Sexual dimorphism in the maturation of the pituitary–gonadal axis, assessed by GnRH agonist challenge

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Abstract

Objective: To assess whether the maturational changes of the pituitary–gonadal axis in a healthy population show gender-specific changes and to establish normative data for the different Tanner stages.

Design: Prospective, cross-sectional study.

Methods: The GnRH agonist leuprolide acetate (500 μg) was administered s.c. to 60 boys and 81 girls (age range, 5–17 years). Serum steroids and gonadotropins were determined at 0 and 24 h and at 0, 3 and 24 h after GnRH agonist challenge respectively, whereas IGF-I, IGF-binding protein-1 (IGFBP-1), IGFBP-3 and sex hormone-binding globulin were measured at baseline.

Results: Baseline and peak LH responses to the agonist in late puberty, and basal and peak FSH levels at all Tanner stages, were higher in girls than in boys. Girls showed higher IGF-I levels than boys throughout puberty, sharper decreases in IGFBP-1 and earlier and greater increases in 17-hydroxypregnenolone, dehydroepiandrosterone (DHEA) and DHEA-sulfate. Testosterone responses to the agonist increased during puberty in males, and showed no changes in females. Conversely, estradiol responses rose throughout puberty in females and remained unchanged until late puberty in males.

Conclusion: Leuprolide acetate stimulates gonadotropin and gonadal steroid secretion during puberty in both sexes and increases FSH levels in prepubertal girls. Pubertal maturation of gonadotrop function is gender specific, as it appears to involve increases in both the releasable and reserve pools of LH in males, and of LH and FSH in females. The earlier increase in Δ5-steroids in girls may suggest a sharper rise in ovarian cytochrome P450c17 activity along the Δ5-steroid pathway, while the failure of estradiol to increase in response to leuprolide acetate in early pubertal males suggests a late maturation of aromatase activity.

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Introduction

The potential utility of gonadotropin-releasing hormone (GnRH) agonist testing in clinical settings has been supported by the observations of distinct patterns of hormonal responses in pubertal disorders and ovarian hyperandrogenism (1–5). In contrast to standard GnRH tests, a single dose of a GnRH agonist not only stimulates the release of gonadotropins but also augments sex steroid secretion within 18–24 h in children and adults (3, 4). The pattern of hormonal secretory responses to the GnRH agonists nafarelin or leuprolide acetate has been previously investigated in small groups of prepubertal and pubertal boys, pubertal girls and adults (6–10). However, the variability and sex-related changes of the pituitary–gonadal responses throughout puberty are not well defined.

We assessed the gonadotropin and gonadal steroid secretion in a healthy population throughout all stages of pubertal development after leuprolide acetate administration to ascertain whether the maturational pattern of hormonal responses is gender specific and to establish normative data for the different Tanner stages.

Subjects and methods

Subjects

Sixty boys (age range, 5.3–16.8 years) and 81 girls (age range, 5.0–17.0 years) agreed to participate in the study. All were healthy, of normal height, weight and body mass index (BMI (11)), and had a normal medical history and physical examination. Thyroid, liver and kidney function tests were normal.

Girls were divided into five groups according to their Tanner stage of breast development (12): prepubertal (B1, n = 19); early pubertal (B2); midpubertal (B3); late pubertal (B4) and postmenarcheal (B5). Boys were...
classified into five groups according to testicular volume and morning levels of serum testosterone (7, 13, 14): prepubertal (G1), testes <4 ml and serum testosterone <25 ng/dl; early pubertal (G2), testes 4–6 ml and serum testosterone 25–50 ng/dl; midpubertal (G3), testes >6–8 ml and serum testosterone >50–150 ng/dl; late pubertal (G4), testes >8–12 ml and serum testosterone >150–250 ng/dl, and postpubertal (G5), testes >12 ml and serum testosterone >250 ng/dl.

The clinical characteristics of the study population are summarized in Table 1.

Assent was obtained from each subject, and informed consent was obtained from the parents. The study protocol was approved by the Institutional Review Board of the Barcelona Hospital.

