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Value of Growth Hormone Treatment in Turner's Syndrome

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Background

Turner's syndrome is an important cause of short stature in girls and primary amenorrhea in young women. First described in 1930 by Otto Ullrich in Germany *(1)* and, subsequently, in 1938 by Henry Turner in the United States *(2)*, it is the most common sex-chromosome abnormality in females, affecting an estimated 3% of all females conceived. However, only 1:1000 embryos with a 45,X karyotype survives to term accounting for about 15% of all spontaneously aborted fetuses *(3)*. Thus the incidence of the loss of all or part of an X chromosome varies from 1:2000 to 1:5000 in liveborn phenotypic females *(3–6)*. In a recent prospective study of 17,038 newborn girls in Aarhus, Denmark, nine karyotypes consistent with Turner's syndrome were detected, for an incidence of 1:1893 live female births *(7)*. There are currently estimated to be from 50,000 to 75,000 girls and women with Turner's syndrome in the United States alone *(8)*.

Endocrine Manifestations of Growth Failure in Turner's Syndrome

Short stature is the only clinical finding invariably associated with the 45,X karyotype; also, it is the only phenotypic abnormality present in virtually 100% of patients *(9)*. Mean adult height of women with Turner's syndrome ranges between 136.7 cm (Japan) and 146.9 cm (Germany) *(10)*.

Many patients with Turner's syndrome are also stocky and have a squarely shaped chest. Affected neonates have congenital lymphedema of the hands and feet, a webbed neck, and a low hairline. Short stature is the single most common physical abnormality in Turner's syndrome and individuals not treated with growth-promoting techniques achieve an adult stature 20 cm shorter than that of the normal population. The height of patients with Turner's syndrome, when plotted on growth curves specific for this disorder, show that growth velocity declines often as early as 2 to 4 years of age below the growth curve normal for females.

In patients with Turner's syndrome, adult height is short due to poor growth rates *in utero*, in infancy, and in childhood, and a pronounced lack of pubertal growth. The normal pubertal growth spurt does not occur in Turner's syndrome. Bone age is further delayed during adolescence owing to the lack of estrogenic influence on the skeleton. However, adult final height of untreated patients is not greater in the approx 25% of girls with Turner's syndrome who experience spontaneous puberty. Final height of untreated patients correlated significantly with midparental height ($r = 0.7$) *(11)*. Recent data *(12)* indicate that growth failure is already present in the first two postnatal years. Furthermore, growth charts of individuals 2–18 years of age demonstrate that the majority of girls with Turner's syndrome are below the fifth percentile for height by the age of 2 yr. Davenport et al. *(12)* observed that mean height SDS fell from –0.5 at birth to –1.7 at age 1 yr and –2.0 at age 1.5 yr. Management of growth failure is now a common part of pediatric endocrine therapy for these patients through diagnosis, and, unfortunately, initiation of therapy is still inexcusably delayed for many patients.

There is no need to measure serum growth hormone levels except possibly in those who are growing more slowly than the average patient with Turner's syndrome. Serum growth hormone is usually normal and measurement will not affect therapy. Third party payers should therefore not require growth hormone secretory assessment of Turner's syndrome prior to initiation of growth hormone therapy.

Growth Promoting Strategies in Turner's Syndrome

In 1983 a multicenter, prospective, randomized trial of human growth hormone, alone or in combination with oxandrolone, was initiated in the United States *(13)*. In 1997, after 12 yr all subjects had completed growth hormone therapy, and an evaluation of the impact of therapy on their adult height could be performed. Seventy-two girls were initially enrolled. At entry their chronological age ranged from 4.7 to 12.4 yr with a mean of 9.3 yr. Mean skeletal age, according to standards of Greulich and Pyle, was 8.0 yr with a maximum bone age of 11.2 yr. Heights at

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entry were at least 1 SD below the mean for normal girls of equivalent chronologic age, and the annualized growth rate was less than 6 cm/yr.

