GONADOTROPIN RELEASING HORMONES ANALOGUES
USAGE IN THE MANAGEMENT OF PRECOCIOUS PUBERTY.

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Background
Puberty arises as a result of an increase in release of the gonadotrophins (sex hormones (LH) luteinising hormone and (FSH) follicle stimulating hormone) from the pituitary gland. The pituitary gland sits at the base of the brain and the secretion of hormones from the gland is controlled by part of the brain known as the hypothalamus (Figure).

The sex hormones are controlled from the hypothalamus by a hormone called gonadotrophin releasing hormone which is secreted in bursts every 90 minutes. Puberty arises as a result of an increase in the height of these bursts. The pituitary responds to these bursts by producing LH and FSH which act on the gonads to produce the sex steroids, testosterone in males and estradiol in females. The bursts of gonadotrophin releasing hormone are critical to the system because if the secretion takes place continuously the pituitary gland becomes unresponsive to the gonadotrophin releasing hormone.

This observation of reduced gonadotrophin release when gonadotrophin releasing hormone is applied continuously led to the development of the gonadotrophin releasing analogues which occupy the gonadotrophin releasing hormone receptor for long periods of time, thereby reducing gonadotrophin secretion from the pituitary.

Precocious puberty is defined as the onset of the secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. The problems that are associated with this early onset of puberty relate to a compromise in final height due to rapid bone maturation and the social consequences of developing puberty at an age inappropriate time. These include behavioural problems in both sexes and early menstruation in girls.

The purpose of gonadotrophin releasing hormone analogue therapy is to dampen down and freeze this process until a more age appropriate time is reached.
**Product licence**
Gonadotrophin releasing hormone analogues are licensed for the management of adult diseases such as prostate and breast cancer which are sex steroid dependent. Currently, only one product (manufactured by Ferring Pharmaceuticals) is in the process of having a product licence granted for specific use in precocious puberty.

**Preparations**
A number of nasal preparations are available, but these are ineffective in the management of precocious puberty. More effective control comes from the use of depot preparations which last either 4 or 12 weeks. The two most popular brands are:
- Astra Zeneca
  - Zoladex (also known as Gosarelin) - 3.6 mg in a syringe applicator given 4 weekly.
  - Zoladex LA - 10.8 mg in a syringe applicator
- Wyeth
  - Leuprolin (also known as Prostap) - a microsphere preparation that requires reconstitution and comes as 3.75 mg vial with 1ml vehicle filled syringe.
  - Leuprorelin Prostap 3 - long acting preparations coming as 11.25 mg vial with 2 ml vehicle filled syringe.

**Dosage and administration**
The preparations when administered on a 4 or 12 weekly basis are given as subcutaneous injections and the dosing is as above.

**Side effects**
The gonadotrophin releasing hormone analogues have an initial stimulatory effect on sex hormone secretion before they attain their full blocking potential. This stimulatory effect may last for 2 to 3 weeks and in girls in particular who are in advanced puberty it may precipitate menstruation. To address this, some Paediatric endocrinologists cover the first 6 weeks of therapy with an oral medication know as cyproterone acetate. Side effects in children are rarely reported although mild breast enlargement is possible in boys. Rashes, itching and injection site reactions have been recorded. A full appraisal of the gonadotrophin releasing hormone analogues can be found on the British National Formulary web site (www.bnf.org).

**Monitoring therapy**
The aim of the therapy is to modulate growth and the rapid advance in bone maturation and puberty and should include:

1. Growth and anthropometric measurements 4 monthly.
2. Bone maturation yearly
3. Ultrasound of the pelvis and pubertal staging initially on each assessment for anthropometric monitoring. Ultrasound examination can revert to yearly measurement once control is established.
4. The Gonadotrophin releasing hormone test and sex steroid measurement. It is still unresolved whether stimulation testing with gonadotrophin releasing hormone test should be undertaken to determine whether full suppression has been achieved. Usually clinical findings are sufficient to direct the clinician, but occasionally further evaluation with the gonadotrophin releasing hormone test or measurements of sex steroid concentration, testosterone or estradiol are required.
5. Bone mineral density usually measured at the end of therapy and yearly thereafter, until adulthood.

**Duration of Therapy**
Up to 11 years of age in girls and 12 years in boys.

**Drug Interactions**
There are no noted drug interactions listed in the British National Formulary.

**Effectiveness**
Studies searched from the literature using the terms gonadotrophin releasing hormone agonist, final height, precocious puberty.
Studies identified are listed in references. None based on randomised control trial model except Cassio et al. Studies range from well conducted control or cohort studies with a low risk of confounding bias or chance and a moderate chance that the therapy has an effect through to studies with high risk of bias and high chance that therapy effect is not present. Overall Grade of recommendation is C (Range A to C where A is highest).

**Short term:** Gonadotrophin releasing hormone analogue therapy when given by depot injection is extremely effective in freezing puberty and allaying the advance in skeletal maturation. There is clear documentation that puberty can be held at the point at which therapy is commenced and to a certain extent the physical appearance reversed. There are no short term data on quality of life associated with this intervention. Equally, information on better psychosocial adjustment resulting from holding up the pubertal process is not available.

**Long term:** A number of studies have demonstrated that gonadotrophin releasing hormone analogue therapy can be valuable in holding the advance in bone maturation and providing the potential for an improvement in stature. The recent publication of a number of large studies (Table) demonstrate that height gains particularly in females can range between 3.4 and 10.5 cms. Gains in males range between 1 and 13.7 cms although because of the predilection of precocious puberty for females the male data lacks adequate numbers.

**Table Effect on final height**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number Female : Male</th>
<th>Average Female Height gain (cms)</th>
<th>Average Male Height gain (Cms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mul et al</td>
<td>87F : 9M</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>Galluzzi et al</td>
<td>22F : 11M</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Oostdijk et al</td>
<td>31F : 5M</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Klein et al</td>
<td>80F : 18M</td>
<td>10.5</td>
<td>15.0</td>
</tr>
<tr>
<td>Paul et al</td>
<td>20F : 6M</td>
<td>7.0</td>
<td>10.7</td>
</tr>
<tr>
<td>Heger et al</td>
<td>50F</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Carel et al</td>
<td>58F : 8M</td>
<td>4.8</td>
<td>13.7</td>
</tr>
<tr>
<td>Arrigo et al</td>
<td>71F</td>
<td>2.8</td>
<td></td>
</tr>
</tbody>
</table>
What is clear is that therapy commencing before the age of 6 years is more likely to be associated with a better overall height gain. A randomised control trial (Cassio et al, 1999) of children aged between 7.5 and 8.5 years given either gonadotrophin releasing hormone analogue or placebo showed no overall effect on final height. As a result clinicians should be cautious at counselling height gain on patients who start therapy after the age of 6 years.

**Bone Mineral density:** Holding up the pubertal process led to concerns that bone mineralisation may be compromised. Studies demonstrate that bone mineralisation density in late adolescent girls (Heger et al, 1999, Antoniazzi et al, 2003) and boys (Bertelloni et al, 2000) is normal.

**Reproductive function:** Two studies have followed patients into early adulthood demonstrating that the onset of menstruation occurs at the normal time (gonadotrophin releasing hormone analogue therapy discontinued age 10½ to 11 years) (Heger et al, 1999, Antoniazzi et al, 2003). No data on pregnancy outcome are available at present for this mode of therapy. Data from a single study in a small number of males has revealed normal sperm reproduction (Bertelloni et al, 2000).

**References**


7. Carel JC, Roger M, Ispas S et al. Final height after long term treatment with triptorelin slow release for central precocious puberty: importance of statural growth


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