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## Recombinant growth hormone for children and adolescents with Turner syndrome (Review)

Baxter L, Bryant J, Cave CB, Milne R

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[Intervention Review]

# Recombinant growth hormone for children and adolescents with Turner syndrome

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## ABSTRACT

### Background

Turner syndrome (TS) affects about one in 1500 to 2500 live-born females. One of the most prevalent and salient features of the syndrome is extremely short stature. Untreated women are approximately 20 to 21 cm shorter than normal women within their respective populations. Recombinant human growth hormone (hGH) has been used to increase growth and final height in girls who have Turner syndrome.

### Objectives

To assess the effects of recombinant growth hormone in children and adolescents with TS.

### Search methods

MEDLINE, EMBASE, *The Cochrane Library*, LILACS, BIOSIS, Science Citation Index and reference lists were used to identify relevant trials.

### Selection criteria

Randomised controlled trials were included if they were carried out in children with TS before achieving final height. Growth hormone had to be administered for a minimum of six months and compared with a placebo or no treatment control condition.

### Data collection and analysis

Two reviewers assessed studies for inclusion criteria and for methodological quality. The primary outcomes were final height and growth. Secondary outcomes included bone age, quality of life, cognitive performance, and adverse effects.

### Main results

Four RCTs that included 365 participants after one year of treatment were included. Only one trial reported final height in 61 treated women to be 148 cm and 141 cm in 43 untreated women (mean difference (MD) seven cm, 95% CI 6 to 8). Short-term growth velocity was greater in treated than untreated girls after one year (two trials, MD three cm per year, 95% CI 2 to 4) and after two years (one trial, MD two cm per year, 95% CI 1 to 2.3). Skeletal maturity was not accelerated by treatment with recombinant growth hormone (hGH). Adverse effects were minimally reported.

## Authors' conclusions

Recombinant human growth hormone (hGH) doses between 0.3 to 0.375 mg/kg/wk increase short-term growth in girls with Turner syndrome by approximately three (two) cm in the first (second) year of treatment. Treatment in one trial increased final height by approximately six cm over an untreated control group. Despite this increase, the final height of treated women was still outside the normal range. Additional trials of the effects of hGH carried out with control groups until final height is achieved would allow better informed decisions about whether the benefits of hGH treatment outweigh the requirement of treatment over several years at considerable cost.

## PLAIN LANGUAGE SUMMARY

### Recombinant growth hormone for children and adolescents with Turner syndrome

Turner syndrome (TS) is a genetic disorder affecting the sexual development and appearance of girls and women. Women with TS are much shorter than other women (by about 21 cm or eight inches). To try to overcome slow growth, recombinant growth hormone (hGH) has been given. The hormone is injected under the skin several times a week until final adult height is achieved. The review found some evidence that hGH does increase short-term growth in girls with TS and adult height (an increase of perhaps five centimeters or two inches). However, girls treated with hGH are still substantially shorter than other women as adults. Final height in 61 treated women was 148 cm and 141 cm in 43 untreated women.

## BACKGROUND

### Description of the condition

Turner syndrome (TS) is the most common sex-chromosome abnormality in females and affects approximately three percent of females conceived (Saenger 1996). However, as there is a high spontaneous miscarriage rate, TS affects one in 1500 to 2500 live-born females (Saenger 1996). Affected individuals either have a single X chromosome (45,X) or display chromosomal mosaicism (45,X/46,XX). Chromosomal mosaicism is a condition in which some cells have one chromosome constitution and others another. This results in an individual having two or more genotypically distinct cell lines. This condition results in individuals who are phenotypically female (in other words whose appearance is female), but who have a very high likelihood of ovarian failure. Girls and women with TS may present with any of a number of physical abnormalities (for example, growth failure, gonadal dysgenesis, abnormalities of some internal organs, "square" appearance) as well as some cognitive difficulties such as difficulties in non-verbal problem solving (for example, mathematics) or visual-spatial processing, although overall intelligence is generally normal (Saenger 1996).

### Turner syndrome: effects on height

Turner Syndrome (TS) is one of the most common organic causes of short stature in girls and between 80 and 100 percent of girls with TS will have growth failure (Saenger 1996). Short stature is the most common finding in TS and is almost always present even in patients who do not display other clinical features. However, short stature may not be present if the girl has inherited her remaining X chromosome from a tall parent.

TS usually involves mild intrauterine growth restriction (about one standard deviation [SD] below normal), decreased growth rates during infancy and childhood (generally about two SD below the normal mean) and pronounced lack of pubertal growth resulting in height approximately four SD below the mean at about age 14 (Ranke 1988; Saenger 1996). Thereafter, growth continues slowly back toward the norm with final height about 2.6 SD below the mean of normal adult women (Ranke 1988). The growth phase is more prolonged than in normal girls not generally being completed before the end of the second decade of life. Although the mechanism of growth failure in TS is not well understood, it "probably results from an impaired response to growth hormone combined with an underlying skeletal dysplasia" (Rochiccioli 1994). Most studies suggest that the adult height of untreated girls with TS generally averages approximately 143 cm to 144 cm (56 in to 57 in), however, individual studies of final height in TS have reported means ranging from 136 cm to 147 cm (Rochiccioli 1994). This is approximately 20 to 21 cm (eight inches) shorter than normal women within their respective populations. Final

height of untreated girls with TS is related to the average of the parents' heights. Although the mean final height of groups of girls with TS generally falls within a fairly narrow range, there is a great deal of variability among individuals (Rochiccioli 1994).

## Description of the intervention

Growth hormone has been administered in girls with Turner syndrome (TS) as well as in children with other aetiologies for growth failure. Although TS does not involve a deficiency of growth hormone, it is believed that growth failure may be related to an impaired response to growth hormone and that administration of additional growth hormone may enhance growth in children and adolescents with TS (Gault 2001).

Recombinant human growth hormone (hGH) has been available since 1985, shortly after growth hormone from cadaveric human pituitaries was withdrawn from use because of its association with the transmission of Creutzfeldt-Jacob disease. Recombinant human growth hormone (somatropin) is produced by recombinant DNA technology and has a sequence identical to that of human growth hormone. Somatropin is available from several manufacturers under several different brand names. The advent of recombinant hGH has meant that hGH is far more available and hGH has been widely used to treat various growth disorders including TS (Gault 2001).

Recombinant human growth hormone is usually prescribed in association with a paediatric endocrinologist or a general paediatrician with a special interest in endocrinology. It is prescribed in milligrams (mg) or International Units (IU) (3 IU = 1 mg) according to body weight or body surface area and is self administered (or given by a parent) at home usually as a subcutaneous injection generally six to seven times per week. Whether dose is computed by weight or body surface area can have a significant effect on the dose given and is particularly relevant in older girls with TS who may have problems with weight gain. Among younger girls (age 5) a dose based on surface area was reported to be as much as 33% greater than one based on weight, whereas among older girls (age 15) the dose based on surface area could be as much as 10% less (Betts 1999). The dose of hGH generally recommended for use in TS is not often specified, but a dose of 0.375 mg/kg/week has been suggested by the American Association of Clinical Endocrinologists (AACE) (Gharib 1998). This dose is approximately double that used in children with growth hormone deficiency. To more closely approximate the natural daily fluctuations in hGH, the injections are usually given at night.

In growth hormone deficiency, hGH is given as replacement therapy (that is, a physiological dose), in which it is intended to supplement low levels of naturally occurring hGH up to normal levels. However, in TS, hGH is given at supra physiological levels - levels considerably higher than a replacement dose. The logic in administering supra physiological doses is generally that children

with TS have a growth deficiency, but not a hormone deficiency, and therefore have some lack of sensitivity to the hormone.

Growth hormone is generally prescribed for a number of years - from the diagnosis of the growth deficit until growth is complete. For an individual child how long this would be will depend upon when TS is diagnosed and whether the child, parents, and physician deem treatment necessary. However, even in congenital disorders of growth such as TS, diagnosis may not occur until the child is several years old. Most trials of hGH have been of relatively short duration (for example, five years), but in practice in many children therapy could continue for as long as 12 years or more. Not all girls with TS will need hGH treatment. A minority will reach a final height within the normal range without treatment and a few will be diagnosed too late for effective treatment. However, it has become common practice to treat girls with TS with hGH and often with an anabolic steroid (for example, oxandrolone) as well.

Oestrogen is commonly administered in TS to promote puberty, but there does not appear to be any evidence that it is a growth-promoting agent - indeed, the opposite, as oestrogen therapy that was started at younger ages resulted in reduced final heights compared with girls in whom oestrogen was started later (for example, after age 14) (Saenger 1996). It is now generally thought that it is important to administer hGH for as long as possible before starting oestrogen therapy.

