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Can Bone Age Determination Provide Criteria for Growth Hormone Treatment in Adopted Girls with Early Puberty?

A comparison of the Greulich-Pyle and the Tanner-Whitehouse 2 methods.

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ABSTRACT

In treatment of idiopathic central precocious puberty, GnRH analogues (GnRHa) have been accepted as the treatment of choice. Since growth velocity may be impaired with GnRHa treatment growth hormone (GH) treatment has been added in clinical trials. Recently, a study followed adopted girls with early or precocious puberty on GnRHa or combined GnRHa and GH treatment to final height. It was found that final height was significantly higher in the combined treatment group, although the difference was small. It was seen that patients that were extremely short at arrival and short at start of treatment seemed to be candidates for combined treatment. We have now analysed the data in order to define criteria for the subgroup in need of combined GnRHa-GH treatment in order to achieve normal final height, i.e. above -2 SDS.

Bone ages of 46 patients at start of treatment, randomized to either GnRHa treatment or GnRHa treatment combined with GH, were examined blindly by the same radiologist and the PAH calculated. The methods according to Greulich-Pyle / Bayley-Pinneau (GP/BP) and Tanner-Whitehouse (TW2) were used. Predictions versus final height data were analysed.

The accuracy of FH prediction was greatest for GnRHa treated group using the GP/BP method. The GP/BP method gave useful cut off limits for when combined treatment was necessary to possibly achieve normal height. If pre-treatment GP/PAH was > 157cm, the patients attained normal height with GnRHa treatment only. Ten out of 13 (77%) such girls could be correctly identified. Using TW2 with

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a cut off of 164 cm, 9 out of 13 could be selected. Using a multi regression equation of best fit the number of correctly selected cases for GnRHa treatment only, could not be further increased in this group.

We conclude that bone age determination and adult height prediction with the Greulich-Pyle/Bayley-Pinneau method, provides useful criteria for selecting the subgroup of adopted girls with early puberty where combined treatment with GnRHa and GH is not necessary to reach normal final height.

INTRODUCTION

Since around 1960 more than 40 000 children from developing countries have been adopted in Sweden. Eventually it was reported from paediatric clinics all over Sweden that many adopted girls developed early puberty and subsequently short final height. The reason for this was unknown. In studies on adopted girls from India it was shown that the degree of stunted growth due to under nutrition at arrival, as well as the velocity of subsequent catch-up growth was associated with the age at menarche. The earliest maturation was found among those most stunted at arrival with the most rapid catch up growth (1-3). Studies that describe an association between being born small for gestational age (SGA), subsequent growth and early maturation point in the same direction (4).

During many years these adopted girls with early pubertal development have comprised a major part of the patients observed and in many cases treated for early or precocious puberty in the paediatric clinics all over Sweden. Similar findings regarding adopted girls have subsequently been reported from the Netherlands, Belgium, Italy, France, Denmark and the United States (5-11).

The treatment to counteract early puberty was gonadotrophin releasing hormone analogues(GnRHa), intranasal preparations first and depot preparations subsequently (12-19). Although this treatment effectively blocked the progress of pubertal development, it was found to be associated with a decrease in height velocity as well (20-22).

It seemed reasonable to hypothesize that patients with early or precocious puberty, treated with GnRHa and simultaneously with growth hormone (GH) to compensate for the possible GH inhibition, would attain a significantly taller final height than patients treated with GnRHa alone.

An open randomized stratified multicentre study was designed, involving 20 paediatric clinics. Half of the 46 patients received GnRHa alone, the other half was given GH in addition to the GnRHa. The patients were followed to final height, defined as growth velocity less than 1 cm height increase per year (23, 24).

As reported elsewhere (24), the patients treated with the combined treatment attained a higher final height compared to the group treated with just GnRHa. Although statistically significant, the mean gain in final height for the whole group might be seen as limited, in view of the high cost of added GH treatment. The question remains whether any subgroup among the patients would be seen to benefit clearly from the

combined treatment. As reported, patients that were short at arrival in Sweden and short at start of treatment seemed to benefit especially from added GH treatment. This indicates that the growth and bone maturation status of the patients before start of treatment might provide additional data toward identification of the subgroup that might benefit from combined treatment. Thus the bone age determination and predicted adult height data are of interest to examine.

