Clinical suppression of precocious puberty with cetrorelix after failed treatment with GnRH agonist in a girl with gonadotrophin-independent precocious puberty

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Abstract
This report presents the case of a 7-year-old girl with gonadotrophin-independent precocious puberty treated with cetrorelix [gonadotrophin-releasing hormone (GnRH) antagonist] after poor response to GnRH agonist therapy was observed in the endocrinology outpatient clinic. Uterine and ovarian morphology returned to within the normal prepubertal range after GnRH antagonist was injected subcutaneously. Vaginal bleeding stopped completely. The effects of GnRH antagonist treatment were comparable to those of GnRH agonist. The potential advantage of GnRH antagonists would be a clinically significant direct effect on the ovary, if it exists, and GnRH antagonists should be available for use in such children.

Keywords: GnRH agonist, GnRH antagonist, precocious puberty

Introduction
Precocious puberty in females is defined as the presence of secondary sexual characteristics, even menarche, before the age of 8 years. Blockade of GnRH (gonadotrophin-releasing hormone) effects using GnRH analogues (particularly agonists) is the established treatment of choice. This report presents the case of a 7-year-old girl with gonadotrophin-independent precocious puberty treated with a GnRH antagonist after poor response to GnRH agonist therapy.

Case report
The girl was born in 1996 as the first child of non-consanguineous healthy parents after a premature spontaneous delivery at 32 weeks gestation without any known brain injury associated with her prematurity. Her birth weight was 1554 g. At 11 months, acute bronchiolitis with erythematous papulomacular lesions was noted. She did not reach the child’s developmental milestones at appropriate ages (about 10–25th percentile) during regular follow-up. However, menarche occurred at the age of 2.6 years.

The patient first presented to the endocrinology outpatient clinic at the age of 3.3 years for evaluation of precocious puberty. Her height was 100.2 cm (75–90th percentile) and she weighed 16.3 kg (75–90th percentile) (Figure 1A, B). Pubertal stages were B2 and P2 and bone age was advanced at 5 years. There was no clinical evidence of McCune–Albright syndrome. Two-dimensional sonographic examination of the pelvic organs showed a pear-shaped uterus with bilaterally multilocular (microcystic) ovaries. There was an increased uterine length of 4.9 cm (normal for age 2.9 ± 0.7 cm) (Buzi et al., 1998) and volume of 11.9 ml (normal for age 1.6 ± 0.8 ml) (Salardi et al., 1985), and an increased ovarian volume of 4.1 ml on the right side.
and 7.5 ml on the left side (normal for age 0.7 ± 0.5 ml and 0.7 ± 0.5 ml respectively) (Buzi et al., 1998). An endometrial echo was also present (3.0 mm).

The results of hormonal evaluation performed immediately before GnRH agonist injection are presented in Figure 2. LH responses to a standard GnRH challenge at the ages of 3.3 and 3.7 years were both negative, without any increase in the LH/FSH ratio, demonstrating no pubertal activation of the hypothalamic–pituitary axis. Plasma oestradiol was measurable, but low. Magnetic resonance imaging of the brain at the age of 3.3 years showed no pathological findings in the hypothalamic–pituitary area. These results led to the diagnosis of gonadotrophin-independent precocious puberty for autonomous ovarian function (although the low oestrogen concentrations were surprising).

Pelvic ultrasound revealed signs of ovulation, with macrocystic ovaries from the age of 3.8 years. As no obvious peripheral lesion was noted, the patient was administered a GnRH agonist [a 1-month leuprorelin acetate depot preparation (Leuplin Depot, Takeda Chemical Industries Ltd, Tokyo, Japan)] 0.3 mg/kg per month from the age of 3.9 years, for 34 months. During this period, LH, FSH and oestradiol were persistently measureable (Figure 2). Pelvic ultrasound demonstrated microcystic ovaries with an occasional macrocystic pattern and vaginal spotting. Bone age was advanced, to 8 years 10 months at the age of 6.6 years. At this time, the girl’s height was 129.9 cm and she weighed 26.2 kg.

As a result of poor control of growth progress and menstruation with the GnRH agonist, treatment with a GnRH antagonist (cetrorelix acetate, Cetrotide, Serono Inc., The Hague, The Netherlands) was initiated in accordance with the expressed wishes of the parents, and after having obtained written informed consent, at the age of 6.6 years. The patient’s acceptance of injections was generally good during the course of GnRH antagonist treatment. She did not develop any local reaction to the injections or other side effects. The only complaint was that the parents and the patient preferred the longer injection interval with the depot GnRH agonist treatment previously administered.