**Study protocol**

Baseline blood samples were obtained between 0800 and 1000 h in the fasting state and in a supine position for measurement of plasma steroid hormones (17-hydroxyprogesterone (17-OHP), 17-hydroxyprogrenolone (17-Preg), androstenedione (Δ4-A), testosterone, dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEAS) and estradiol), gonadotropins, insulin-like growth factor-I (IGF-I), IGF-binding protein-1 (IGFBP-1), IGFBP-3 and sex hormone-binding globulin (SHBG). Leuprolide acetate (500 μg, Procrin, Abbott, Madrid, Spain) was then administered s.c.: gonadotropins and serum steroids were measured at 3 h and 24 h and at 24 h after GnRH agonist challenge respectively. The timing of blood sampling was selected according to previously reported data indicating that maximal pituitary and gonadal stimulation occurs 3–4 h and 18–24 h respectively after leuprolide acetate administration (2, 9, 15). Serum DHEAS levels were only measured at baseline, as values for this steroid have been shown to be unchanged by GnRH agonist administration (2, 9). In postmenarcheal girls, the study was scheduled for the follicular phase of the menstrual cycle.

**Hormone assays**

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured using a commercially available microparticle enzyme immunoassay (IMX System, Abbott, Chicago, IL, USA). The intra-assay and interassay coefficients of variation (CVs) were 3.0 and 5.4% respectively for LH and 4.1 and 6.9% respectively for FSH. DHEA was assayed using a tritiated kit (ICN Biomedical Inc., Carson, CA, USA). The intra-assay and interassay CVs were 7 and 14% respectively. After ethyl acetate–hexane (3:2) extraction and Celite column chromatography, 17-Preg was determined by RIA with 3H-labeled standard and antibody provided by ICN Biomedical (9). Serum testosterone, estradiol, 17-OHP, DHEAS, Δ4-A and SHBG levels were measured by RIA, as described (15). Serum IGF-I was determined by RIA after acid extraction and protein saturation by IGF-II (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA), and IGFBP-1 and IGFBP-3 were determined using a commercially available kit (DSL, Webster, TX, USA) (16).

**Statistical analysis**

Anthropometric data and hormonal results are expressed as means ± S.E.M. unless otherwise stated. Gonadotropin and steroid data are expressed as baseline and maximal peak. Independent variables were compared by one-way ANOVA corrected by Scheffe’s test for multiple comparisons. A P value below 0.05 was considered statistically significant.

**Results**

**Gonadotropins**

Baseline LH and FSH levels increased significantly from midpuberty in both sexes (P < 0.01). Leuprolide acetate stimulated gonadotropin release in all study groups. LH responses to the agonist at 3 and 24 h, which are indexes of the readily releasable and reserve pituitary