## Adverse effects of the intervention

British National Formulary recommendations are that growth hormone therapy is contraindicated in cases of tumour activity and should not be used after renal transplant in seriously ill children or for growth promotion in children with closed epiphyses (BNF 2002). Side effects can include headache, visual problems, nausea and vomiting, fluid retention (peripheral oedema), arthralgia, myalgia, paraesthesia, antibody formation, hypothyroidism and reactions at injection site. There has been concern that growth hormone would induce new tumours or increase the likelihood of tumour relapse. Reports suggest, however, that the risk of new tumours or tumour recurrence is not elevated in children treated with growth hormone who have no other increased risk factors (Blethen 1996; Frisch 1997; GH Soc 2001). Antibody formation is generally not of clinical consequence, although in some patients this can be associated with growth rate deceleration (Blethen 1996).

## How the intervention might work

### Evaluating effects of growth hormone

Height (and growth velocity, see below) is often reported in length units (cm) or in standard deviation scores (SDS).

The standard deviation is a measure of the variation of observations around the mean. Heights of populations of adults or children generally form normal distributions such that 95.4% of a population will have heights that fall within two standard deviations (SD) from the mean. Individual observations can be compared with heights corresponding to points on the height distribution for a particular age to determine how a child's (or adult's) height compares with their peers. Standard deviation score is defined by the formula: actual height minus mean height for age divided by standard deviation of height for age. Standard deviation scores using controlled data collected from an appropriate population base allow comparison of measures independent of age. In this system the normal population mean is zero and a normal SD score will lie between approximately -2 and +2 SD. A healthy individual's SDS will not change during the growth years. Increased SDS implies catch-up growth and a decrease implies growth failure.

The best measure of how recombinant growth hormone (hGH) affects growth is to measure final adult height (in cm or SDS). Measuring final height requires that the child has finished growing. The most reliable measures of final height use multiple criteria to determine that growth is complete or nearly complete. Generally, it is considered that children have completed or nearly completed their growth when their growth rate within a year has slowed to less than some specified amount (for example, 1 to 2 cm) and skeletal maturity assessed by radiographs of the wrist and hand indicate that the epiphyses have closed (often expressed as bone age greater than a certain value, for example, 14 to 15 years) (Frindik 1999). Acknowledging that measures may be taken before growth is fully complete, 'near final height' is sometimes reported. This is a measure of height when it is presumed that growth is complete as discussed above.

Although the overall effectiveness of hGH in treating short stature is to be found in measures of final height, it has been argued that short-term measures of growth are also of importance. Children and parents may be concerned with whether growth within a certain time frame is comparable to that of a child's peers. Velocity may also be a better interim growth measure than height attained at a particular age as it is independent of growth in previous years. Growth velocity (GV) is a measure of the height gained (cm) within a specified time period (usually a year). This outcome is also often referred to as 'height velocity.' Growth velocity can also be considered in relation to a child's age by considering growth velocity relative to the distribution of growth velocities for children of a particular age (growth velocity standard deviation score - GVSDS). As with height, growth velocity SDS measures are dependent upon the reference data used (Haeusler 1994).

Bone age is a measure of skeletal maturity. It is customarily determined by examining the relative positions of the bones in the left hand and wrist from a radiograph. The measurement of bone age relative to chronological age is important in height prediction models. In addition, bone age assessments are used to evaluate when the epiphyses have closed and growth is complete. Growth

cannot occur after the epiphyses (ends of the long bones) have closed. The interim assessment of bone age is important in determining whether treatment is advancing bone maturity. Accelerated bone age in treated individuals would indicate that treatment was shortening the growth period and might therefore have the paradoxical effect of premature closure of the epiphyses and decreased final height. Therefore, if hGH were an effective growth promoting agent without inducing premature skeletal maturity, then there would be a lack of treatment effects on bone age.

It is of considerable interest to determine whether treatment with hGH affects children's sense of well-being or quality of life. A number of measures have been designed to assess quality of life. In addition, there are many measures of self-concept, psychosocial functioning and so on that might be affected by hGH treatment. Turner syndrome can include psychological or cognitive characteristics. It is therefore of interest to determine whether hGH treatment might affect cognitive functioning.

### Existing evidence on the use of growth hormone in Turner syndrome

Growth hormone has been used for some years in TS. Although many consider that hGH has demonstrated beneficial effects in increasing growth and height in girls with TS, the results from trials have been variable. Within trials there is also variation among individuals in response to treatment. Whether hGH is effective in increasing height in patients with TS is still somewhat controversial. How much height may be gained is also an important consideration as hGH treatment is quite costly.

### Costs

A recent review of the clinical and cost-effectiveness of recombinant growth hormone in the UK (Bryant 2002) included a model that suggested that approximately 97% of the cost of treating patients with Turner syndrome for short stature was drug (growth hormone) cost. This model showed that mean total cost of treatment assuming treatment for five years with a final height benefit of 4.4 to 4.8 cm was approximately £63,000 (93,909 EURO) resulting in an incremental cost per centimetre of final height gain of approximately £16,000 to £17,500 (23,850 EURO to 26,090 EURO).

### Why it is important to do this review

Although there have been some reviews of the use of recombinant growth hormone in Turner syndrome (for example, Donaldson 1997; Guyda 1999), there have been no reviews that have used systematic methods to locate and evaluate the best possible evidence. For instance, existing reviews have not used methods that exhaustively searched the available literature for relevant trials.

Previous reviews have also included studies that have varied in the interventions used. These results combine not only the effects of hGH, but also in some cases effects of other concomitant interventions such as oxandrolone. Although it may eventually be demonstrated that height optimisation requires the use of multiple interventions, it is initially valuable to evaluate the effectiveness of hGH alone.

## OBJECTIVES

To assess the effects of recombinant growth hormone on short-term growth and final height in children and adolescents with Turner syndrome.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials or quasi-randomised trials were included. Trials had to evaluate one or more of the height or growth outcomes described below.

For short-term growth outcomes, recombinant growth hormone (hGH) should be administered for a minimum of six months. For final height outcomes, hGH should be administered until final height is achieved. Criteria used within trials for the attainment of final height were accepted (for example, growth velocity less than two cm per year). Trials that reported 'near final' height (using criteria that presume that growth is nearly complete, but being more conservative in calling growth complete) were also included.

#### Types of participants

Participants were children/adolescents with Turner syndrome (TS). The participants had to have TS confirmed by karyotype. All TS karyotypes accepted within studies meeting other inclusion criteria were included. All participants treated prior to closure of epiphyses were included.

#### Types of interventions

The active intervention was recombinant human growth hormone (hGH): that is, biosynthetic human growth hormone (somatropin), with a sequence identical to that of human growth hormone, marketed under any brand name.

The following comparisons were considered:

- administration of hGH for a minimum of six months versus administration of placebo;
- administration of hGH for a minimum of six months versus no treatment.

Human pituitary derived growth hormone is no longer used since it was implicated in the transmission of Creutzfeldt-Jacob disease in the 1980's. There are no other forms of growth hormone currently used to promote height in humans.

### Types of outcome measures

#### Primary outcomes

Outcomes focused on those deemed clinically relevant to children with Turner syndrome with growth deficiencies and growth failure. Trials for inclusion had to report a height or growth outcome. Other outcomes specified below that were reported in the context of growth or height were also included.

- final height: The gold standard outcome measure of effectiveness of growth hormone treatment is final height (in cm or height standard deviation [HtSDS] relative to a normal population). Height is often reported in standard deviations relative to some population. HtSDS gives an indication of height relative to other children of the same age or relative to other adults in the case of final height. HtSDS can also be reported relative to a population with TS. Although this measure would also indicate whether treated patients are taller than an untreated TS sample or population, this would not be the best comparison for evaluating a patient-relevant outcome. The most salient comparison is how children and adults with TS compare in height relative to the normal population with whom they interact;

- short-term growth: Because many trials are of insufficient duration to collect final height, short-term growth responses to treatment including height standard deviation score at a point prior to final height (HtSDS; or change in HtSDS over some treatment period) and growth velocity (change in cm per treatment interval; or velocity standard deviation score) have been included. Short-term height gains may be important to children and adolescents with TS whose growth tends to lag behind that of their peers at a time when they may be particularly sensitive to height comparisons with their peers.