The two since long used methods in clinical practice are those according to Greulich-Pyle (GP) (25) and Tanner-Whitehouse 2 (TW2) (26), and they were used in this study.

The aim of the present paper was to compare the usefulness of the two methods of bone age determination regarding the prediction of post treatment final height and identification of criteria for combined GnRHa and GH treatment in this group of patients.

PATIENTS AND METHODS

The inclusion criteria for the clinical trial were a) girls below 9.5 years of age adopted into Sweden from a developing country with no sign of puberty at the time of arrival in Sweden, b) breast development defined as stage 2 or stage 3 according to Tanner (27), c) pubic hair development defined as at least stage 2 according to Tanner or an increase in height of at least 6 cm during the last year, and d) a normal serum level of TSH.

Fifty girls were recruited for the study. 25 girls were randomized for treatment with only GnRHa and the remaining 25 for treatment with GnRHa and GH. Four children were subsequently excluded from the study: two girls because of misdiagnosis of precocious puberty, one girl due to GH-deficiency and one girl because of hepatitis C.

Of the 46 remaining girls, 22 were in the GnRHa group and 24 girls in the GH/GnRHa group. During the first two years of treatment, GnRHa was administered as nasal spray 6 times daily. After a protocol amendment, 37 of the girls continued for a third year and eleven of them for a fourth year. During these additional years GnRHa was given as a subcutaneous implant every 8 weeks. All the 46 patients were followed until they had attained final height.

Before start of treatment all girls had a radiograph of the least active hand (usually the left) taken. Bone age according to Greulich-Pyle and Tanner-Whitehouse 2 was estimated blindly by the same experienced paediatric radiologist (TL). Reference tables for GP (25) and, TW2 (26) were used.

Statistics

Conventional descriptive statistics have been used. Means, standard deviations, medians, minima and maxima are given in table 1. Pearsonian bivariate correlation and multiple stepwise regression analyses have been applied. A p-value less than 0.05 was considered statistically significant. Standard Deviation Score (SDS) for height was calculated as:

(observed height – mean)/SD,

where mean and SD are the reference values and standard deviations for Swedish children of corresponding age and gender to that child. Mean adult height for girls was set to 165.9 cm with an SD of 6.29 cm (28). -2SDS corresponds to a height of 153.32 cm.

Table 1. Auxological data, bone age and predictions and final height.

	Mean	N	SD	Median	Min	Max
Age at arrival, yrs	2.3	45	2.30	1.1	0.1	7.3
Height, cm, at arrival	75.8	45	21.71	67.0	46.0	117.0
Height SDS at arrival	-2.5	45	1.96	-2.2	-6.9	0.7
Age, BL	8.3	46	0.80	8.4	6.7	9.7
Height, cm, BL	131.2	46	6.52	130.8	117.6	145.3
Height SDS, BL	0.4	46	1.03	0.2	-1.1	2.9
Bone age, TW, BL	10.7	46	1.20	10.7	8.1	13.2
Bone age, GP, BL	10.0	46	0.90	10.3	7.8	11.8
Predicted Adult Height, TW, BL	163.3	46	4.92	162.6	153.4	172.7
Predicted Adult Height, GP, BL	155.9	46	6.01	155.2	144.0	172.1
Final height, cm	157.5	46	6.26	157.3	146.4	171.5
Adult Height SDS	-1.4	46	0.99	-1.4	-3.1	0.9

RESULTS

Chronological age and height at arrival, chronological age, bone age, height and predicted adult height (PAH) at start of treatment and at final height (FH), subdivided according to treatment group and method of bone age determination are presented in table 1. Baseline data did not differ significantly between the two treatment groups, as was to be expected, since the groups were randomly selected. Mean final height differed 3 cm between the groups, which is approximately 0.5 SDS. 13 out

of 22 girls not treated with GH, and 21 of 24 of those GH treated, attained a final height above -2SDS, indeed one of the three remaining girls was only 148 cm, but the other two very close to 153 cm.