Subjects were randomly assigned to one of four study arms:

1. A control group receiving no therapy.
2. Oxandrolone at 0.125 mg/kg/d.
3. Human growth hormone 0.125 mg/kg/3X/wk.
4. Combination of human growth hormone and Oxandrolone at the doses stated previously.

After 1 to 2 yr, in the first phase of the study, subjects receiving growth hormone alone, continued to receive this treatment, whereas all other subjects received the combination of oxandrolone, although the latter at a reduced dose of 0.625 mg/kg/d. After two years, in the second phase of the study, recipients of growth hormone alone continued to receive only growth hormone at a total weekly dose of 0.375/mg/kg, which was divided into seven daily administrations. Subjects receiving growth hormone plus oxandrolone were randomly assigned to continuing combination treatment with growth hormone administered either daily or 3X/wk at the same total weekly dose of 0.375 mg/kg. Estrogen therapy was delayed in all subjects until they had a reached a minimum chronologic age of 14 yr and had been in the study at least 3 yr. Administration of conjugated estrogens were begun at .3 mg/d (Premarin®) and increased to 0.625 mg/d after 6 mo. After 1 yr estrogen replacement was given cyclically and progesterone was added.

The mean adult height for recipients of growth hormone alone was 150.4 ± 5.5, 8.4 ± 4.5 cm above the projected adult heights. Thus 58 of the 62 growth-hormone-treated subjects (94%) attained adult height greater than their projected adult heights *(15)*. For the 43 subjects treated with a combination of growth hormone and oxandrolone, the mean adult height was 152.1 cm ± 5.9 cm, 10.3 ± 4.7 cm taller than their projected adult heights. These results compare favorably not only with a matched American control group but also with previous reports of final heights of girls with untreated Turner's syndrome from the United States and many other countries *(16–19)*. The mean adult height attained by a retrospective control group as part of this study was 144.2 ± 6.0 cm.

These results also compare favorably to preliminary data from a second U.S. study in which 29 girls receiving growth hormone alone (plus estrogen replacement at 15 years of age) achieved a mean height of 16.3 ± .9 yr or 150.4 ± 6.0 cm, 8.4 ± 4.3 cm above their pretreatment projected adult heights *(20,21)*. The patients whose estrogen therapy was delayed until age 15 yr grew an average of 8.4 cm beyond their projected height, whereas those girls starting after age 12, grew only 5.1 cm on average beyond their projected height.

A multivariant analysis was used to examine several factors that might influence the gain in stature. The number of years of growth hormone therapy prior to estrogen treatment was a strong predictor. These data show that the early introduction of estrogen has a significant negative impact on adult height. A variety of published studes have reported that growth hormone therapy results in an average height gain of 5–10 cm, a range that represents a surprising variability in outcome *(22–26)*. It appears that at least some of this variability may be due to differences in the ages in which estrogen therapy was begun in these patients. Some of the reports showed that patients who had more modest apparent gains in final height also had relatively short periods of growth hormone administration prior to the introduction of estrogen therapy *(24,26)*.

The method used to estimate what the adult height would have been without treatment with growth hormone will affect the observed gain in height. Attie and associates *(27)* compared five methods of predicting adult height in patients with Turner's syndrome, using data from patients with Turner's syndrome in the United States who had not been given growth-promoting drugs. They found that the Lyon projection method *(15)*, used in our study, was one of the most reliable means of predicting adult height, with a mean overproduction of only 0.3 cm.

Several studies that did not achieve such reassuring gains in final height *(24,26)* were also utilizing lower growth hormone doses than the U.S. study groups *(14)*. This became particularly apparent in several studies carried out by the Dutch Advisory Group on growth hormone *(27,28)*. Their final assessment clearly shows that in a carefully conducted frequency response and dose response study the increased dose of growth hormone led to impressive increases in final height exceeding even the data seen in the U.S. study. Seven year results and preliminary final height data of this ongoing dose response study are now available.