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### Secondary outcomes

When they were reported, the following outcomes were extracted from trials that reported a growth or height outcome described above. Trials were not included if they reported one or more of the following outcomes, but did not report a growth or height outcome.

- bone age, a measure of skeletal maturity;
- quality of life or psychological adjustment assessed using validated scales (Because no included trials reported quality of life, but psychological measures such as self-concept were reported, psychological adjustment was added as an outcome);
- measures of cognitive performance that were assessed using validated instruments. For instance, these could include measures of visual-spatial or mathematics performance;
- adverse effects such as benign intracranial hypertension, slipped capital epiphyses, effects on glucose metabolism, and incidence of malignant disease

### Exclusion criteria

Randomised controlled trials that considered hGH against another active treatment rather than placebo or no treatment were excluded. The objective of the review was to consider the efficacy of hGH as a growth promoting treatment. Trials that compared hGH with other treatments known or presumed to affect growth would not be informative about the fundamental efficacy of hGH. Dose-response trials (which do not include a zero dose or placebo group) were also excluded as they do not address whether hGH works. Trials that compared hGH plus some other active treatment against only the active treatment were also excluded. In this type of design the effects of hGH may be different than when hGH is administered alone. Because the aim was to evaluate the effects of hGH, designs in which hGH may interact with another treatment were excluded.

## Search methods for identification of studies

### Electronic searches

Searches were not conducted for trials before 1980 because the intervention (recombinant hGH) was not introduced until 1985. Earlier trials using growth hormone derived from human pituitary were not included as pituitary-derived growth hormone is no longer used.

The following electronic databases were searched to identify relevant trials:

- *The Cochrane Library* (Issue 4, 2005);
- MEDLINE (up to July 2006);
- EMBASE (up to June 2002);
- Science Citation Index (up to June 2006);
- BIOSIS (up to June 2006).

The MEDLINE search strategy was adapted for searches of EMBASE, The Cochrane Library and HMIC. Other databases that do not have facilities for complex search strategies were searched using a combination of “growth hormone” and “Turner\* syndrome”. For a detailed search strategy, see [Appendix 1](#)

The following sources were searched for ongoing trials:

- National Research Register (Issue 3, 2006),
- Current Controlled Trials (<http://controlled-trials.com/>, search 16 August 2006).

### Searching other resources

The following sources were searched for grey literature: Web of Knowledge Proceedings (the Institute for Science Information Proceedings allow access to abstracts from papers delivered at international conferences, symposia, seminars, colloquia, workshops, and conventions; searched 16 August 2006), Health Management Information Consortium (HMIC; this database focuses on community care and health systems management in the UK, Europe and developing countries including journals, books, reports, official publications and grey literature; searched 16 August 2006).

Experts were contacted for advice and peer review, and to identify additional published and unpublished references. The following pharmaceutical companies were contacted for additional trials: Eli Lilly, Ferring, Novo Nordisk, and Pharmacia. No additional studies were obtained from the pharmaceutical companies.

Bibliographies of related papers were assessed for relevant studies.

## Data collection and analysis

### Selection of studies

Titles, abstracts and keywords of all retrieved records were reviewed for inclusion. Full articles were retrieved for further assessment if the information available suggested that the study



was a randomised controlled trial that: 1) included children with Turner syndrome (TS), 2) compared recombinant growth hormone (hGH) with placebo or no treatment, and 3) assessed one or more of the growth or height outcomes to be included. Full articles were also retrieved for clarification if there was doubt about inclusion eligibility. Inclusion criteria were assessed independently by two reviewers (LB and JB or CC and JB) with any disagreements resolved through discussion with a third reviewer (RM).

### Data extraction and management

The following data were extracted using a data extraction form:

- general information: authors, reference, country, year of publication, study design;
- intervention: dose, route, timing, control intervention (placebo or no treatment), any other relevant treatments;
- participants: total number and number in comparison groups, age, trial inclusion and exclusion criteria, height baseline characteristics, setting;
  - outcomes specified above;
  - results for outcomes listed as reported within trials;
  - trial characteristics: methodological (allocation to treatment groups, blinding, baseline comparability, method of analysis and adequacy of sample size, and attrition), general (generalisability, appropriateness of outcome measures, inter centre variability, conflicts of interest);
  - quality assessment.

Data extraction was done by two reviewers (LB and JB or CC and JB) with any disagreements resolved through discussion with a third reviewer (RM).

### Assessment of risk of bias in included studies

The quality of included RCTs was judged primarily using Jadad criteria (Jadad 1996). In particular, the following were assessed:

- adequacy of randomisation (was the study described as randomised and was the method to generate randomisation described and appropriate);
- adequacy of blinding (was the study described as double blind and was the method of blinding described and appropriate); and
- reporting of dropouts and withdrawals (were withdrawals and dropouts described and quantified). Quality criteria were assessed by two reviewers (CC and JB) with any disagreements resolved through discussion.

### Assessment of heterogeneity

In the event of substantial clinical or methodological or statistical heterogeneity, study results will not be combined in meta-analysis. Heterogeneity was identified by visual inspection of the forest plots, by using a standard  $\chi^2$ -test and a significance level of  $\alpha$

= 0.1, in view of the low power of such tests. Quantification of heterogeneity was also examined with  $I^2$ , ranging from 0% to 100% including its 95% confidence interval (Higgins 2002).  $I^2$  demonstrates the percentage of total variation across studies due to heterogeneity and will be used to judge the consistency of evidence.  $I^2$  values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003). When heterogeneity is found, we will attempt to determine potential reasons for it by examining individual study characteristics and those of subgroups of the main body of evidence.

### Data synthesis

Data were summarised statistically if they were available, sufficiently similar and of sufficient quality. Statistical analysis were performed according to the statistical guidelines referenced in the newest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005).

When only one study reported an outcome, a mean difference (MD) was reported.

### Subgroup analysis and investigation of heterogeneity

There were insufficient data to allow for any subgroup analyses. Should sufficient data in future permit, the following subgroup analyses would be of interest:

- duration of treatment: fewer than two years, two to four years, more than four and less than six years, more than six and less than eight years, more than eight years;
- injection frequency: three times weekly versus six or seven times weekly;
- treatment begun before puberty or after puberty.

### Sensitivity analysis

There were insufficient data to allow for any sensitivity analyses. Should sufficient data in future permit, the following sensitivity analyses would be of interest:

- repeating the analysis excluding any unpublished studies (if there are any);
- repeating the analysis taking account of study quality, as specified above;
- repeating the analysis excluding any very large studies to establish how they dominate the results.
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

## RESULTS

## Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

## Results of the search

Across all searches 620 records were located (excluding duplicates). Titles, abstracts and keywords of all records were reviewed by two researchers (LB and JB or CC and JB). Any disagreements were resolved through discussion. Reasons for exclusion included: studies not conducted in humans, studies conducted in adults, studies in participants who do not have Turner syndrome (TS), studies in which recombinant growth hormone (hGH) was not administered, studies in which there was no untreated group, studies in which there was no control group (single group studies), studies in which groups were not randomised or quasi-randomised, studies in which there was no growth or psychological outcome, reviews that were not conducted systematically, studies of hGH dose (without a “zero dose” condition), duplicate publications, reports of results from databases.

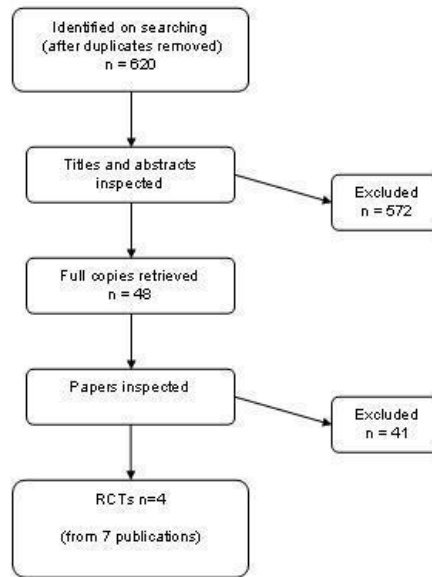
On the basis of review of the abstracts, 48 full records were retrieved. Abstracts had suggested that they would meet inclusion criteria or there was a need for additional information to deter-

mine whether the study met inclusion criteria. These full reports were assessed by two researchers (LB and JB or CC and JB). Reference citations are included for all retrieved references, either as included or excluded studies. Based on review of the full reports 41 studies were excluded. These are listed in table [Characteristics of excluded studies](#) with reasons for exclusion.

