Objective  To evaluate the adult reproductive outcome in girls with early puberty who participated in a previous random study.

Study design  A total of 22 subjects treated with triptorelin 3.75 mg every 4 weeks (group 1), 18 subjects not treated (group 2), and 22 age-matched normal volunteers (control group) underwent a physical examination, serum hormone level determination, and pelvic ultrasonography.

Results  The characteristics of menstrual cycles, serum hormone levels, and ultrasound results did not differ significantly among the 3 groups examined. The mean ovarian volume and the uterine volume tended to increase in the subjects of group 2, but the differences were not significant. The percentage of subjects who reported being sexually active at the time of the examination was greater in the 2 groups with previous early puberty than in the controls (76% of cases in group 1, 72% in group 2, and 59% in the control group).

Conclusions  Neither early puberty nor its treatment seems to significantly affect the normal adult function of the pituitary-gonadal axis. (J Pediatr 2006;149:532-6)

Gonadotropin-releasing hormone (GnRH) analog depot preparations have now been in use for more than 15 years and have become the treatment of choice for central precocious puberty (CPP). Many short-term follow up studies have documented the effectiveness, safety, and reversibility of the suppressive effects of this treatment.1-3 For the many persons with CPP who have reached adulthood, long-term data is lacking on some outcomes, including gonadal and reproductive function, the appearance of polycystic ovary syndrome (POS), and body composition.4-8 In particular, there have been no randomized controlled trials assessing long-term outcome in these persons to determine whether some aspects of the supposed side effects of treatment are instead consequences of the disease itself.5,9,10

In a previous study, we examined 46 girls referred to us for early puberty and divided them randomly into 2 groups, 1 group treated with triptorelin and the other followed without treatment.11 The aim of the present study was to evaluate the adult reproductive outcome in these 2 groups and in a normal control group.

METHODS

Patient Population

A total of 46 girls referred to our center between 1991 and 1992 for early puberty (ie, onset of puberty at a mean of 7.7 years) were randomly divided into 2 groups: 1 group treated with triptorelin 3.75 mg every 4 weeks (group 1) and the other group followed without treatment (group 2). In group 1, treatment with triptorelin was provided for a mean of 25 months, and the subjects were followed up after treatment for a mean of 33 months until they reached adult height. The subjects in group 2 were followed up for a mean of 41 months. The final heights of the treated and untreated subjects were not significantly different.11 In all cases, magnetic resonance imaging of the pituitary gland and pelvic ultrasound were performed to exclude organic pathologies.
From June to December 2003, all girls previously recruited for the study were recalled, and 40 adult subjects (22 subjects of group 1, mean age [± standard deviation] 20.3 ± 2.2 years; 18 subjects of group 2, mean age, 20.0 ± 2.1 years) agreed to participate in the new examination. For comparative purposes, 22 age-matched normal volunteers (postgraduate students of a nursing school, mean age 21.1 ± 1.6 years) were examined as a control group. Written informed consent was obtained from all study participants.

Protocol

The following endocrine evaluations were obtained on days 17 to 23 of the menstrual cycle in subjects with sufficiently regular menses and at any point in the menstrual cycle in the other subjects:
- Gynecologic history, with evaluation of menstrual pattern and oral contraceptive use
- Physical examination, with evaluation of height, weight, and symptoms of hyperandrogenism (acne and/or hirsutism)
- Blood samples to determine basal levels of leutinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, and delta-4-androstenedione
- Pelvic ultrasonography to assess uterine and ovarian volumes, uterine echos, and ovarian structure.

We report hormonal and ultrasound data only for those subjects not taking oral contraception at the time of the study (17 subjects in group 1, 14 subjects in group 2, and 16 subjects in the control group).

The characteristics of menstrual cycles were evaluated in a semistructured interview carried out by an expert clinician. The frequency of menstrual bleeding was classified as follows: regular (menses every 25 to 35 days), irregular (menses every 25 to 60 days), oligomenorrhea (menses at > 35-day intervals), and polimennorrhea (menses at < 22-day intervals). Dysmenorrhea was defined as menstrual pain that necessitated analgesic drugs and/or did not permit normal daily activity.