These investigators treated 68 patients with chronological ages between 2 and 11 yr and heights below the 50th percentile for healthy Dutch girls. The dosages employed were 1.3 mg/m^2/d (0.23 mg/kg/wk) to as high as 2.7 mg/m^2/d, i.e., 0.6 mg/kg/wk. It is clear from the Dutch data that there is a dose response curve and that patients with the higher growth hormone dose grew significantly better.

During the first year of treatment all groups received growth hormone at a dose of 1.3 mg/m^2/d; in the second year two subgroups were switched to doses of 2 mg/m^2/d and a third group was switched to 2.7 mg/m^2/d in the third year. All were then treated at these doses for the remainder of the study period. After seven years of growth hormone treatment mean final heights of 25 of the girls were 159.1, 161.8, and 162.7 respectively, for the three groups. These investigators concluded that after seven years of growth hormone treatment, most girls with Turner's syndrome are

Table 1
Final Height in Turner's Syndrome

	Dose (mg/kg/wk)	Final Height (cm)	Gain (cm)	Duration of Treatment (yr)
U.S. Study[a] (Genentech)				
GH				
n = 17	0.375	150.4 ± 5.5	8.4 ± 4.5	7.6 ± 2.2
GH + Oxandrolone				
n = 43	0.375 + Ox = 0.0625 (mg/kg/d)	152.1 ± 5.9	10.3 ± 4.5	6.1 ± 1.9
U.S. Study[b] (NCGS)				
n = 622	0.35	148.3 ± 5.6	6.4 ± 4.9	3.7 ± 1.9
Dutch Study[c] (Dose Response)				
n = 68	0.46	159.1	12.5	7
	to	(148.3–172.4)	(7.8–15.7)	
	to	to	to	
	0.63	162.7	16.0	7
	(mg/kg/wk)	(154.3–170.3)	(10.2–24.8)	

[a]Rosenfeld, R. G., et al. (1998). *J. Pediatr.* **132,** 319–324, ref. *14*.
[b]Plotnick, L., et al. (1998). *Pediatrics* **102,** 479–481, ref. *30*.
[c]Sas, T. C., et al. (1999). *Arch. Dis. Child.* **80,** 36–41, ref. *28*.

Table 2
Final Height in Turner's Syndrome

	Dose (mg/kg/wk)	Final Height (cm)	Gain (cm)	Duration of Treatment (yr)
Belgian Study[a]				
n = 28	0.35[b]	151.4	8.1	5.3
	range =	(141.1–163.3)	(–0.1–17.9)	(2.5–7.3)
n = 28	0.35[c]	153.5	7.5	5.2
		(143–160.9)	(1.8–15)	(2.5–7.3)
n = 10	0.35[d]	151.1	7.8	5.9
		(141–160)	(3.8–12.7)	(4.1–8.4)

[a]Heinrichs, C. D., et al. (1999). *Horm. Res.* (Abstract) **51,** ref. *29*.
[b]Puberty was induced with 100 ng/kg/d EE2 after >2 yr of GH.
[c]Puberty was induced with 50 ng/kg/d EE2 after >1.5 yr of GH.
[d]Puberty developed spontaneously.

growing within the height range for healthy normal girls. Growth hormone treatment increased predicted adult height, and their preliminary results show that long-term growth hormone treatment considerably increases final height gain (*see* **Table 1**).

A carefully conducted Belgian study also documents that growth hormone increases final height of girls with Turner's syndrome with rather large individual differences in response to therapy. Induction of puberty at a relatively late chronological age (14.5 and 15 yr) using too low ethinyl estradiol dosages did not affect final height (**Table 2**). These data indicate *(29)* age at onset of puberty, or spontaneous puberty for that matter, do not significantly affect final height in Turner's syndrome.