Four studies met the inclusion criteria. All were sponsored by or received support from pharmaceutical companies. A total of seven references reported on four studies. These included a [Canadian 93/98/05](#) study that reported final height results in a full report, one and two year growth results in one publication, final height results in an abstract, and psychological adjustment measures in another publication ([Rovet 1993](#)). Two more trials reported growth outcomes ([Rosenfeld 1989](#); [Quigley 2002](#)). A final study ([Kollmann 1991](#)) met the inclusion criteria in design, but did not report data for the controlled phase of the trial. Both the author and the sponsoring pharmaceutical company were contacted for the data, but neither responded. Therefore, the data from three studies were analysed, using the latest publication for the Canadian study.

For a flow-chart of study selection in an adapted QUOROM (quality of reporting of meta-analyses) version ([Moher 1999](#)) see [Figure 1](#) under 'Additional figures'.

**Figure 1. Flow-chart of study selection in an adapted QUOROM (quality of reporting of meta-analyses) version**



### Included studies

All included studies were randomised controlled trials with parallel designs. Only one study used a placebo control whereas the others used a no treatment control. Therefore, the participants in three of the four studies were aware of their treatment status. The trials varied in the duration of the controlled phase. Although participants in all four of the primary studies were treated until they achieved final height, only the [Canadian 93/98/05](#) study maintained a control group until final height, with a small subset of girls participating in an addendum follow up. The [Rosenfeld 1989](#) and [Kollmann 1991](#) studies maintained a control group for one year and the [Quigley 2002](#) study maintained a placebo control for 18 months. Results from uncontrolled phases are not included in this review.

Two studies were conducted in the USA, one in Canada and one in Germany. All included children had a diagnosis of TS confirmed by karyotype. At enrolment, children varied between five years and 14 years old. In one study ([Canadian 93/98/05](#)) girls received a

weekly hGH dose of 0.30 mg/kg in six doses. In the [Quigley 2002](#) study, two hGH doses were used: 0.27 mg/kg and 0.36 mg/kg; each in three injections per week during the controlled phase. In the [Rosenfeld 1989](#) study, the weekly hGH dose was 0.375 mg/kg administered in three injections. In the [Kollmann 1991](#) study, two doses were used and were computed on the basis of body surface area. The doses were two international units (IU) per square meter per week and three IU per square meter per week administered in daily injections. Additional details of the studies can be found in [Characteristics of included studies](#).

The [Quigley 2002](#) and [Rosenfeld 1989](#) studies included treatments in which hGH was combined with other agents. Results from these treatments were not included in this review.

### Risk of bias in included studies

The methodological quality of included studies was assessed using the Jadad scale ([Jadad 1996](#)).

The included studies were of moderate quality. Additional information is included in [Characteristics of included studies](#). None of

the studies described the method of randomisation. The [Canadian 93/98/05](#) study stratified girls for height relative to chronological age at entry and randomly assigned them to GH treatment or no treatment. The method of treatment allocation was not reported in the other studies. In the [Quigley 2002](#) study, participants and investigators were blinded as to treatment status. Because the other three studies used a no treatment control, blinding was not possible. Attrition was relatively high in the [Canadian 93/98/05](#) study. In the final report at protocol completion, it is reported that 19.7% of the treated group, and 44.8% of the control group had dropped out. The [Quigley 2002](#) study reported that eight participants (3%) left the study within the first 180 days. Otherwise, attrition for the placebo controlled phase of the study was not reported. The [Rosenfeld 1989](#) study reported that three participants (4%) withdrew in the first 12 months. The [Kollmann 1991](#) study did not report on attrition.

## Effects of interventions

There is one trial that is still ongoing ([NICHD](#)). This trial, being conducted in the USA, has not yet reported any results.

### Final height

Only one study ([Canadian 93/98/05](#)) reported final height in both recombinant growth hormone (hGH) treated and untreated groups. Although the other included studies treated participants until final height was achieved, they did not maintain a control group until final height. In the [Canadian 93/98/05](#) study, the girls who were treated with hGH achieved a final height of  $148 \pm 6$  cm and the girls who did not receive treatment achieved a final height of  $141 \pm 5$  cm. This seven cm difference (95% confidence interval (CI) 6.0 to 8) was statistically significant. Likewise, the treated girls had a  $1.6 \pm 0.6$  standard deviation change in their height standard deviation score (HtSDS) (age-specific Turner) from baseline whereas the untreated girls had a  $0.3 \pm 0.4$  SD change in their HtSDS (age specific Turner) (mean difference (MD) 1.3 SD, 95% CI 1.1 to 1.5). Normally, HtSDS does not change during growth so the change in HtSDS for the treated girls indicates catch-up growth.

### Height standard deviation score (HtSDS)

Height standard deviation score can be measured at any point during growth and indicates height relative to other children (or adults) of the same age. One study ([Canadian 93/98/05](#)) reported HtSDS scores for adult height at protocol completion. Ideally, one would compare the participants with Turner syndrome (TS) to normal girls of the same age as this is the comparison that is salient to the girls themselves. However, this study reported HtSDS using a TS population standard. HtSDS (age specific Turner) was 1.2 SD (95% CI 1.0 to 1.5) greater in treated than untreated girls

and HtSDS (adult Turner) was 1.0 SD (95% CI 0.8 TO 1.3) greater at protocol completion. These were statistically significant differences.

### Growth velocity (GV)

Three studies reported GV in cm per year. Two studies ([Canadian 93/98/05](#); [Rosenfeld 1989](#)) reported GV after one year of treatment. Treated girls grew approximately three cm more in the year than did untreated girls (MD 3 cm per year, 95% CI 2 to 4). One study ([Quigley 2002](#)) reported GV after 18 months of treatment. GV was three cm per year (95% CI 2 to 3) greater in the treated girls (0.36 mg/kg/wk dose) than in the untreated girls. The [Canadian 93/98/05](#) study reported GV after two years of treatment that was two cm per year (95% CI 1.3 to 2.3) greater in treated girls than in untreated girls. These results suggest that growth improvements in treated girls does tend to decline over longer treatment intervals.

### Growth velocity standard deviation score (GVSDS)

Growth velocity standard deviation score represents how quickly children are growing relative to their same age peers. As with HtSDS it would be ideal to compare girls with TS with their normal peers. However, two studies ([Canadian 93/98/05](#); [Rosenfeld 1989](#)) that report GVSDS used a TS population standard. These two studies demonstrated that the GVSDS for the first year of treatment in treated girls was approximately three SD greater than in untreated girls (MD 3.2, 95% CI 2.8 to 3.6). One study ([Canadian 93/98/05](#)) reported GVSDS after two years of treatment showing that GVSDS was 1.6 SD greater (95% CI 1.0 to 2.2) in hGH treated girls than in untreated girls. As with the GV results these results again suggest that increased growth declines over longer treatment intervals.

### Bone age

Bone age is a measure of skeletal maturity. If hGH treatment accelerates skeletal maturity, then growth benefits might be limited by a shorter overall growth period (i.e., treated children might grow faster, but stop growing sooner). If skeletal maturity is not accelerated by hGH treatment, then changes in bone age should approximate changes in chronological age such that a ratio of changes in bone age to chronological age should be approximately one. One study ([Canadian 93/98/05](#)) reported the ratio of changes in bone age to changes in chronological age. After one year of treatment the difference in the ratio was 0.2 (95% CI -0.03 to 0.4). After two years of treatment the difference in the ratio was -0.1 (95% CI -0.5 to 0.3). Although statistics are underpowered to conclude that there is no difference in the ratios, hGH does not appear to accelerate bone age as the ratio of bone age to chronological age was approximately one at both time points in both treated and untreated groups.

### Recombinant growth hormone (hGH) dose

Although the current review was not undertaken to evaluate the effects of hGH dose, one included trial (Quigley 2002) did include two hGH doses in addition to a placebo control. The two doses were 0.27 mg/kg/wk and 0.36 mg/kg/wk. Over 18 months of treatment the annualised growth velocity for girls on the two doses did not significantly differ (MD 0.20, 95% CI -0.3 to 0.7). Other studies that manipulated hGH dose, but that did not include a placebo or no treatment control were not included in this review. Therefore, no strong conclusions should be drawn about hGH dose effects.

### Psychological outcomes

Only one trial (Rovet 1993) reported on psychological outcomes in relation to hGH treatment (see Appendix 3). This report was based on tests performed on a sub-group of the participants in the Canadian growth study (Canadian 93/98/05). These psychological results are not presented more formally because the reported results are a selection of the tests given to the children and their parents. The selective reporting of results leaves in doubt the nature of the unreported results. In addition, the reported results are based on a subset of the girls who were participating in the trial at the time and no explanation is offered for why the data from only a subset of the participants were presented. The fact that these evaluations are self-reports (or parent reports) in the context of an unblinded study should also be considered. Bearing in mind possible biases, the presented results suggest the possibility that girls treated with hGH do have better psychological adjustment than untreated girls.

