinued</td>
<td></td>
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<tr>
<td>2-3 weeks</td>
<td></td>
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<tr>
<td>Pubertal Pituitary-gonadal Function Reactivated</td>
<td></td>
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<tr>
<td>3 mo - 2 years</td>
<td></td>
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<tr>
<td>Menarche Attained</td>
<td>12 (10.5-14.0)</td>
</tr>
<tr>
<td>1 - 4 years depending on bone age</td>
<td></td>
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<tr>
<td>Final Height Attained</td>
<td>13 (12.0-15.0)</td>
</tr>
</tbody>
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Fig 4. Schematic representation of experiences which have grown from use of GnRH agonists in the longitudinal study reported herein. The chronological ages presented approximated the mean ± SD from our studies in CPP girls.
Treatment of Central Precocious Puberty

The variation in final heights correlated with the underlying diagnosis, the duration of therapy, and the age and bone age at which therapy was begun. In addition, as is the case with most if not all growth disorders, there remains a significant correlation with target height even in children with abnormal growth patterns.

**Conclusions**

Figure 4 reviews the experience from our study regarding the ages at which patients started and stopped therapy, achieved menarche, and attained their final heights. To date, most patients with CPP who have completed this “journey” have tended to be those who began GnRHa at older chronological ages and bone ages. It is in this somewhat skewed subset of patients that final height data is available. Those CPP patients who have achieved their final height significantly exceeded the prediction made prior to therapy, but did not reach their genetic target. Even at this stage of our experience with these agents, several important questions remain. Continued follow-up is still required to determine whether or not patients whose puberty is suppressed at earlier stages reach their genetic potential. With their data in hand, we will be better equipped to address additional questions about the use of GnRH agonists in the therapy of growth disorders including, “Will growth hormone in combination with GnRHa provide additional benefit in some patients with CPP?” and “Will suppressing a normally-timed puberty result in increased adult stature in other growth disorders (eg. GH deficiency)?” While preliminary data looks promising, there is not short-cut to the longitudinal studies that are required to address these important issues.

Now that GnRH agonists have been utilized in children for more than a decade, their track record of safety is excellent. Most importantly, resumption of puberty post-therapy appears to be normal. Our data and others regarding the reactivation of puberty, attainment of menarche and ovulatory function have been quite reassuring. Nevertheless, like any early therapeutic experience in children, it will be important to be rigorous in our surveillance of these still-young patients, especially with respect to issues of future fertility. Our work is not done yet!

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