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Treatment of Delayed Puberty and Hypogonadism in Girls

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Abstract. The therapeutic management of female delayed puberty depends more on the objectives than on the underlying cause. We will have to consider the development of sex characteristics, the occurrence of menarche and the promotion of growth. In this paper, we will review how girls with delayed puberty of different etiologies can benefit from the following therapeutic alternatives: follow-up without hormonal therapy; administration of growth hormone, anabolic steroids (e.g. oxandrolone) or estrogens and progestogens, and psychological support.

Introduction

Delayed sexual maturation in girls is defined as the absence of breast development after 13.5 years or primary amenorrhea after 15.5 years of age. The therapeutic attitude depends more on the therapeutic objectives than on the underlying cause. The goals of therapy depend on the clinical manifestations at presentation including the degree of sexual infantilism and the possibly associated short stature [1]. For each patient, we will have to consider the development of sexual characteristics, the occurrence of menarche and the promotion of growth. To attain those objectives, different therapeutic modalities can be used. Table 1 summarizes our current recommendations for each of the objectives considered [1].

In this paper, we will review the relevance of different therapeutic alternatives for delayed puberty: follow-up without hormonal therapy; administration of growth hormone (GH), anabolic steroids (e.g. oxandrolone) or estrogens and progestogens, and psychological support.

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The therapeutic induction of fertility using pulsatile gonadotropin-releasing hormone or gonadotropins will not be discussed. These treatments are not proposed for the initial induction of pubertal development, particularly since other less expensive and more convenient treatments are available for such purposes. However, teenagers with delayed puberty may be concerned by their reproductive capacity and they should be given clear explanations on possible therapies to be used later.

Follow-Up without Hormonal Therapy

In conditions resulting in transient delay of puberty, the elucidation of the underlying disorder will be crucial for an appropriate therapeutic management. In patients with chronic diseases such as severe asthma, cardiopathy, cystic fibrosis, celiac or Crohn's disease, chronic arthritis and malignancies, the treatment of the specific etiology will usually result in spontaneous pubertal development. In these conditions, as in young gymnasts, an impaired nutritional balance can contribute to delayed puberty while the role of nutritional factors may be pre-

Table 1. Symptom-based hormonal therapy in female delayed puberty

Treatment objective	Treatment modality
Sexual development and growth	Year 1: ethinylestradiol 0.05–0.1 µg/kg/day at an appropriate chronological age for psychosocial reasons Year 2: ethinylestradiol 0.1–0.2 µg/kg/day Year 3: 4-week cycle of ethinylestradiol 0.2–0.3 µg/kg/day (day 5–25) + dydrogesterone 10 mg/day (day 15–25) or low-dose combined estrogen-progestin preparation
Growth	Oxandrolone 0.05 (–0.1) mg/kg/day Recombinant GH: for hypopituitarism at 0.07 (–0.1) U/kg/day s.c. for Turner syndrome at 0.15 U/kg/day s.c.
Development of pubic hair	Dehydroepiandrosterone sulfate: not effective 1 or 2% testosterone ointment?
Menarche	Progesterone challenge test (dydrogesterone 10 mg/day or progesterone 200 mg/day for 2 weeks): if positive, cyclic progestin supplementation if negative, sequential association of estradiol (valerate or micronized 2 mg/day, day 5–25) with progestogen (day 15–25) or low-dose oral contraceptive

dominant in conditions like anorexia nervosa. Thus, besides the etiologic therapies, monitoring the dietary intakes can have some place in the management of many of these disorders.

In endocrine disorders such as hypothyroidism or isolated GH deficiency (IGHD), there is an overall delay of maturation including puberty. Replacement thyroxine or GH therapy will subsequently result in onset or resumption of pubertal development. A particularly complex situation is chronic renal failure since impaired growth cannot be or only partially be reversed by the etiologic therapy [2].

Constitutional delay of growth and puberty (CDGP) is the most frequent cause of delayed sexual maturation and growth. Boys seem to complain much more commonly than girls, though we see an increasing number of female patients with this condition. In the management of this situation, we take the following guidelines into consideration. At some time during the initial visit, the patient should be seen alone to allow personal contact. It should be understood how she feels about growth and sexual characteristics, respectively. Each single patient has to be provided with clear explanation about the nonpathological aspect of the 'late-bloomer' situation which can be regarded as an extreme variant of the 'slow-normal' tempo of growth. When a relative has experienced a similar situation, it may be argued that this person has achieved normal adult height and sexual maturity. Also, the possibility of adjuvant therapies has to be mentioned. Based on these informations, the patient can be assisted by the physician in choosing either to wait until a reevaluation some weeks later or to start a therapy after appropriate diagnostic assessment [1, 3]. The therapeutic modalities using estrogens are similar to those proposed for permanent hypogonadism (table 1), although a treatment course of 3–12 months will usually be sufficient. (As far as oxandrolone therapy is concerned, see table 1 and below.)