### Adverse effects

Reporting of adverse effects was minimal. Two of the included trials (Quigley 2002 Canadian 93/98/05) mentioned adverse effects (see Appendix 2). In the placebo controlled phase of the Quigley 2002 trial, otitis media occurred or worsened in 29% of girls treated with hGH and in 13% of girls in the placebo group. The longer-term adverse effects reported from this trial were not reported separately for treatment groups. In the Canadian study there were significant differences in 'treatment emergent' adverse effects between the treated and control groups (see Appendix 2).

## DISCUSSION

The results available suggest that recombinant growth hormone (hGH) is effective in improving growth, final height and possibly psychological adjustment in girls with Turner syndrome (TS). Girls treated with hGH grew approximately three cm more in one year than did untreated girls and they grew approximately two

cm per year more than untreated girls after two years. Expressing growth in growth velocity standard deviation (SD) scores reveals similar results. It does appear that initial growth improvements decline over longer treatment periods. However, there are insufficient data available to explicitly test this hypothesis.

The most important indicator of the efficacy of hGH for improving growth is the final height of women with TS who have been treated with hGH during their childhood. One study has reported final height results that show that final height was seven cm greater in women who had been treated with hGH than in women who remained untreated. The treated women had a 1.6 SD change in their height from baseline whereas the untreated women had a 0.3 SD change, again indicating that the treated women had catch up growth during treatment. Measures of bone age early in treatment did not indicate that bone age was accelerated and the eventual greater height of treated women supports the conclusion that hGH treatment does not accelerate skeletal maturation.

The current review was focused on a stringent evaluation of the efficacy of hGH in TS. For this reason evidence was limited to randomised controlled trials in which a control group received either placebo or no treatment. The presented results support the efficacy of hGH, particularly in improvement of growth and final height. It should be noted that these conclusions are supported by findings from other research designs in which treatment and control groups were not randomised or treated groups are compared with historical controls or with height predictions. Two of the included trials (Quigley 2002; Rosenfeld 1998) treated participants until final height but did not maintain the control group beyond the period included in this review. Both of these studies reported that the final height of treated women was improved relative to expectations.

The one included trial that evaluated final height did not report the average duration of hGH treatment. However, many currently available studies may not have treated participants optimally. Current recommendations are that treatment should be started early (ideally before age eight) and continue until final height is achieved. This would correspond to treatment for approximately eight years or longer. Most reported results are based on treatment for shorter durations. In addition, two of the included trials involved hGH injections three times per week. Current practice is to inject hGH six or seven times per week. Therefore final height improvements might be expected to be greater than reported here if hGH treatment is started earlier and dosing is optimised.

There are concerns about attrition in the reported trials. The trial reporting final height had lost approximately one third of the participants at the time of reporting. It is possible that treated girls who were achieving a poor response would be more likely to leave the trial. Similarly, girls in the control group who were growing

more slowly might be more likely to leave the trial. Both of these kinds of attrition would bias results, albeit in opposite directions.

Adverse effects were minimally reported. In the included trials there is little indication of serious adverse effects, however these small trials are seriously underpowered to detect rare events. Over longer term surveillance and outside the context of randomised controlled trials it seems that adverse effects are rare, but can be serious. Girls with TS may be at increased risk for a number of conditions that might be affected by hGH treatment such as diabetes mellitus, slipped capital femoral epiphyses, idiopathic intracranial hypertension, oedema and lymphoedema, or scoliosis (Blethen 1996; Frisch 1997; GH Soc 2001).

## AUTHORS' CONCLUSIONS

### Implications for practice

The reported results indicate that recombinant growth hormone (hGH) does improve growth and final height in girls with Turner syndrome (TS). The doses used in the included trials were approximately 0.3 to 0.375 mg/kg/wk (in one trial dose was computed by surface area). In one trial conducted to final height, hGH treatment increased final height in girls with TS by approximately seven cm. Although treated women are taller than untreated women, the final height achieved in treated women was approximately 148 cm. This is still below the normal range (i.e., more than 2 standard deviations below the normal mean) for adult women. Therefore it should be a matter for individual consideration as to whether this expected height gain is substantial enough to merit frequent or daily injections for probably 5 or more years. The cost of hGH is also substantial and it is a matter of debate as to whether the gains in height justify the expense. Finally, although serious adverse effects may be rare, as TS may already increase the risk of certain adverse effects, particular care should be taken to monitor girls with TS who are treated with hGH.

### Implications for research

The current review has focused on a strict evaluation of the efficacy of hGH primarily for improving growth and final height. Within this context, additional trials that include a control group until final height and that conduct an intention to treat analysis would be very helpful to solidify the current findings. However, it may already be felt that the merits of hGH are sufficiently demonstrated that randomised control groups cannot be justified. If so,

it is unfortunate that those making treatment decisions (patients, their parents and clinicians) will not know the extent to which hGH may affect final height under optimal treatment conditions. Although results from randomised controlled trials cannot be directly applied to individuals, there are problems with interpretation of results from studies based on surrogate measures of height improvement such as height prediction models (Taback 1999).

Despite the interest in the effects of hGH, treatment of short stature in girls with TS does not generally consist only of hGH. hGH is also often prescribed to girls with TS in combination with other growth-stimulating agents such as oxandrolone. If the efficacy of hGH has been adequately demonstrated, then focus should move to trials in which combinations of agents, doses, and timings are manipulated. Although there is merit in demonstrating short-term growth effects for such manipulations, these trials should be conducted with unchanging conditions until final height is achieved.

Existing evidence seems to indicate that growth and final height can be improved in TS. Perhaps the more pressing research question now is the cost-effectiveness of such treatment. To optimally evaluate cost effectiveness requires a good estimate of clinical effectiveness. This should not depend upon surrogate measures of efficacy such as changes from predicted height or comparison with a historical control, but should be based upon comparison between randomised groups of patients who receive hGH treatment and who do not. It may already be too late to collect more such data.

A full consideration of the costs and benefits of hGH treatment in TS should include not only effects on height, but other outcomes such as psychological or cognitive effects, which in the past have received little attention in the evaluation of hGH in TS.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Canadian 93/98/05

Methods	<p>RCT (Canada)</p> <p>Allocation to treatment groups: randomised (stratified by chronological age and height at entry)</p> <p>Blinding: unblinded</p> <p>Comparability of treatment groups: no statistically significant differences at baseline in age, BA, height, HtSDS, midparental height, or weight. Comparability may be compromised in final height comparisons due to attrition</p> <p>Method of data analysis: Differences between groups: 1 way ANOVA or Fisher's exact test. Mean +/- SD</p> <p>Sample size/power calculation: none</p> <p>Attrition/drop-out: At protocol completion 19.7% of the GH treated group had withdrawn; 44.8% of the control group had withdrawn</p>	
Participants	<p>For final height results starting n = 154</p> <p>At protocol completion 104 achieved final height and formed the basis of the report. hGH: 61, Control: 43</p> <p>Inclusion:</p> <ul style="list-style-type: none"> <li>· Age 7 yr - 13 yr</li> <li>· Documentation of diagnosis by karyotype</li> <li>· Height : &lt;10th centile on growth charts of National Centre for Health Statistics of the United States.</li> <li>· Normal fasting serum levels of glucose</li> <li>· Endogenous serum growth hormone of 8 µg/L on provocative or physiological testing</li> <li>· All forms of TS and variant included, including Y chromosome mosaic forms if gonadal remnants surgically removed</li> <li>· Annualised GV &lt; 6 cm/yr during 6 mo pre-randomisation period</li> </ul> <p>Setting: not specified</p>	
Interventions	<p>1. hGH: 0.30 mg/kg six times weekly (Humatrope®). Maximum dose 15mg</p> <p>2. No Treatment</p> <p>Girls with primary ovarian failure received oestrogen/progesterone treatment starting age 13</p>	
Outcomes	<ul style="list-style-type: none"> <li>· Final height</li> <li>· Height change from baseline (HtSDS)</li> <li>· Change in BA</li> </ul> <p>(for psychological adjustment outcomes see Rovet 1993 study below)</p>	
Notes	<p>Generalisability: participants seem representative of target population</p> <p>Outcome measures: final height, HtSDS and BA appropriate (although use TS standard)</p> <p>Inter-centre variability: not assessed.</p> <p>Conflict of interests: support from Eli Lilly Canada.</p> <p>Final height = growth rate &lt; 2 cm/yr and bone age &gt;= 14 years</p>	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>