Figure 1 shows the PAH and actual FH for each bone age determination method and each treatment group. It is seen that the GP method is fairly accurate in predic-

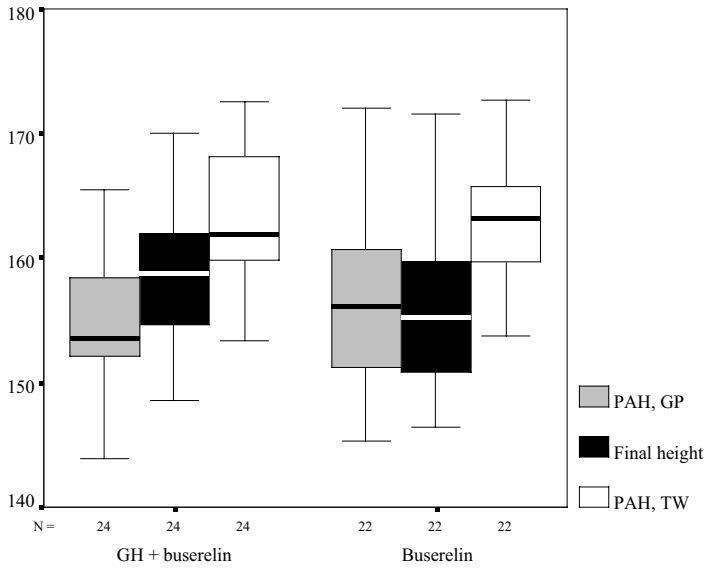

Fig1. Prediction of adult height according to the GP and TW2 methods at start of treatment in the two treatment groups. Relation to final height.

ting the FH in the GnRHa treatment group, while TW2 overestimates markedly in this group. In the combined treatment group both methods are inaccurate, GP underpredicting and TW2 overpredicting.

Greulich - Pyle

Further analysis of PAH according to GP and final height (Fig 2), showed that all subjects with a PAH >157 cm (19 patients out of 46, 10 in the GnRHa group and 9 in the combined group), attained normal final height (>-2SDS or 153 cm) irrespective of treatment with GH. All subjects with a GP prediction < 151 cm became short without GH treatment. If GP prediction was between 151.1 and 156.6 cm, 8 out of

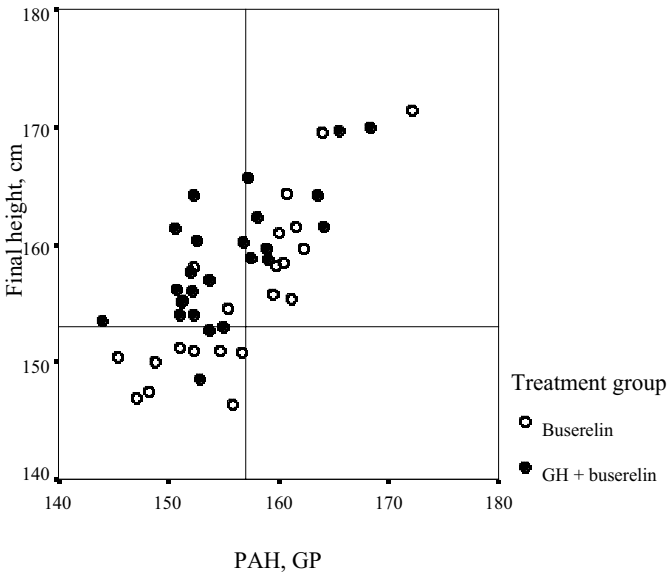

Fig 2. Individual final height in relation to prediction using the GP/BP method.