Administration of Growth Hormone

In CDGP, a transient 'physiological' GH deficiency has been documented, on account of the absent priming of GH secretion by estradiol [4–7]. Increased plasma estradiol concentrations during spontaneous puberty or therapy will result in a normal pubertal pattern of GH secretion with increased amplitude of GH peaks. Based on these findings and other aspects related to convenience and cost effectiveness, we do not recommend the use of GH in the treatment of CDGP.

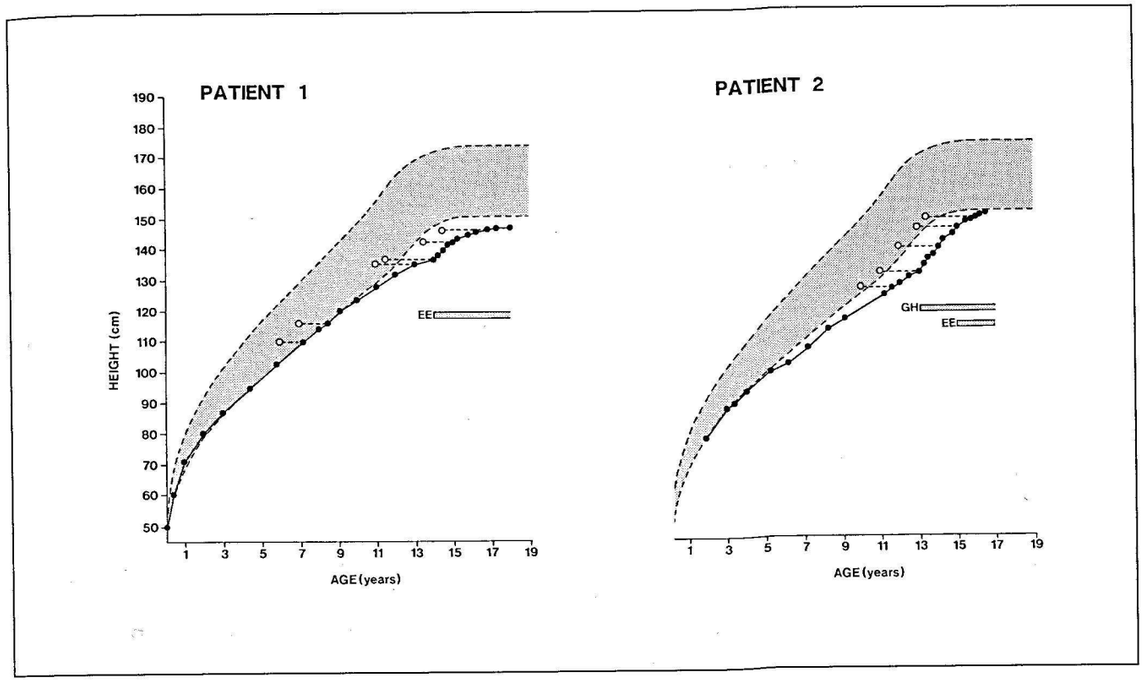

Fig. 1. Growth curves of 2 representative Turner patients. Patient 1 was treated only with ethinylestradiol (EE); patient 2 was treated initially with GH and later with EE (● = height for chronological age; ○ = height for bone age). The shaded area represents the normal growth according to Tanner standards (3rd–97th percentile). Following onset of therapy at 11 years of bone age, GH accounted for a subsequent height gain of 21 cm while it was 12 cm using EE as a single therapy.

In girls with IGHD treated using GH, puberty results in a peak height velocity of normal amplitude as long as puberty starts at an appropriate bone age (11–12 years) [8]. While pubertal development can progress more rapidly in some of these patients [8, 9], the length of pubertal growth seems to be normal in patients entering spontaneous puberty at normal bone age. Since the amplitude of GH pulses increases significantly during puberty, it could be asked whether the doses of GH treatment should be increased during puberty in patients with IGHD. In fact, the growth response of pubertal GH-deficient patients was found to be not related with GH doses ranging from 0.23 to 0.5 U/kg/week given in 3 injections [8–11]. It might be that, using daily GH injection at higher dosages, different data would come up. Presently, we do not recommend to increase GH dosage during puberty in IGHD patients since their pubertal height gain is within normal limits in such therapeutic conditions which are far from physiology. Early initiation of GH therapy is certainly a better way of maximizing final height [12].