Allocation concealment?	Yes	A - Adequate
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**Kollmann 1991**

Methods	RCT (Germany) Allocation to treatment groups: not described Blinding: no information Comparability of treatment groups: no statistical comparisons of baseline characteristics. 2 IU/m <sup>2</sup> group slightly older, taller, and heavier at baseline Method of Data analysis: no statistical analysis presented Sample size/power calculation: group sizes computed to detect an effect using a one-sided test Attrition/drop-out: not reported
Participants	84 enrolled 2 IU group: 29 3 IU group: 26 No treatment: 29 Include: · prepubertal · age >= 5 and <= 14 · height <= 2 SD for age according to Swiss standard
Interventions	1. hGH 2 IU/m <sup>2</sup> /wk (5.18 mg/m <sup>2</sup> /wk) in daily injections 2. hGH 3 IU/m <sup>2</sup> /wk (7.77 mg/m <sup>2</sup> /wk) in daily injections 3. No treatment
Outcomes	· GV · HtSDS (normal population standard) · Ht SDS (TS population standard) · Changes in BA/Changes in CA · Adverse Effects
Notes	No complete data for any outcome are presented. Therefore, no data from this trial are included in the current review Generalisability: Inclusion criteria are objective (although no description of types of TS karyotypes were included). Participants seem representative Outcome measures: appropriate Conflict of interests: Eli Lilly Study Group

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Quigley 2002

Methods	<p>RCT (USA)</p> <p>Allocation to treatment groups: not described</p> <p>Blinding: Patients and investigators blinded to treatment status, observer for BA analysis blinded</p> <p>Comparability of treatment groups: No statistically significant differences in baseline measures of GV or height, other measures appear similar except that placebo/placebo group (group 5) older, with greater BA and taller at baseline</p> <p>Method of data analysis: hypothesis tests: one-way ANOVA, Chi Square, Fisher's exact test for baseline measures; ANCOVA, stepwise regression and backward elimination models used for post-manipulation results</p> <p>Sample size/power calculation: no mention</p> <p>Attrition/drop-out: 8 left study within first 180 days, 133 (57%) not included in near FH analysis, otherwise not reported</p>
Participants	<p>232 enrolled</p> <p>stratified by age (5-8, &gt;8-10, &gt; 10-12, &gt; 12) then randomised</p> <p>Baseline data reported for n=224 who received hGH for 180 days</p> <p>Group 1: n=45</p> <p>Group 2: n=47</p> <p>Group 3: n=49</p> <p>Group 4: n=42</p> <p>Group 5: n=41</p> <p>99 in analysis of near FH</p> <p>Include:</p> <ul style="list-style-type: none"> <li>· TS, karyotypically proven</li> <li>· Age =&gt;5 years</li> <li>· BA =&lt; 12 years</li> <li>· Prepubertal</li> <li>· &lt; 10th percentile for height on National Centre for Health Statistics (NCHS) standard</li> <li>· GV &lt; 6 cm/yr</li> </ul> <p>Exclude:</p> <ul style="list-style-type: none"> <li>· Presence of any Y chromosomal component</li> <li>· Concurrent treatment with any agent that might influence growth</li> <li>· Clinically significant systemic illness</li> </ul> <p>setting: multicentre, otherwise not specified</p>
Interventions	<ol style="list-style-type: none"> <li>1. hGH 0.27 mg/kg/wk with oral placebo</li> <li>2. hGH 0.27 mg/kg/wk with low dose oestrogen</li> <li>3. hGH 0.36 mg/kg/wk with oral placebo</li> <li>4. hGH 0.36 mg/kg/wk with low dose oestrogen</li> <li>5. Placebo injection with oral placebo</li> </ol> <p>current review included groups 1, 3, &amp; 5 for 1st 18 months only (controlled phase)</p> <p>Injections 3x/wk for first 18 mo, thereafter 6x/wk (Humatrope®)</p> <p>Oestrogen dose based on age and weight.</p> <p>Open label sex steroid replacement at age 13.5 yr.</p> <p>Group 5 maintained for 18 months thereafter all treated with hGH (joined group 3)</p>
Outcomes	<ul style="list-style-type: none"> <li>· GV</li> <li>· near FH (not reported in current review because no untreated group)</li> </ul>

Quigley 2002 (Continued)

Notes	Generalisability: Inclusion criteria are objective and seem representative Outcome measures: measures appropriate Inter-centre variability: not assessed - 50 sites Conflict of interests: Eli Lilly sponsored
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*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Rosenfeld 1989**

Methods	RCT (USA) Allocation to treatment groups: Randomised, but method not discussed Blinding: no information Comparability of treatment groups: Comparable in pretreatment growth. Other variables not compared Method of Data analysis: no statistical comparisons between groups Attrition/drop-out: 3 withdrawn within first 12 months
Participants	n = 71, age 9.3 yr (4.7 - 12.4) hGH: 17 GV: 4.5 ± 0.8 GVSDS: 0.5 ± 0.8 Control: 18 GV: 4.2 ± 1.1 GVSDS: 0.2 ± 1.2 OX: 19 GV: 4.1 ± 1.9 GVSDS: 0.2 ± 1.0 hGH + OX: 17 GV: 4.3 ± 0.9 GVSDS: 0.2 ± 0.9 Only data from hGH and control groups included in current review height ≥ 1SD below mean for age pretreatment growth rate < 6cm/yr normal thyroid function provocative serum GH ≥ 7 ng/ml Setting: not specified
Interventions	1. Met-hGH: 0.125 mg/kg/ 3x/wk intramuscular 12 - 20 mo 2. Control: no treatment 3. Oxandrolone (OX) 0.125 mg/kg/day 4. Combination OX and hGH doses as above
Outcomes	· Growth velocity · Growth velocity SD relative to TS standard

Rosenfeld 1989 (Continued)

Notes	<p>Generalisability: Subjects appear representative of target group</p> <p>Outcome measures: Growth velocity and TS standardised growth velocity are appropriate, although normal population standard would be more useful</p> <p>Inter-centre variability: not assessed</p> <p>Conflict of interests: support from Genentech</p>
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*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rovet 1993

Methods	<p>RCT (Canada)</p> <p>Allocation to treatment groups: Method of randomisation not reported.</p> <p>Blinding: none reported</p> <p>Comparability of treatment groups: Baseline comparability of groups still participating was reported but the comparability of sub-groups as analysed was not reported</p> <p>Method of data analysis: Analysis not on an ITT basis. Point estimates and CI of differences was not reported. Significance levels estimated using ANOVA. No corrections for multiple comparisons</p> <p>Sample size / power calculations: no power calculations</p> <p>Attrition / drop-out: 49% drop-out rate from those still participating in trial</p> <p>Subjective ratings by children and parents may be affected by the unblinded nature of the study. Consider possible effects such as justification of effort</p>
Participants	<p>122 enrolled</p> <p>95 participating at time of evaluation (51 hGH; 44 no treat)</p> <p>86 compliant</p> <p>65 available for evaluation at 18 months</p> <p>48 in analysis (28 hGH; 20 no treat)</p> <p>Inclusion:</p> <ul style="list-style-type: none"> <li>· Turner syndrome (included Y mosaic forms provided gonadal remnants removed)</li> <li>· Age range 7 - 12 yr 11 mo</li> <li>· Height =&lt;10th centile on TS chart</li> <li>· Documented height velocity for previous 6 months</li> <li>· Normal fasting serum glucose</li> <li>· Endogenous growth hormone <math>\geq 8</math> mg/l on provocative physiological testing</li> </ul> <p>Baseline characteristics of 95 participating:</p> <ul style="list-style-type: none"> <li>· Age: hGH: <math>10.8 \pm 0.2</math>, no treat: <math>10.7 \pm 0.2</math></li> <li>· BA: hGH: <math>9.0 \pm 0.2</math>, no treat: <math>8.8 \pm 0.2</math></li> <li>· Ht (cm): hGH: <math>121.0 \pm 1.2</math>, no treat: <math>120.1 \pm 1.1</math></li> </ul> <p>Exclude:</p> <ul style="list-style-type: none"> <li>· Coincident disease likely to influence growth</li> <li>· Previous radiation to CNS / spinal axis</li> <li>· Previous treatment with adrenal androgens, oestrogen or hGH</li> <li>· Untreated hypothyroidism</li> <li>· started oestrogen treatment (in current trial)</li> </ul>