<table>
<thead>
<tr>
<th>Tanner stage</th>
<th>CA (years)</th>
<th>BA (years)</th>
<th>Height SDS</th>
<th>BMI (kg/m²)</th>
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<tbody>
<tr>
<td>Boys (n = 60)</td>
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<tr>
<td>G1 (n = 15)</td>
<td>9.6 ± 0.7</td>
<td>8.9 ± 0.6</td>
<td>−1.3 ± 0.3</td>
<td>16.7 ± 0.7</td>
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<td>G2 (n = 12)</td>
<td>12.0 ± 0.4</td>
<td>11.3 ± 0.1</td>
<td>−1.0 ± 0.2</td>
<td>16.5 ± 0.8</td>
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<tr>
<td>G3 (n = 9)</td>
<td>13.1 ± 0.5</td>
<td>12.4 ± 0.1</td>
<td>−1.1 ± 0.3</td>
<td>19.7 ± 1.1</td>
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<tr>
<td>G4 (n = 10)</td>
<td>14.8 ± 0.5</td>
<td>13.9 ± 0.1</td>
<td>−1.2 ± 0.2</td>
<td>19.1 ± 0.6</td>
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<td>G5 (n = 14)</td>
<td>16.2 ± 0.1</td>
<td>15.9 ± 0.1</td>
<td>−1.1 ± 0.1</td>
<td>20.9 ± 0.1</td>
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<tr>
<td>Girls (n = 81)</td>
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<tr>
<td>B1 (n = 19)</td>
<td>7.9 ± 0.3</td>
<td>8.3 ± 0.3</td>
<td>0.2 ± 0.1</td>
<td>16.0 ± 0.2</td>
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<tr>
<td>B2 (n = 16)</td>
<td>10.3 ± 0.3</td>
<td>10.6 ± 0.1</td>
<td>−0.4 ± 0.2</td>
<td>17.9 ± 0.3</td>
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<tr>
<td>B3 (n = 15)</td>
<td>12.3 ± 0.1</td>
<td>12.2 ± 0.1</td>
<td>−1.0 ± 0.2</td>
<td>18.5 ± 0.7</td>
</tr>
<tr>
<td>B4 (n = 11)</td>
<td>13.7 ± 0.5</td>
<td>13.3 ± 0.1</td>
<td>−1.0 ± 0.1</td>
<td>18.1 ± 0.4</td>
</tr>
<tr>
<td>B5 (n = 20)</td>
<td>15.3 ± 0.2</td>
<td>14.9 ± 0.1</td>
<td>−0.9 ± 0.2</td>
<td>20.4 ± 0.4</td>
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</tbody>
</table>

CA: chronological age; BA: bone age; SDS: standard deviation score.
pools respectively, rose during puberty in both sexes, and were significantly higher in girls than in boys in late puberty ($P = 0.002$ and $P = 0.0004$ respectively) (Fig. 1). Both baseline and peak FSH responses to the agonist showed striking sex-related differences as they were significantly higher in girls than in boys at all Tanner stages ($P < 0.01$) (Fig. 2).

**Steroid hormones**

Baseline estradiol levels in girls increased significantly with pubertal onset ($P < 0.05$ vs prepubertal levels) and experienced a second and sustained rise at midpuberty ($P = 0.003$ compared with early pubertal levels) (Table 2). In boys, estradiol concentrations increased from midpuberty to adulthood ($P < 0.01$). Peak estradiol responses to leuprolide acetate rose significantly throughout puberty in females and remained unchanged until late puberty in males.

Baseline testosterone levels rose significantly at B2 in girls ($P < 0.0001$ vs prepupertal values), and showed a second and significant increase at B5 ($P < 0.0001$ vs early pubertal levels). In boys, basal testosterone concentrations showed a significant increase from

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**Figure 1** Serum LH levels before and after leuprolide acetate administration in females (top) and in males (bottom) throughout all stages of pubertal development. The absolute mean values are depicted on top of each column. *$P < 0.01$ vs males.*
midpuberty to adulthood ($P < 0.0001$). Testosterone responses to GnRH agonist challenge rose progressively during puberty in boys, and demonstrated no significant changes in girls.

Basal levels of 17-OHP, $\Delta^4$-A, 17-Preg, DHEA and DHEAS rose significantly during puberty in both sexes ($P < 0.01$). Girls showed earlier and greater increases in 17-Preg, DHEA and DHEAS, whereas boys showed higher 17-OHP concentrations than girls by the end of puberty ($P < 0.0001$) (Fig. 3). In both sexes, most steroid precursors increased significantly in response to GnRH agonist challenge from midpuberty, with the exception of $\Delta^4$-A and DHEA.

**Growth factors and SHBG levels**

IGF-I and IGFBP-3 levels rose significantly during puberty in both sexes ($P < 0.01$), while IGFBP-1 and SHBG levels progressively declined (Table 3). Girls showed higher IGF-I levels than boys throughout puberty ($P < 0.01$), and a sharper decrease in IGFBP-1 concentrations with pubertal onset ($P = 0.0001$ vs early pubertal boys).