It should be pointed out that final height data reported by many groups in different countries using different study protocols *(18,22–26)* are still most likely conservative estimates of the effect of therapeutic intervention with growth hormone on height potential in patients with Turner's syndrome. Many of the patients were enrolled at older ages thus limiting the duration of growth hormone therapy. Growth hormone doses employed were often well below

the 0.375 mg/kg/wk utilized in the United States *(30)*. Some investigators began estrogen replacement as early as 14 yr and used relatively high dosages of estrogen. This will only hasten epiphyseal fusion and thus compromise height potential. Large-scale postmarketing studies have reported final heights that are more modest *(30)*. These results, which show, nonetheless, significant gains in final height, are most likely due to the same factors cited above.

Compliance with medical therapy such as daily injections of growth hormone is sometimes suboptimal. Anticipated introduction of long-acting growth hormone therapy may obviate that concern to some extent.

Conclusions

While the treatment with growth hormone is invasive, laborious, and expensive, the adult height of patients with Turner's syndrome can be improved significantly and final heights of 150 cm are a reasonable goal *(15)*. Early diagnosis and early intervention are still the cornerstones for further improvements in the treatment of growth disorders in patients with Turner's syndrome.

Spontaneous puberty occurs in about 25% of patients with Turner's syndrome *(31)*. Final height in those with spontaneous puberty is not different from those with no puberty.

Spontaneous sexual development in Turner patients seems not to exert a significant influence on their final height. Therefore, girls with complete spontaneous puberty do not reach a taller stature than those with induced puberty *(30)*, although the growth pattern of the former patients is characterized by an earlier spurt leading to a transitory higher stature compared with that in the latter patients.

Physicians should consider the diagnosis of Turner's syndrome in any girl with an unexplained failure to thrive, or with short stature even during the first years of life. Therapy should be initiated when the child falls below the normal female growth curve. This may be as early as 2–4 yr of life and it is in those patients that predictably the best outcomes, as far as height is concerned, will ensue.

Earlier correction of the height deficit might then also allow earlier introduction of physiologic doses of estrogen replacement, thus achieving for most girls with Turner's syndrome relatively normal growth and sexual maturation.

A metaanalysis is underway to analyze and reconcile historical treatment data from various studies *(24,32)*. This study will undoubtedly confirm the efficaciousness of growth hormone therapy in Turner's syndrome as long as patients are treated early with appropriate doses of growth hormone for prolonged periods of time.

The care of patients with Turner's syndrome continues of course well beyond growth promotion and requires long-term estrogen and progestin replacement. The care should be placed in the hands of physicians knowledgeable about the natural history of the unique medical and behavioral problems and medical needs associated with the syndrome *(9)*. To improve the quality of life requires a team approach of physicians together with the efficient and compassionate support groups of the Turner's syndrome Society both in the United States and abroad.