**Rovet 1993** (Continued)

Interventions	1) hGH: 0.05 mg/kg sc 6 evenings / week. Maximum weekly dose of 15 mg. (Humatrope®) 2) No treatment Length of treatment: 18 months Other interventions: none reported for this sub-group
Outcomes	· Olson's FACES III (protectiveness and stability) · Piers Harris self concept test (child self report; global self-concept and 6 subscales) · Achenbach's Child Behaviour Checklist (completed by parents) · Youth Self-Report (child) · GV (see Canadian 1993/1998) Not all outcomes were reported. Results from non-reported outcomes are unknown
Notes	Generalisability: Inclusion and exclusion criteria were defined. Analysis limited to 48 out of 95 participating in trial (51%) who had been followed up for 18 months. Therefore results may not be representative Outcome measures: Limited to psychological assessment with subjective ratings by child and parents in unblinded study. No objective confirmation of reports. Study not blinded, so cannot exclude differing input to those on active compared to no treatment (whether from parents / researchers). Short term outcomes (18 months treatment). Dropout analysis apparently based on 65 participants among whom the dropout was considerably greater in treated than untreated. This could bias results although evaluation of dropouts from the final analysis appears not to have been conducted Inter-centre variability: not assessed (13 sites) Conflict of interests: support from Eli Lilly, Canada

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

TS: Turner syndrome; GV: growth velocity; BA: bone age; IU: International Units; HtSDS: height standard deviation score. Interim HtSDS denotes a standard deviation score measured at some point before growth is complete.

**Characteristics of excluded studies [ordered by study ID]**

Study	Reason for exclusion
Arnal 1988	No untreated group
Bertelloni 2000	Not RCT
Bertrand 1996	No untreated group
Chernausk 2000	No untreated group



(Continued)

De Schepper 1994	No untreated group
Gyorgy 1993	Not RCT
Haeusler 1995	No untreated group
Heinrichs 1995	No untreated group
Holland 1991	Duplicate publication with Canadian study
Job 1991	No untreated group
Johnston 2001	No untreated group
Keizer-Schrama 1999a	No untreated group
Keizer-Schrama 1999b	No untreated group
Kollmann 1990	Abstract - No data presented
Lin 1988	No untreated group
Mahachoklertwattana	Not RCT
Massa 1995	No untreated group
Mazzanti 1995	Not RCT
Nilsson 1996	No untreated group
Rocchiccioli 1994	Not RCT
Rongen-Westerlaken	No untreated group
Rosenfeld 1992a	No untreated group at final height
Rosenfeld 1992b	No untreated group after 12-24 months
Rosenfeld 1998	No untreated group at final height
Ross 1997	No growth outcome reported
Sas 1999a	No untreated group
Sas 1999b	No untreated group
Sas 1999c	No untreated group

(Continued)

Sippell 1991	Not RCT
Stahnke 1992	No untreated group
Stahnke 1999	No untreated group
Takano 1989	Not RCT
Takano 1990	No untreated group
Takano 1993a	No untreated group
Takano 1993b	No untreated group
van Teunenbroek 1996	No untreated group
van Teunenbroek 1997	No untreated group
Vanderschueren 1990	No untreated group
Werther 1991	No untreated group
Werther 1993	No untreated group
Werther 1995	No untreated group

### Characteristics of ongoing studies [ordered by study ID]

#### NICHD

Trial name or title	Effect of biosynthetic growth hormone and/or ethinyl estradiol on adult height in patients with Turner syndrome
Methods	
Participants	TS by karyotype (no Y chromosome component) >= 5 years old below 10th percentile in height for age (for additional info see <a href="http://clinicaltrials.gov">http://clinicaltrials.gov</a> )
Interventions	1. low dose estrogen 2. growth hormone 3. low dose estrogen and growth hormone 4. placebo
Outcomes	adult height

**NICHD** (Continued)

Starting date	09/1987
Contact information	NICHD 9000 Rockville Pike Bethesda, Maryland 20892 USA prpl@mail.cc.nih.gov
Notes	Recruitment has stopped, but trial is expected to run another 2-4 years as participants finish growth

## DATA AND ANALYSES

### Comparison 1. Growth hormone versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Final height	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Final height in cm	1		Mean Difference (IV, Random, 95% CI)	Not estimable
1.2 Change in final height standard deviation score from baseline (relative to Turner syndrome population)	1		Mean Difference (IV, Random, 95% CI)	Not estimable
2 Growth velocity (growth velocity in cm per year)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Growth velocity after one year of treatment	1		Mean Difference (IV, Random, 95% CI)	Not estimable
2.2 Growth velocity after 18 months of treatment	1		Mean Difference (IV, Random, 95% CI)	Not estimable
3 Growth velocity standard deviation score (relative to Turner syndrome population)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Growth velocity standard deviation score after one year of treatment	1		Mean Difference (IV, Random, 95% CI)	Not estimable

### Comparison 2. Growth velocity for growth hormone doses

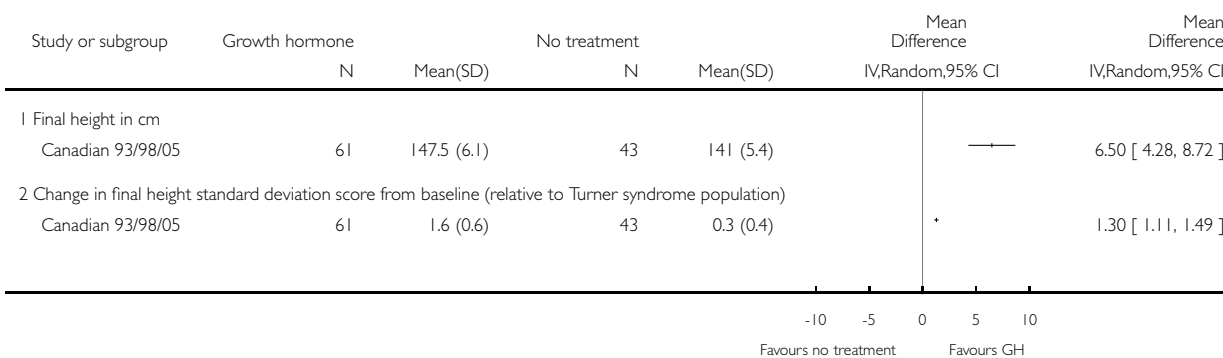
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Higher dose growth hormone versus lower dose growth hormone	1	94	Mean Difference (IV, Random, 95% CI)	0.20 [-0.25, 0.65]

### Analysis 1.1. Comparison 1 Growth hormone versus placebo or no treatment, Outcome 1 Final height.

Review: Recombinant growth hormone for children and adolescents with Turner syndrome

Comparison: 1 Growth hormone versus placebo or no treatment

Outcome: 1 Final height

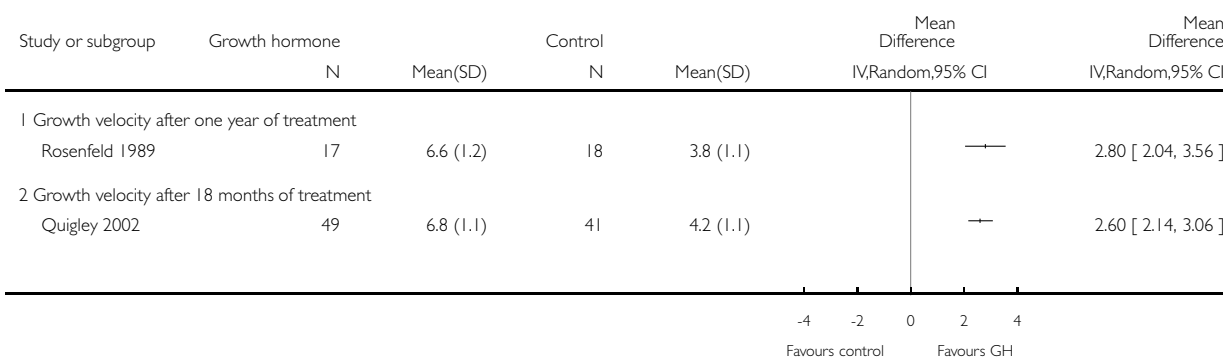


### Analysis 1.2. Comparison 1 Growth hormone versus placebo or no treatment, Outcome 2 Growth velocity (growth velocity in cm per year).