The growth chart showed a continued growth rate after initiating GnRH antagonist treatment, including weight and height, without the pubertal growth spurt. However, bone maturation slowed down, as demonstrated by the bone age. Suppression of LH, FSH and oestradiol was present and remained stable throughout the course of treatment until the last visit (Figure 2). Clinical signs of puberty regressed (B2) and menstrual bleeding did not occur. Regular sonographic monitoring showed regression of uterine and ovarian size to the normal range for age (Table 1). Ovarian morphology changed from a macrocystic to microcystic pattern 1 month later, and to a homogeneous pattern 3 months later. During follow up, there was an intermittently microcystic ovarian pattern, but no macrocystic ovary occurred.

To make the treatment more convenient, the injection interval could be lengthened as a result of effectively suppressing the pituitary–gonadal axis. The frequency of GnRH antagonist administration was decreased from 3 mg per week to 3 mg every other week for 3 months, and then to 3 mg every 4 weeks, until now. The course of GnRH antagonist treatment was uneventful and without any oestrogen deprivation symptoms.

**Discussion**

The aim of this pilot case was to investigate the efficacy of a GnRH antagonist in a paediatric indication, and to compare it with that of a GnRH agonist depot preparation. There are only limited data on GnRH antagonists in early puberty in animal models, and this is the first published report on the use of antagonists to control premature puberty in humans. Using a female rat model, GnRH antagonists, without the initial ‘flare-up’ seen with GnRH agonists, showed better control of FSH and LH concentrations and stronger pituitary gene suppression (Roth et al., 2000). Roth et al. (2001) showed, again in a female rat model, that GnRH antagonists and agonists exert different GnRH/receptor expression at hypothalamic, ovarian

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**Figure 1.** Growth chart of girl with precocious puberty during treatment. The body weight (A) and height (B) of this patient with precocious puberty are plotted on the growth chart for Chinese female children.
and uterine concentrations. Any isolated alteration of GnRH neuronal systems in these extrapituitary structures may result in the premature activation of pulsatile GnRH release, and could thus lead to idiopathic precocious puberty. This may be one possible reason why GnRH agonists fail to suppress activation of the pituitary–gonadal axis.

Extrapituitary GnRH receptors are also seen in humans, and GnRH analogues may affect extrapituitary structures such as the ovary, oocyte, granulosa cells and embryo. Negative effects on processes such as folliculogenesis, implantation and embryo development are not relevant in the treatment of precocious puberty, however. In contrast, it is possible to utilize the possible intrinsic direct effects of GnRH antagonists on human extrapituitary sites to treat cases of failure of GnRH agonist therapy, as in this patient.

The initial GnRH challenge test was negative, and GnRH agonist treatment did not achieve optimal control of clinical symptoms. Extrapituitary gonadotrophin/steroid production are not relevant in the treatment of precocious puberty, however. In contrast, it is possible to utilize the possible intrinsic direct effects of GnRH antagonists on human extrapituitary sites to treat cases of failure of GnRH agonist therapy, as in this patient.

However, it is difficult to find the ideal dose and time interval for administration in such cases. Although cetrorelix is well known for its limited duration and rapid recovery, the activity of ovarian follicles was still affected when pituitary secretion of gonadotrophins was restored after cessation of GnRH antagonist treatment in the goat model (Gonzalez-Bulnes et al., 2005). This was why increased serum oestradiol value during the last endocrine laboratory examination (Figure 2) was not associated with any sign of menstruation during the following treatment courses of GnRH antagonist. In women undergoing ovarian hyperstimulation who were treated with GnRH antagonist, the follicular fluid oestradiol concentration was significantly decreased (P < 0.02) compared with those treated with GnRH agonist (García-Velasco et al., 2001). This means that GnRH antagonists exert a more significant effect on ovarian follicular steroidogenesis than GnRH agonists. In addition, the inhibitory effect of cetrorelix on pituitary and ovarian gene expression of the GnRH receptor and LH in the female rat model may explain a more direct and controlled medical result for precocious puberty when compared with GnRH agonist regimen (Roth et al., 2004).

A high weekly dose (3 mg) of cetrorelix was chosen, but it was divided into two 1.5 mg doses per week regimen because of the patient’s weight and age. The starting dose was 736.2 µg/kg per month, which gave excellent results during

### Table 1. Development of three-dimensional measurements of internal genital of the girl with precocious puberty during gonadotrophin-releasing hormone antagonist (cetrorelix) treatment. SD = standard deviation.