References

1. Ullrich, O. (1949). *Am. J. Hum. Genet.* **1,** 179.
2. Turner, H. H. (1938). *Endocrinol.* **23,** 566–574.
3. Cockwell, A. E., MacKenzie, M., Youings, S., et al. (1991). *J. Med. Genet.* **28,** 152–155.
4. Hook, E. B., Hamerton, J. L. (1977). In: Population Cytogenetics, Hook, E. B., Porter, I. H. (eds.). Academic Press, New York, pp. 63–82.
5. Hook, E. B., Warburton, D. (1983). *Hum. Genet.* **64,** 24–29.
6. Jacobs, P., Betts, P. R., Cockwell, A. E., et al. (1990). *Ann. Hum. Genet.* **54,** 209–214.
7. Nielsen, J., Wohlert, M. (1991). *Hum. Genet.* **87,** 81–89.
8. Saenger, P. (1996). *N. Engl. J. Med.* **335,** 1749–1754.
9. Lippe, B. M. (1996). In: *Pediatric Endocrinology*, 3rd ed. Sperling, M. (ed.). W. B. Saunders: Philadelphia, pp. 387–421.
10. Ranke, M. B. (1992). *Baillieres Clin. Endocrinol. Metab.* **6,** 603–619.
11. Brook, C. G. D., Murset, G., Zachmann, M., et al. (1974). *Arch. Dis. Child.* **49,** 789–795.
12. Davenport, M. L., Punyasavatsut, N., Gunther, D., et al. (1999) *Acta Paediatr.* Suppl. **433,** 118–122.
13. Rosenfeld, R. G., Hintz, R. L., Johanson, A. J., et al. (1986). *J. Pediatr.* **121,** 49–55.
14. Rosenfeld, R. G., Attie, K. M., Frane, J., et al. (1998). *J. Pediatr.* **132,** 319–324.
15. Lyon, A. L., Preece, M. A., and Grant, D. B. (1985). *Arch. Dis. Child.* **60,** 932–935.
16. Bernasconi, S., Giovannelli, G., Volta, C., et al. (1991). In: *Turner's Syndrome and Growth-Promoting Therapies*. Ranke, M. B. and Rosenfeld, R. (eds). Elsevier: Amsterdam, pp. 53–57.
17. Ranke, M. G., Pfluger, H., Rosendahl, W., et al. (1983). *Eur. J. Pediatr.* **141,** 81–88.
18. Hibi, I., Tanae, A., Tanaka, T., et al. (1991). In: *Turner's Syndrome and Growth-Promoting Therapies*. Ranke, M. B. and Rosenfeld, R. (eds). Elsevier: Amsterdam, pp. 75–81.
19. Lippe, B., Plotnick, L., Attie, K. M., et al. (1993). In: *Basic and Clinical Approach to Turner Syndrome*. Hibi, I. and Takano, K. (eds.). Elsevier: Amsterdam, pp. 77–82.
20. Attie, K. M., Chernausek, S. D., Frane, J., et al. (1995). In: *Turner Syndrome in a Life-Span Perspective Research and Clinical Aspects*. Albertsson-Wikland, K. and Ranke M. (eds.). Elsevier: Amsterdam, pp. 175–181.
21. Chernausek, S. D. and Attie, K. M. (1999) *Acta Paediatr.* Suppl. **433,** 130–132.
22. Attanasio, A., James, D., Reinhardt, R., et al. (1995). *Horm. Res.* **43,** 147–149.
23. Nilsson, K. O., Albertsson-Wikland, K., Alm, J., et al. (1996). *J. Clin. Endocrinol. Metab.* **81,** 635–640.
24. Taback, S. P., Collu, R., Deal, C. L., et al. (1996). *Lancet* **348,** 25–27.
25. Takano, K., Shizume, K., Hibi, I., et al. (1995). *Horm. Res.* **43,** 141–143.
26. Van den Broeck, J., Massa, G. G., Attanasio, A., et al. (1995). *J. Pediatr.* **127,** 729–735.
27. Attie, K. M., Frane, J. W. (1997). *Horm. Res.* **48,** 60 (Abstract).

28. Sas, T. C., de Munick Keizer-Schrama, S. M., Stijnen, T., et al. (1999). *Arch. Dis. Child.* **80,** 36–41.
29. Heinrichs, C. D., Schepper, J., Verlinden, F., et al. (1999). *Horm. Res.* 51 (Abstract).
30. Plotnick L, Attie, K. M., Blethen SL, et al. (1998). *Pediatrics* **102,** 479–481.
31. Pasquino, A. M., Passeri, F., Pucarelli, I., et al. (1997). *J. Clin. Endocrinol. Metab.* **82,** 1810–1813.
32. Taback, S. P. and Van Vliet, G. (1999). In: *Current Indications for Growth Hormone Therapy*. Hindmarsh, P. C. (ed.). S. Karger Publ: Basel, Switzerland, pp. 102–117.