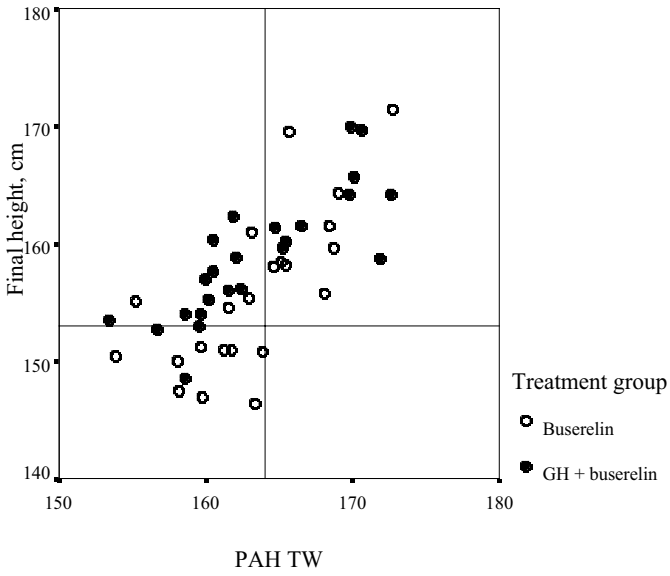

Fig 3. Individual final height related to prediction using TW2.

10 attained normal FH with GH treatment, while those who did not receive GH showed no certain trend either way. Out of 7 girls who did not receive GH treatment 4 became short and 3 attained normal FH. Two of those with short FH had a height on

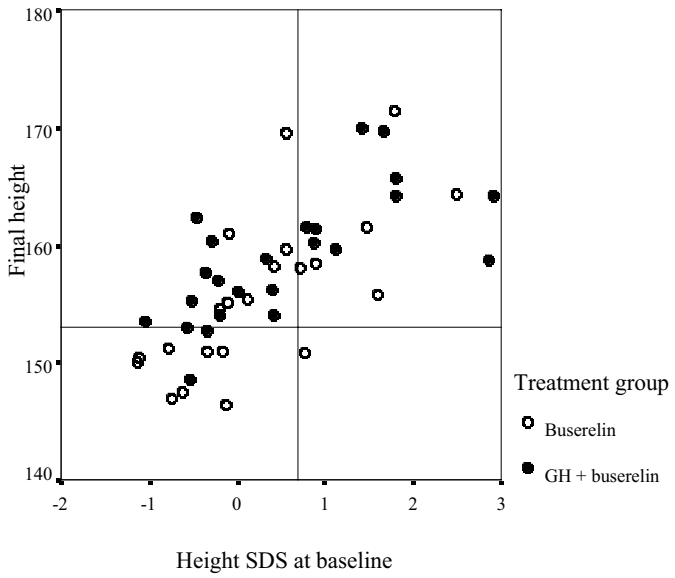

Fig 4. Final height (cm) in relation to height at start of treatment (SDS).

arrival in Sweden of <- 4 SDS.

Tanner – Whitehouse 2

Only in the group with a TW2 prediction of >164 cm, also 19 out of 46, all individuals attained a normal FH irrespective of treatment with GH (Fig 3).

Height at start of treatment

The relationship between height SDS at start of treatment and FH is illustrated in Fig 4. It was seen that if height at start of treatment is > 0.7 SDS, then normal FH is attained irrespective of treatment group. A lower height SDS at start of treatment was associated with a lower final height in both treatment groups.

Height SDS at arrival

The relationship between height SDS at arrival in Sweden and their final height is seen in Fig 5. In the very few cases where height SDS at arrival was above 0 normal FH was attained irrespective of treatment. If height at arrival was below 0 SDS, normal FH was only attained in about half of the cases if GH was not added.