<table>
<thead>
<tr>
<th>Duration of treatment (months)</th>
<th>Endometrium thickness (mm)</th>
<th>Uterine length (cm/SD)</th>
<th>Uterine volume (ml/SD)</th>
<th>Right ovarian volume (ml/SD)</th>
<th>Left ovarian volume (ml/SD)</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>2.95</td>
<td>5.23/+3.43</td>
<td>21.00/+12.23</td>
<td>11.66/+21.06</td>
<td>6.25/+10.33</td>
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<td>4.76/+2.77</td>
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<td>4.57/+2.48</td>
<td>13.18/+7.25</td>
<td>4.47/+7.23</td>
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</tr>
<tr>
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<td>1.10</td>
<td>3.93/+1.57</td>
<td>7.03/+3.33</td>
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<td>12.50/+9.51</td>
<td>2.93/+1.86</td>
<td>1.31/-0.14</td>
</tr>
</tbody>
</table>

### Figure 2. Hormonal data of the girl with precocious puberty before and during 4 years of treatment. E₂ = oestradiol, FSH = follicle-stimulating hormone, LH = luteinizing hormone.
the initial 3 months. Because she was the first case in which GnRH antagonist was used to control the onset of puberty, lower doses were tested and the time interval when dosing with cetrorelix was decreased, following the request of her family, which may suffice in the treatment of precocious puberty. When steady-state serum concentrations were reached after 3 months, the dose was decreased to 242.9 µg/kg per month (3 mg biweekly) for 3 months and, at the last visit, to 117.6 µg/kg per month (3 mg monthly). A prolonged injection interval was thus suitable, as the clinical symptoms were controlled. This also has the advantage of lowering treatment costs.

Ultrasound evaluation showed that endometrial thickness and uterine volume were reduced after 1 month of GnRH antagonist administration, when compared with GnRH agonist treatment. This finding is consistent with that of Tur-Kaspa et al. (2001), who showed that the mean endometrial volume on the day of embryo transfer was significantly less ($P < 0.01$) in patients given GnRH antagonists, when compared with a GnRH agonist group, without affecting uterine blood flow or oestradiol concentration. Furthermore, lower implantation rates are seen with GnRH antagonists in IVF cycles (Orthmann, 2001), so perhaps there is a direct effect of such treatment on the endometrium, and not on the quality of oocytes or embryos. Ovarian volumes decreased to normal 3–6 months later, showing a similar pattern to the uterus. In this patient, the left ovary at first demonstrated a macrocystic pattern; 1 month later, a microcystic pattern was observed, and 3 months later a homogeneous ovary was visible. The better results obtained at 3 months of cetrorelix therapy regarding endometrium thickness, uterine length and uterine volume, and at 4 months regarding right ovarian volume in Table 1, followed by a slight restoration of uterine and ovarian sizes by 7 months of treatment may be due to decreased doses of GnRH antagonist in the latter months. However, the inhibitory effect in the ovary seems more profound than that in the uterus from the data of ultrasonography, and she did not demonstrate any clinical picture of menstruation during GnRH antagonist treatment course. This may support the theory that GnRH analogues exert an organ-specific regulation since different actions were noted at the hypothalamic, ovarian and uterine levels (Roth et al., 2001). In addition, the activity of ovary is more affected by GnRH antagonist than the activity of pituitary (Gonzalez-Bulnes et al., 2005). It may be considered that the cumulative effect of continuous administration of GnRH agonist for almost 3 years as contributing to the first few months of GnRH antagonist treatment. However, it has no advantageous effect when compared with GnRH antagonist treatment alone. Antagonist alone expressed stronger inhibition of gonadotrophins than combined agonist/antagonist in the female rat model (Roth et al., 2004), which may imply more manageable treatment with GnRH antagonists rather than agonists.

The potential advantage of GnRH antagonists would be a clinically significant direct effect on the ovary, if it exists, and they should therefore be available for use in the children with precocious puberty. In this case, GnRH antagonist treatment demonstrated an outcome that was as effective as established GnRH agonist therapy, with good patient acceptance. However, the main disadvantages of current antagonist preparations are an effective duration of only 1–3 days, a higher cost than depot GnRH agonists, and more physician visits are necessary. The long-acting depot antagonist preparations in the primate-testing phase offer potential advantages and will be more convenient for patients in this indication (Roth, 2002). Adjustment of the antagonist treatment schedule and dosage will be further studied to optimize outcome and increase compliance. In addition, comparative, randomized studies should be undertaken to investigate the long-term effects of GnRH antagonists in precocious pubertal patients, with the aim of making them available for routine clinical use.

References


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