In Turner patients, treatment with daily subcutaneous injection of biosynthetic GH, 0.15 U/kg/day, results in a 2-fold increase in height velocity during the first year of therapy [13, 14]. This growth response seems to be obtained during subsequent years as well. The rate of bone maturation does not accelerate unduely during GH therapy. The growth curves of 2 patients with Turner syndrome are shown in figure 1. While estrogen therapy obviously does not promote growth (see below), GH therapy results in an increased growth rate though this treatment was only started by 11 years of bone age in these representative patients. While some Turner patients may show a reduced GH response to provocative tests (on account of the absence of sex steroids), therapy with replacement GH doses does not increase the growth rate [15]. Therefore, GH testing seems to be useless in these patients who should be given

Table 2. Estrogen preparations usable in female delayed puberty

Nature	Origin	Route	Approximate equivalence
17β-Estradiol	synthetic	oral	1 mg/day
Conjugated estrogens	natural (mare urine)	oral	0.3 mg/day
Ethinylestradiol	synthetic	oral	0.01 mg/day
Estradiol esters (valerate, etc.)	synthetic	i.m. (long-acting)	2 mg/month
		oral	1 mg/day
Estradiol	synthetic	percutaneous, transdermal	?

GH at supraphysiological dosages to obtain a significant growth response.

The growth response is inversely correlated with chronological age and bone age at onset of therapy [14]. Thus, when possible, treatment with GH should be started during early childhood in an attempt to have height within normal limits as soon as possible. While we do not know the effect on ultimate stature yet, it is possible that the child would psychologically benefit from early normalization of stature. We have studied the effects of combining low-dose estrogens (25 ng/kg/day) with GH in patients as young as 6 years of age [14]. The purpose was to prime the effect of GH on growth without inducing sexual development. A weak and nonsignificant potentiation of the effects of GH on growth velocity was observed. In addition, breast developed in 9/20 patients as early as 7 years of age, while among patients treated using GH only 3/20 patients showed some breast development. Based on these findings, estrogen therapy is not to be recommended in young prepubertal girls. It is still unclear whether or not combined estrogen and GH therapy could elicit a pubertal growth spurt in Turner patients. Obviously, the appropriate bone age for obtaining such a hypothetical effect is unknown as well. The data of Rosenfeld et al. [13] indicate that there is a synergism between oxandrolone and GH therapy in Turner syndrome. The ultimate assessment of the effect of GH therapy (alone or combined with steroids) will not be possible before final height is attained in the ongoing studies. However, an increase of final height is likely to occur based on the increase in predicted or projected adult height (extrapolated from pretreatment growth curve).

So far, no obvious adverse effects of GH therapy have been reported. Particularly, there is no change in glucose tolerance during therapy, while hyperinsulinism is well documented. We feel very concerned by the possible side effects in the long term. Therefore, we recommend careful follow-up of the patients during and after therapy, within controlled studies rather than on a single basis.

Administration of Anabolic Steroids (e.g. Oxandrolone)

A short course of low-dose oxandrolone can accelerate growth in boys and girls with CDGP [16]. This therapy results usually in a significant acceleration of bone age which accounts for the absence of a promoting effect on final height. It is likely that the growth-promoting effect of oxandrolone takes place at the cartilage level since this nonaromatizable androgenic steroid does not prime GH secretion, in contrast to testosterone and estradiol [17]. The side effects include mild virilization which can be minimized using a dosage of 0.0625 mg/kg/day [13]. Oxandrolone treatment should be primarily considered in girls with CDGP who are much more concerned about their height status than pubertal delay. In Turner syndrome, the combination of GH therapy and oxandrolone has been shown to increase height velocity more efficaciously than GH alone [13] (see above). However, it is still to be determined whether combination therapy will result in a different final height than single GH therapy. In addition, it is possible that both therapies result in a similar final stature requiring a longer period of GH administration using this latter treatment alone. When GH therapy is not available for Turner patients, the use of oxandrolone will result in an obvious acceleration of growth, though there is only a possible minor increase in adult height [18].