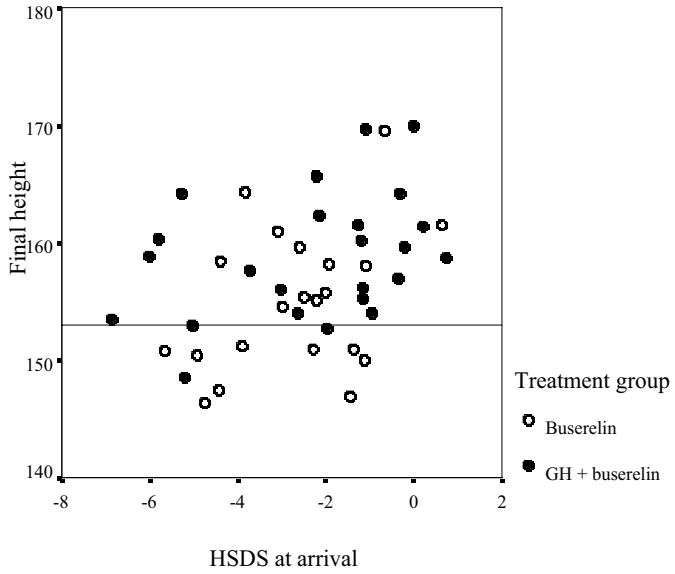

Fig. 5. Final height in relation to height SDS at arrival in Sweden.

Bivariate correlation analyses

In bivariate correlation analyses to find predictors of final height, height at start of treatment and predicted height according to the bone age estimations demonstrated correlation coefficients between 0.68 and 0.83 for the two treatment groups (table 2). For the GnRHa treated, the highest correlation was found with GP prediction (0.83). For the combined group TW2 prediction demonstrated the highest correlation (0.81). Height SDS at start of treatment also demonstrated a high correlation to final height, 0.72 for the GnRHa group, as good as the correlation between TW2 prediction and final height (0.72). Bone age acceleration and age at start of treatment were not significantly correlated to final height in the bivariate analysis.

Multiple regression analysis

Multiple regression step-wise forward analyses were carried out in order to search for a set of predictors of possible use for prediction of treatment result on final height. Data for each treatment group was analyzed separately. The candidate predictors for inclusion in the analyses were the same as presented in table 2 on bivariate correlation analyses.

The best fit for the combined treatment (GnRHa+GH) group was found for the following function:

FHcm= 7.8 + 0.95 * PAHTW + 1.5*(Age at baseline – BoneageTW),

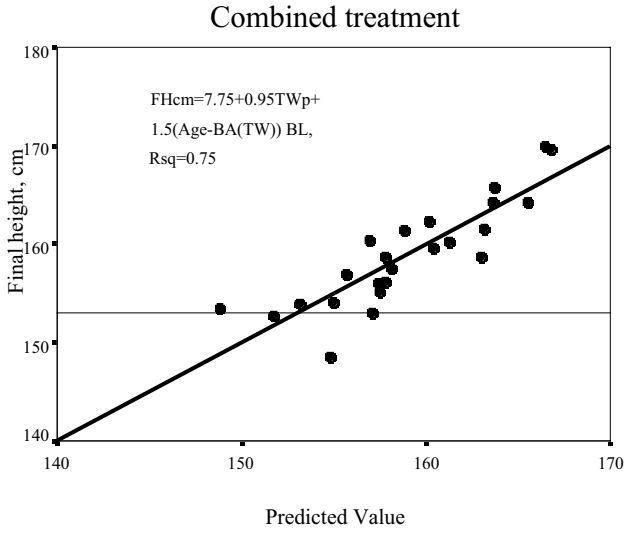

Fig.6. Relation between TW2 prediction and final height with equation of best fit.

where the coefficient of multiple determination (R2) was 0.75. This function indicates the aforementioned overestimation of PAH according to TW2 and that the less pronounced the bone maturation is at start of treatment the taller will the final

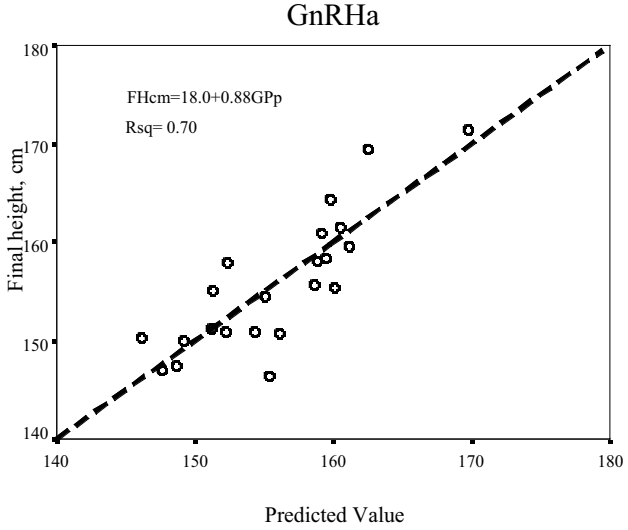

Fig.7. Prediction according to GP in relation to final height in the GnRHa treated group.

height become (fig.6).