**Discussion**

A single dose of leuprolide acetate stimulates gonadotropin secretion both in normal males and in females.
<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
<th>B5</th>
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<tr>
<td>17-OHP (ng/dl)</td>
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<tr>
<td>Basal</td>
<td>34.3 ± 3.5</td>
<td>37.9 ± 2.6</td>
<td>57.5 ± 6.6</td>
<td>53.9 ± 4.7</td>
<td>81.9 ± 6.5</td>
<td>30.8 ± 4.8</td>
<td>47.9 ± 2.9</td>
<td>46.3 ± 5.4</td>
<td>48.0 ± 3.9</td>
<td>57.5 ± 6.5</td>
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<tr>
<td>Peak</td>
<td>27.4 ± 2.4</td>
<td>36.1 ± 3.4</td>
<td>91.1 ± 8.2</td>
<td>102.5 ± 17.0</td>
<td>165.4 ± 11.1</td>
<td>33.8 ± 5.8</td>
<td>59.1 ± 5.2</td>
<td>84.8 ± 9.3</td>
<td>92.9 ± 6.7</td>
<td>96.5 ± 7.4</td>
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<td>Δ^4A (ng/dl)</td>
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<tr>
<td>Basal</td>
<td>39.6 ± 5.3</td>
<td>104.4 ± 12.4</td>
<td>94.0 ± 7.0</td>
<td>155.9 ± 17.9</td>
<td>301.7 ± 34.1</td>
<td>54.7 ± 8.1</td>
<td>111.2 ± 10.7</td>
<td>150.7 ± 19.3</td>
<td>145.3 ± 30.8</td>
<td>155.9 ± 14.4</td>
</tr>
<tr>
<td>Peak</td>
<td>35.9 ± 5.0</td>
<td>105.7 ± 13.5</td>
<td>142.9 ± 14.0</td>
<td>160.9 ± 26.6</td>
<td>204.0 ± 20.8</td>
<td>52.4 ± 5.6</td>
<td>128.2 ± 9.7</td>
<td>198.8 ± 24.4</td>
<td>180.5 ± 28.3</td>
<td>173.1 ± 14.2</td>
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<td>Testosterone (ng/dl)</td>
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<tr>
<td>Basal</td>
<td>5.5 ± 0.9</td>
<td>16.7 ± 3.2</td>
<td>105.1 ± 10.2</td>
<td>405.4 ± 51.0</td>
<td>538.2 ± 41.9</td>
<td>6.7 ± 0.6</td>
<td>15.0 ± 1.6</td>
<td>20.7 ± 2.7</td>
<td>19.9 ± 3.4</td>
<td>28.8 ± 2.3</td>
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<tr>
<td>Peak</td>
<td>8.6 ± 1.5</td>
<td>106.4 ± 19.3</td>
<td>313.4 ± 64.0</td>
<td>662.9 ± 99.0</td>
<td>812.6 ± 42.0</td>
<td>7.5 ± 0.7</td>
<td>16.4 ± 1.8</td>
<td>24.6 ± 2.2</td>
<td>25.7 ± 2.6</td>
<td>32.9 ± 2.8</td>
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<td>Estradiol (pg/ml)</td>
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<tr>
<td>Basal</td>
<td>2.6 ± 0.8</td>
<td>2.5 ± 1.0</td>
<td>5.3 ± 0.6</td>
<td>10.6 ± 1.5</td>
<td>15.0 ± 1.9</td>
<td>4.5 ± 1.1</td>
<td>8.1 ± 1.5</td>
<td>26.4 ± 5.6</td>
<td>26.8 ± 5.8</td>
<td>35.0 ± 9.1</td>
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<tr>
<td>Peak</td>
<td>3.8 ± 0.7</td>
<td>3.2 ± 0.9</td>
<td>24.3 ± 4.0</td>
<td>25.2 ± 5.1</td>
<td>40.6 ± 3.9</td>
<td>19.5 ± 2.0</td>
<td>96.2 ± 11.6</td>
<td>187.6 ± 26.6</td>
<td>188.8 ± 28.7</td>
<td>138.1 ± 13.7</td>
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<td>17-Preg (ng/ml)</td>
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<tr>
<td>Basal</td>