Estrogen Therapy

Nature and Forms of Estrogen Therapy, and Side Effects

Estrogens are available as natural or synthetic preparations (table 2). While all the available forms of estrogens are well effective, the choice of a preparation will take into account the possible adverse effects on blood clotting, lipid and carbohydrate metabolism, liver enzymes and blood pressure. There is a great concern about these side effects in patients receiving relatively high dosages such as in contraceptive pills. However, there are few or no data indicating that the low doses used for induction of puberty would result in metabolic disturbances or adverse effects on target tissues. Although such undesirable effects could be potentially greater with oral and purely synthetic forms than with intramuscular or percutaneous forms and natural preparations, this deserves careful studies before selecting an optimal preparation. Also, the effects on bone mineralization in relation to the dosage and the form used are to be studied. After an initial period of continuous therapy, it is important to switch to a cyclic mode of estrogen administration with associated progestogens (table 2). This has been shown to be important to prevent endometrial hyperplasia and the risk of adenocarcinoma.

Impact of Estrogen Dosage on Growth

Estrogens can promote growth through complex mechanisms involving a potentiation of GH secretion and peripheral effects on the production of insulin-like growth factor I and its binding proteins as well as direct cartilage effects [19–21]. In hypopituitary girls, few data on growth during estrogen therapy have been reported [8, 22–25]. These studies were restricted to patients beginning such therapy at late ages. Most informations bearing on the importance of estrogen dose and bone age at onset of therapy have been obtained in Turner syndrome. However, these patients provide a limited model because the absence of pubertal growth spurt may involve some cartilage resistance to growth-promoting therapies. In addition, most studies have reported data on the initial growth response to therapy, while we have few informations on the total pubertal growth spurt and final height in those patients.

Early studies using relatively high estrogen doses did not show any significant effect on final height in Turner patients [26]. A biphasic dose-response relationship between ethinylestradiol and short-term growth of ulna has been reported [27]. During a 6-month therapy, low-dose ethinylestradiol (50–100 ng/kg/day) is able to stimulate growth velocity whereas there is no improvement of growth using higher dosages (400–800 ng/kg/day) [28]. Those studies prompted the use of low dosages such as 100 ng/kg/day. In such condition, Martinez et al. [29] did not find any change in predicted adult height. Thus, we have no evidence that final height of Turner patients can be modulated by estrogen therapy. In fact, differences in age at onset of estrogen therapy may have biased the studies on estrogen dosages [8, 25, 26]. The rate of bone maturation can be accelerated by estrogen, particularly using high doses. This can be of importance to the effects on final height. Using a daily dose of ethinylestradiol ranging from 100 to 400 ng/kg, the ratio of change in bone age to change in chronological age (ΔBA/ΔCA) was 2.92 [30]. A slower progression of bone maturation was observed using a lower dose of 100 ng/kg: ΔBA/ΔCA was 0.92 and 1.65 [28, 29].

Impact of Age at Onset of Estrogen Therapy on Growth

In hypopituitary girls, bone age at onset of puberty has an obvious influence on the response of growth [25]. In patients receiving estrogen therapy started at a mean bone age of 12.3–13.3 years, a minimal total pubertal height gain (6.3, 2 and 5.2 cm) was reported by 3 different groups [8, 23, 24]. In contrast, girls with IGHD treated using similar GH doses showed a greater pubertal height gain (mean: 17.9 cm), which can be explained by an earlier onset of spontaneous puberty (mean bone age: 11.1 years) [8]. In Turner patients with gonadal dysgenesis, the response of growth to estrogen therapy declines with age at the beginning of therapy [25].

In contrast to the effect of age at onset of puberty on pubertal growth, there is no effect on final height. This can be shown after spontaneous as well as induced puberty in hypopituitary girls [8]. Similarly, adult Turner patients with (partial) spontaneous puberty are not taller than girls with gonadal dysgenesis [31]. This, together with the normal adult height of untreated patients with Kallman syndrome [32], suggests that normal gonadal activity is not a prerequisite to the achievement of the full growth potential. In contrast, reduction of adult stature in girls with very early exposure to estrogens is well established [33]. Taking all these observations into account, it seems reasonable to propose to start estrogen therapy earlier than in the past, though the optimal bone age remains to be determined. Also, psychological aspects can play an important role in determining the appropriate age for onset of puberty [25].

Development of Sex Characteristics

During the first year of therapy using low doses of ethinylestradiol (100 ng/kg/day) on a continuous basis, development of breast occurs, a Tanner stage 3 being attained by most patients [28, 34]. A subsequent 2- or 3-fold increase in ethinylestradiol dosage given 3 weeks out of 4 and associated with a progestogen results in periodic menstruations of apparently normal duration and abundancy.

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