Regarding the GnRHa treatment group, the best fit with an R2 of 0.70 was:

FH=18 cm+0.88 x GP prediction (fig 7). All girls with a predicted height above 157 cm, according to this function, reached final height above -2 SDS.

DISCUSSION

The aim of the present paper was to find a practical method of evaluation of candidates for combined treatment with GnRHa and GH, based on growth data and bone age determination.

The first task was to examine the bone age determination methods commonly used, and assess their suitability for providing criteria for the subgroup that could really benefit from combined treatment with GnRHa and GH, i.e. attain normal height with this more advanced treatment only.

It could not a *priori* be expected that pre-treatment PAHs would accurately predict PAH in this very special group of patients, as the standards are basically constructed for normal, healthy children. Accurate prediction could only be expected when pre-treatment growth potential had not been modified to any great extent by an intervention. However, we found the pre-treatment GP/PAH reasonably accurate on the group level, when only GnRHa was given, indicating that growth potential was not much modified by the GnRH analogue treatment. When combined treatment was used, the pre-treatment GP/PAH under estimated final height, which might indicate that the treatment had increased final height.

Still, on the group level, TW2/PAH was found to largely overestimate the FH in patients with GnRHa treatment. Even in the combination group, TW2/PAH overestimated the FH.

The analysis of GP/PAH in relation to the FH results show that quite a few cases do not need addition of GH to attain a final height above -2SDS. Those who definitely need it in order to attain normal final height are those with GP/ PAH < 151 cm. In the interval GP/ PAH 151cm – 157cm an additional indicator is needed to identify those who would be candidates for combination treatment. Girls with a GP prediction above 157 cm or a TW2 prediction above 164 cm attained normal final height irrespective of treatment.

As reported earlier, the height SDS at start of treatment is strongly correlated to the FH (24), which is to be expected as it is known that the closely preceding measure of the height at pubertal onset (HAPO), is known to be significantly correlated to FH (29). That the height SDS at treatment start is within the normal range is explained by the effect of the pubertal growth spurt.

The height SDS at arrival was, at least according to our earlier, more superficial analysis, correlated to FH (24), and could thus provide an additional indicator for the need of optimal treatment. Patients with height at arrival <-4SDS obviously

would need combination treatment in most cases, but height at arrival seems to be of little value as predictor for the whole group (fig 5).

The equation of best fit for prediction of FH resulting from the multiple regression analysis, was found to contain GP/PAH and TW2/PAH as important factors. The R2 values were sufficiently high to possibly be of some clinical use for making a FH prognosis. The correlation between GP/PAH and TW2/PAH was highly significant (r=0.78) and both predictions were highly correlated to final height (r=0.74). Therefore, the inclusion of either prediction in the multivariate analyses could be seen as random. In the case of the group with single treatment the regression analysis only made a correction to the GP/PAH prediction formula and in the group with combined treatment the analyses corrected the TW2/PAH prediction and added the value of low bone age maturation to give a better final height prediction.

It can, however, be argued that 46 subjects is too limited a population on which a prognostic formula is to be based. On the other hand, 46 randomized patients in this very special patient category, all followed longitudinally from start of treatment to final height after around 10 years without drop-outs, may be a study population hard to improve on.

We conclude that bone age determination can indeed provide criteria for combination treatment with GnRHa and GH of early puberty in transnationally adopted girls. One aim in this study was to define those girls who would attain final height within normal range without expensive treatment with growth hormone.