<td>1.1 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>0.9 ± 0.1</td>
<td>1.7 ± 0.2</td>
<td>1.8 ± 0.1</td>
<td>1.0 ± 0.2</td>
<td>3.0 ± 0.3</td>
<td>3.5 ± 0.6</td>
<td>3.1 ± 0.5</td>
<td>2.4 ± 0.5</td>
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<tr>
<td>Peak</td>
<td>1.0 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>1.2 ± 0.1</td>
<td>2.4 ± 0.4</td>
<td>2.5 ± 0.3</td>
<td>0.9 ± 0.1</td>
<td>3.9 ± 0.3</td>
<td>4.5 ± 0.6</td>
<td>3.8 ± 0.7</td>
<td>3.2 ± 0.6</td>
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<td>DHEA (ng/dl)</td>
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<tr>
<td>Basal</td>
<td>98.5 ± 11.2</td>
<td>167.9 ± 13.2</td>
<td>279.5 ± 9.3</td>
<td>408.2 ± 39.2</td>
<td>435.0 ± 43.7</td>
<td>147.0 ± 13.0</td>
<td>304.5 ± 30.5</td>
<td>285.4 ± 29.0</td>
<td>245.8 ± 36.5</td>
<td>517.4 ± 79.9</td>
</tr>
<tr>
<td>Peak</td>
<td>93.6 ± 8.2</td>
<td>148.1 ± 13.5</td>
<td>317.6 ± 19.3</td>
<td>375.9 ± 41.7</td>
<td>422.2 ± 42.5</td>
<td>152.4 ± 11.0</td>
<td>344.9 ± 33.6</td>
<td>317.7 ± 32.8</td>
<td>291.2 ± 52.8</td>
<td>599.0 ± 92.5</td>
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<tr>
<td>DHEAS (pg/dl)</td>
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<tr>
<td>Basal</td>
<td>47.6 ± 10.0</td>
<td>54.8 ± 7.2</td>
<td>135.0 ± 19.3</td>
<td>191.7 ± 16.8</td>
<td>184.7 ± 24.4</td>
<td>37.6 ± 3.9</td>
<td>82.4 ± 7.2</td>
<td>92.7 ± 11.5</td>
<td>73.1 ± 9.1</td>
<td>125.3 ± 11.8</td>
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^a P ≤ 0.01 and ^b P ≤ 0.0001 vs pubertal stage-matched girls; ^c P ≤ 0.01 and ^d P ≤ 0.0001 vs pubertal stage-matched boys. To convert to SI units multiply by the following factors: 17OHP, 0.03026; Δ^4^-A, 0.0349; testosterone, 0.03467; estradiol, 3.671; 17-Preg. 0.332; DHEA, 0.03467; DHEAS, 0.02714.
starting in the prepubertal period. Pituitary responsiveness to GnRH agonist challenge shows sex-specific differences with boys demonstrating less secretion of both LH and FSH at all pubertal stages. The LH rise is unsustained during prepuberty and early puberty in both sexes, but becomes increasingly prolonged with sexual maturation; this appears to be attributable to increases in both the pituitary readily releasable and reserve pools of LH (8). FSH responsiveness to the agonist showed striking sex-related differences. FSH responses at 3 and 24 h were significantly higher in girls than in boys at all pubertal stages tested, supporting the early and sustained reported activity of the female neuroendocrine–pituitary axis (17). In boys, FSH responses tended to parallel those of LH during puberty, but changed less consistently with pubertal maturation. This pattern has already been described after nafarelin stimulation (7, 8), and is compatible with earlier reports showing that FSH responsiveness to native GnRH increases very little during puberty in males (18, 19).