Review: Recombinant growth hormone for children and adolescents with Turner syndrome

Comparison: 1 Growth hormone versus placebo or no treatment

Outcome: 2 Growth velocity (growth velocity in cm per year)

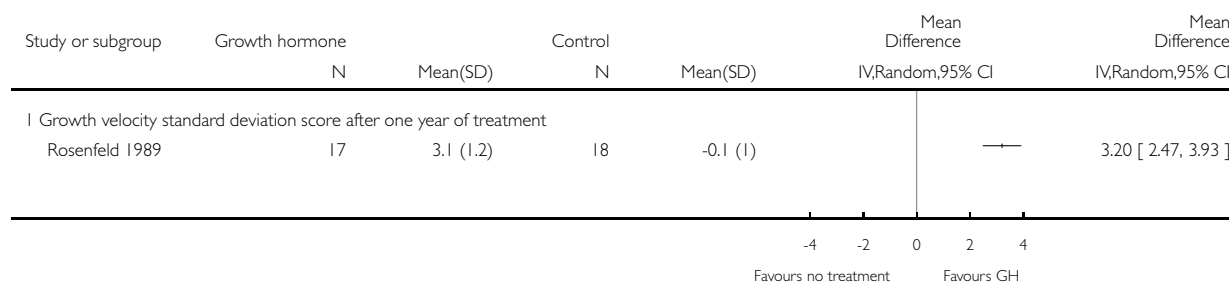


### Analysis 1.3. Comparison 1 Growth hormone versus placebo or no treatment, Outcome 3 Growth velocity standard deviation score (relative to Turner syndrome population).

Review: Recombinant growth hormone for children and adolescents with Turner syndrome

Comparison: 1 Growth hormone versus placebo or no treatment

Outcome: 3 Growth velocity standard deviation score (relative to Turner syndrome population)

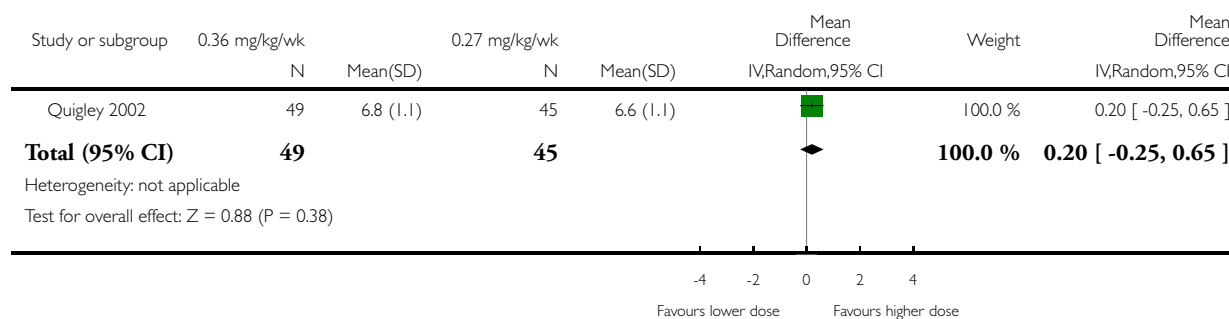


### Analysis 2.1. Comparison 2 Growth velocity for growth hormone doses, Outcome 1 Higher dose growth hormone versus lower dose growth hormone.

Review: Recombinant growth hormone for children and adolescents with Turner syndrome

Comparison: 2 Growth velocity for growth hormone doses

Outcome: 1 Higher dose growth hormone versus lower dose growth hormone



## APPENDICES

### Appendix I. Search strategy

#### Search terms

Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign (\$) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent.

- 1 explode "Somatropin"/ all subheadings
- 2 somatropin\*
- 3 somatotropin\*
- 4 somatotrophin\*
- 5 growth hormone
- 6 genotropin\*
- 7 humatrope\*
- 8 norditropin\*
- 9 saizen\*
- 10 zomacton\*
- 11 nutropin\*
- 12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
  
- 13 child\*
- 14 adolescen\*
  
- 15 #13 or #14
- 16 #12 and #15
  
- 17 "TURNER-SYNDROME"/ all subheadings
  
- 18 #17 and #16
  
- 19 RANDOMIZED-CONTROLLED-TRIAL IN PT
- 20 CONTROLLED-CLINICAL-TRIAL IN PT
- 21 RANDOMIZED-CONTROLLED-TRIALS
- 22 RANDOM-ALLOCATION
- 23 DOUBLE-BLIND-METHOD
- 24 SINGLE-BLIND-METHOD
- 25 #19 or #20 or #21 or #22 or #23 or #24
- 26 CLINICAL-TRIAL IN PT
- 27 explode CLINICAL-TRIALS/ all subheadings
- 28 (CLIN\* near TRIAL\*) in AB, TI
- 29 (singl\* or doubl\* or trebl\* or tripl\*) near (blind\* or mask\*)
- 30 placebo\*
- 31 (RANDOM\*) in TI, AB
- 32 RESEARCH-DESIGN
- 33 #26 or #27 or #28 or #29 or #30 or #31 or #32
- 34 #33 not #25
- 35 TG = "COMPARATIVE-STUDY"

(Continued)

36 explode "Evaluation-Studies"/ all subheadings  
 37 "Follow-Up-Studies"  
 38 "Prospective-Studies"  
 39 (control\* or prospective\* or volunteer\*) in ti,ab  
  
 40 #35 or #36 or #37 or #38 or #39  
 41 #40 not (#25 or #34)  
 42 #25 or #34 or #41  
 43 #18 and #42

## Appendix 2. Reported adverse effects

Study	Effect	Number or Proportion
Quigley 2002 (placebo controlled phase)	Otitis Media occurred or worsened	29% of GH treated; 13% of placebo treated
Rosenfeld 1989		No discussion of adverse effects
Canadian 2005	Surgical procedures; otitis media; ear disorders; joint disorder; respiratory disorder; sinusitis; goiter	37 of GH treated, 17 of untreated; 35 GH treated, 17 of untreated; 15 of GH treated, 4 of untreated; 10 of GH treated, 2 of untreated; 8 of GH treated, 1 of untreated; 14 of GH treated, 4 of untreated; 0 of GH treated, 4 of untreated
Rovet 1993		No discussion of adverse effects
Kollmann 1991		No discussion of adverse effects by treatment groups

## Appendix 3. 18 months psychological results from Canadian study (Rovet et al, 1993)

Psych. Measure	GH treated	Untreated control	treated v control
Global self-concept (self-report)	76.5 +/- 18.9	64.4 +/- 21.7	p = 0.001
Appearance (self-report)	67.0 +/- 24.5	55.7 +/- 24.9	p = 0.08
Intelligence (self-report)	75.0 +/- 23.8	56.2 +/- 25.2	p = 0.01
Peer Relations (self-report)	66.4 +/- 27.4	32.4 + 25.6	p = 0.001



(Continued)

Friendships (mother rating)	3.15 +/- 0.6	2.72 +/- 0.83	p = 0.05
Popularity (mother rating)	66.4 +/- 27.4	32.4 +/- 25.6	p = 0.001
Teasing (parent rating)	0.69 +/- 0.55	1.05 +/- 0.61	p = 0.05
Hyperactivity (mother rating)	59.6 +/- 7.6	65.2 +/- 8.0	p = 0.05
Protectiveness (mother rating)	1.10 +/- 1.31	0.63 +/- 0.9	p = .10

## WHAT'S NEW

Last assessed as up-to-date: 30 July 2006.

Date	Event	Description
3 November 2008	Amended	Converted to new review format.

## HISTORY

Protocol first published: Issue 4, 2002

Review first published: Issue 3, 2003

Date	Event	Description
31 July 2006	New search has been performed	38 publications were identified by the updated searches. One full record was retrieved from the updated search

## CONTRIBUTIONS OF AUTHORS

LOUISE BAXTER: selection of studies, data extraction, drafting of update review, data analysis, data presentation

JACKIE BRYANT: selection of studies, data extraction, drafting of protocol and review, data analysis, data presentation

CAROLYN CAVE: selection of studies, data extraction, drafting of protocol and review, data analysis, data presentation

RUAIRIDH MILNE: drafting of protocol/review, data presentation

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- Wessex Institute, University of Southampton, UK.

### External sources

- No sources of support supplied

## NOTES

An additional reviewer has been added to the review (L Baxter).

## INDEX TERMS

### Medical Subject Headings (MeSH)

Adolescent; Body Height; Growth Disorders [\*drug therapy; etiology]; Growth Hormone [\*therapeutic use]; Randomized Controlled Trials as Topic; Recombinant Proteins [therapeutic use]; Turner Syndrome [\*complications]

### MeSH check words

Child; Female; Humans