Using baseline height SDS when the girls already are in puberty, 15 girls out of 46 had a height SDS of +0.8 or higher. Five of them did not get GH. All these girls attained normal final height.

By adding bone age criteria (GP/PAH>157 cm or TW2 > 164 cm) a total of 19 girls (41 %) all attained normal height. Ten of those with the high GP prediction (>157 cm) and nine of those with the high TW2 prediction were not GH treated.

Using only height at start of treatment, 5 of the 13 who did not need GH to attain normal height could be selected. By adding a simple GP prediction with cut off of 157 cm 10 out of the 13 could be predicted. Even if the equation of best fit was used, this figure, which may be of practical use, could not be further increased.

Using the same criteria, i.e. GP > 157 cm on the GH treated group showed that all girls fulfilling it ended up well above 153 cm, indeed above 158 cm.

In conclusion, these data indicate that in the great majority of cases of adopted girls with early puberty final height after GnRH analogue treatment can be predicted using Greulich – Pyle / Bayley – Pinneau prediction. Patients in need of more intensive therapy can then be selected.

REFERENCES

1. Adolfsson S, Westphal O (1981) Early pubertal development in girls adopted from Far-Eastern coun-

tries. Pediatr Res 15:82 (Abstr).
2. Proos LA, Hofvander Y, Tuvemo T (1991) Menarcheal age and growth pattern of Indian girls adopted in Sweden. I. Menarcheal age. Acta Paediatr Scand. 80:852-8.
3. Proos LA, Hofvander Y, Tuvemo T(1991) Menarcheal age and growth pattern of Indian girls adopted in Sweden. Catch-up growth and final height. Indian J Pediatr. 58:105-14.
4. Neville KA, Walker JL (2005) Precocious pubarche is associated with SGA, prematurity, weight gain, and obesity. Arch Dis Child 90:258-61.
5. Bourguignon JP, Gérard A, Alvarez Gonzales ML, Fawe L, Franchimont P (1992) Effects of changes in nutritional conditions on timing of puberty: clinical evidence from adopted children and experimental studies in the male rat. Horm Res 38 (suppl):97-108.
6. Virdis R et al (1994) Precocious puberty (PP) in Indian girls adopted in Italy. (Abstract) Horm Res 37: (suppl) 4:33.
7. Oostdijk W, Yap YN, Rekers-Momberg ITM, Massa GG, Brand R, Drop SLS. The impact of early puberty on final height in foreign born adopted children in the Netherlands. In:Oostdijk W:Central precocious puberty and gonadotrophin releasing hormone agonist treatment. Doctoral dissertation 1996, Erasmus University, Rotterdam, ISBN 90-9009946-8.
8. de Monleon JV, Geneste B , Huet F (1999) Puberté précoce chez les enfants adoptés, un risque à ne pas oublier. Arch Pediatr 6:589-90.
9. Baron S, Battin J, David A, Limal JM (2000) Puberté precoce chez les enfants adoptés de pays étrangers. Arch Pediatr 7:809-16.
10. Teilmann G, Main K, Skakkebaek N, Juul A (2002) High frequency of central precocious puberty in adopted and immigrant children in Denmark. Horm Res 58 (Suppl 2):135(Abstract).
11. Mason P, Narad C, Jester T, Parks J (2000) A survey of growth and development in the internationally adopted child. Pediatr Res 47:209A (abstract).
12. Crowley Jr WF, Comite F, Vale W, et al (1981) Therapeutic use of pituitary desentization with a long-acting LHRH agonist: a potential new treatment for idiopathic precocious puberty. J Clin Endocrin Metabol 52:370-2.
13. Comite F, Cutler Jr GB, Rivier J, et al (1981) Short-term treatment of idiopathic precocious puberty with long-acting analogue of luteinising hormone releasing hormone. N Engl J Med 1546-50.
14. Mansfield J, Beardsworth DE, Loughlin JS, et al (1983) Long-term treatment of central precocious puberty with long-acting analogue of luteinizing hormone-releasing hormone. Effect on somatic growth and skeletal maturation. N Engl J Med 309:1286-90.
15. Boepple PA, Mansfield MJ, Crawford JF, Crigler Jr JF. Blizzard JM, Crowley JR WF (1990) Gonadotrophin-releasing hormone agonist treatment of central precocious puberty: an analysis of growth data in a developmental context. Acta Paediatr Scand (Suppl) 367:38-43.
16. Boepple PA, Crowley Jr WF (1991) Gonadotrophin-releasing hormone analogues as therapeutic probes in human growth and development: evidence from children with central precocious puberty. Acta Paediatr Scand (Suppl) 372:33-8.
17. Kletter GB, Kelch RP (1994) Effects of gonadotrophin-releasing hormone analog therapy on adult stature in precocious puberty. J Clin Endocrin Metabol 79:331-4.
18. Antoniazzi F, Cisternino M, Nizzoli G, Bozzola M, Corrias A, De Luca F, De Sanctis C, Rigon F, Zamboni G, Bernasconi S, Chiumello G, Severi F, Tato T (1984) Final height in girls with precocious puberty: comparison of two different luteinizing hormone-releasing hormone agonist treratments. Acta Paediatr 83:1052-6.
19. Tuvemo T, Gustafsson J, Proos LA; Swedish Growth Hormone Group (2002) Suppression of puberty with short-acting intranasal versus subcutaneous depot GnRH agonist. Horm Res. 57:27-31.
20. Hermanussen M (1995) Growth promotion by oxandrolone in a girl with short stature and early pubertal development treated with growth hormone gonadotropin-releasing hormone analogue, A case study. Acta Paediatr. 84:1207-10.
21. Oostdijk W, Drop SLS, Odink RJH, Hummelink R, Partsch CJ, Sipell WG (1991) Long –term results with a slow release gonadotrophin-releasing hormone agonist in central precocious puberty. Acta Paediatr Scand 372 (Suppl): 39-45.
22. Saggese G, Pasquino AM,Bertelloni S, Baronelli GI, Battini R, Pucarelli I, Segni M, Franchi G (1995) Effect of combined treatment with gonadotropin releasing hormone analogue and growth hormone in patients with central precocious pubert who had subnormal growth velocity and impaired height prognosis. Acta Paediatr 84:299-304.