Baseline estradiol levels in girls increased significantly with pubertal onset and experienced a second and sustained rise at midpuberty. Estradiol responses to leuprolide acetate rose significantly throughout puberty in females, and were as great as those of postmenarcheal girls at midpuberty, although the LH and FSH responses were lower. This apparent increased sensitivity of the pubertal ovary to gonadotropins is compatible with the concept that gonadotropin signal is either amplified more or down-regulated less in the ovary during puberty than during adulthood (3, 17). In boys, both baseline estradiol concentrations and estradiol responses to GnRH agonist administration increased moderately from midpuberty to adulthood. The estradiol response was maximal in mature boys, and was coincident with a maximal rise in FSH levels. The apparent failure of estradiol to increase in response to the agonist in early pubertal males, despite substantial concomitant increases in testosterone levels, supports previous reports suggesting that testicular and/or peripheral aromatase activity does not fully mature in males until puberty is complete (7, 8). Although pubertal maturation of aromatase seems to be, at least in part, FSH dependent, these findings suggest that other specific, gonadotropin-independent developmental processes still unknown may in fact control aromatase maturation.

Baseline testosterone levels rose significantly during puberty in girls but showed not significant increases after GnRH agonist stimulation. In boys, testosterone concentrations showed a progressive increase from early puberty through adulthood in response to the agonist. However, GnRH agonist administration was unable to elicit significant testosterone responses in prepubertal boys, suggesting that at least in midchildhood when the neural restrain upon gonadotropin release is maximal, GnRH agonists do not stimulate gonadotropin secretion sufficiently to cause testicular testosterone secretion. Previous reports demonstrate that GnRH agonist administration induces testosterone secretion in prepubertal boys with delayed puberty (4, 20). These discrepancies may be explained by the fact that these patients, although prepubertal, were on the verge of pubertal hypothalamic–pituitary function, and showed peak gonadotropin levels in the early pubertal range (4, 8, 20).

Baseline levels of most steroid precursors rose significantly during puberty in both sexes. Girls
showed earlier and greater increases in 17-Preg, DHEA and DHEAS suggestive of a sharper rise in the 17-
hydroxylase and 17–20 lyase activities of cytochrome P450c17 along the Δ5-steroid pathway. Both males and
females show significant increases in most steroid precursors in response to the agonist from midpuberty
onwards, with the exception of Δ4-Δ and DHEA. Boys showed higher baseline and poststimulated 17-OHP
concentrations than girls only when puberty was completed. Therefore, the previously described ‘masculin-
ized’ response of the 17α-oxidase toward the Δ4-Δ steroid pathway in males, suggestive of an increased activity of 17-hydroxylase
(1), was only evident at the end of pubertal development.

IGF-I and IGFBP-3 levels rose significantly during puberty in both sexes. Girls showed higher IGF-I levels
than boys during puberty, and higher IGFBP-3 concentrations during mid and late puberty. These findings
are in agreement with previous normative data in both Spanish and American populations (21, 22). The
observed gender-related differences may be dependent on the increase in growth hormone production
throughout puberty, although a direct stimulatory effect of estradiol in IGFBP-3 secretion cannot be ruled
out (21, 23).

SHBG and IGFBP-1 concentrations decreased with advancing puberty in both sexes, as expected (16, 24,
25). The sharper and earlier decrease in IGFBP-1 levels in girls and the sex-related differences in SHBG
concentrations at pubertal onset might be secondary to the sexual dimorphism in insulin sensitivity during
puberty (26, 27). In fact, insulin resistance at puberty has been well documented to occur earlier and to be
more pronounced in girls than in boys (16, 26, 27). In humans, insulin is the main physiological regulator of
SHBG and IGFBP-1 production before and during puberty, with sex steroids playing a secondary role
(24, 28–30); low SHBG and IGFBP-1 levels have been associated with hyperinsulinemia both in children and
in adolescents (15, 31).

In conclusion, a single dose of the GnRH agonist leuprolide acetate is a useful tool for assessing the
maturation of the neuroendocrine–gonadal axis. The pattern of gonadotropin release both before and
throughout puberty is gender specific, as males show less secretion of LH and FSH in response to the
agonist, which implies a smaller capacity to synthesize gonadotropins anew. The isolated failure of estradiol
to increase in response to the agonist in early pubertal males suggests that maturation of aromatase activity is
only appreciable in late puberty.

References

1 Barnes RB, Rosenfield RL, Burstein S & Ehrmann DA. Pituitary–
 ovarian responses to nafarelin testing in the polycystic ovary


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