23. Tuvemo T, Gustafsson J, Proos LA (1999) Growth hormone treatment during suppression of early puberty in adopted girls. Swedish Growth Hormone Advisory Group. Acta Paediatr. 88:928-32.
24. Tuvemo T, Jonsson B, Gustafsson J, Albertsson-Wikland K, Aronson AS, Häger A, Ivarson S, Kriström B, Marcus C, Nilsson KO, Westgren U, Westphal O, Åman J, Proos LA (2004) Final height after combined growth hormone and GnRH analogue treatment in adopted girls with early puberty. Acta Paediatr 93:1456-62.
25. Greulich WW, Pyle SI Radiographic Atlas of Skeletal Development of the Hand and Wrist, 2nd edn. Stanford UniversityPress, Stanford, CA. 1959.
26. Tanner JM, Whitehouse RH, Marshall WA, Carter BS (1975) Prediction of adult height from height, bone age and occurrence of menarche, at ages 4 to 16 with allowance for mid parent height. Arch Dis Child 50:14-26.
27. Tanner JM. Growth at adolescence. 2nd ed. Oxford: Blackwell, 1962.
28. Karlberg P, Taranger J, Engström I, Lichtenstein H, Svennberg-Redegren I (1976) The somatic development in an urban Swedish community. Acta Paediatr Scand (Suppl) 258:7-76.
29. Proos LA, Karlberg J, Hofvander Y, Tuvemo T (1993) Pubertal linear growth of Indian girls adopted in Sweden. Acta Paediatr 82:641-4.
30. Tato L, Saggese G, Cavallo L, Antoniazzi F, Corrias A, Pasquino AM, Cisternino M (1995) Use of combined Gn-RH agonist and hGH therapy for better attaining the goals in precocious puberty treatment. Horm Res. 44 (Suppl 3):49-54.

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