The body mass index (BMI) was calculated as weight in kg/height in m². Hirsutism was assessed using the Ferriman and Gallwey scale.12

Hormonal determinations were performed using commercial kits as follows: FSH and LH were measured using an immunochemiluminometric assay (ICMA) commercial method (Bayer Healthcare, Diagnostic Tarrytown, NY). Commercial ICMA kits were used also for progesterone and estradiol (Bayer Healthcare), and for delta-4-androstenedione (DPC, Los Angeles, CA). In accordance with Apter,13 progesterone levels >2 ng/mL in the premenstrual phase of the cycle were assumed to signify an ovulatory cycle.

The equipment used in the ultrasound (US) examinations included Sonoline Versa Plus (Siemens, Issaquah, WA) and SSD 1700 Aloka DynaView II (Aloka Co., Ltd, Tokyo, Japan) instruments, with 5-MHz transabdominal and 6.5-MHz transvaginal probes. Transabdominal scans were performed through the conventional full-bladder technique, with the transvaginal route was used in sexually active subjects. All US examinations were carried out by the same sonographer, who was blinded to the subjects’ diagnoses.

Uterine and ovarian volumes were calculated using the formula of the ellipsoid, as reported previously.14 The mean ovarian volume was considered representative of both ovaries in each subject. The characteristics of the endometrium echos were evaluated to determine the uterine phase of the menstrual cycle.14,15 The ovarian structure was defined as follows according to our experience14,15 and literature data16,17:
- Normal, with functional signs of early/late follicular phase or luteal phase
- Multifollicular: Increased or normal ovarian volume, cystic areas of 4 to 10 mm diameter in an irregular distribution, normal stroma
- Micropolycystic: Normal ovarian volume, cystic areas of 2 to 8 mm diameter in a circumferential arrangement, hyperchoic stroma
- Polycystic: Increased ovarian volume, cystic areas of 2 to 8 mm diameter in a circumferential arrangement, large hyperchoic stroma.

Statistical Analysis

Results are expressed as mean ± standard deviation. Statistical analysis was performed with SPSS version 11.0.1 (SPSS Inc, Chicago, IL). Differences between the groups were assessed by analysis of variance, and percentage differences were compared using the χ² test. All results nominally significant at P < .05 were indicated.

RESULTS

Table I reports the menstrual patterns in the patients and controls examined. In group 1, the mean time at onset of menarche after discontinuation of triptorelin therapy was 16 ± 9 months (range, 2 to 36 months). All subjects were examined more than 6 years after menarche.

Table II reports clinical, US, and hormonal findings in the patients and controls examined. Four of the 22 subjects in group 1, 2 of the 18 subjects in group 2, and 4 of the 22 subjects in the control group had BMI values between 25 and 30 kg/m². No subjects showed marked obesity (BMI > 30 kg/m²).

Ovarian volume was > 10 mL in 19% (3/17) of the group 1 subjects, in 21% (3/14) of the group 2 subjects, and in 16% (2/16) of the controls. The characteristics of ovarian structures observed on US did not differ significantly among the 3 groups examined. A greater percentage of normal results was found in the group 1 subjects; a normal ovarian structure was observed in 14 of the 17 group 1 subjects (82%), 10 of the 14 group 2 subjects (71%), and 12 of 16 controls (75%). Direct signs (corpus luteum) or indirect signs (endometrial echo, progesterone levels) of ovulation were observed in 13 of the 14 normal subjects in group 1, in 9 of the 10 normal subjects in group 2, and in 10 of the 12 normal controls, with
normal functional signs of early or late follicular phase seen in the others. In all subjects with normal ovarian structure, the serum levels of gonadotropins, estradiol, and progesterone were within normal ranges for the phase of the menstrual cycle and were comparable in all groups.

Table III reports clinical, US, and hormonal findings for those subjects in whom a multifollicular, micropoly cyclic, or polycystic ovarian structure was observed. In the 2 patients in whom a polycystic ovarian structure was observed at the diagnosis of CPP (Table III, cases 3 and 7), mean ovarian volume was 5.6 mL and 5.1 mL and the ovarian structure was microcystic.\(^*\)

The percentage of subjects who reported being sexually active at the time of the examination was greater in patients with previous early puberty than in controls, but this difference was not significant (76% of cases in group 1, 72% in group 2, and 59% in the control group). The number of subjects who used oral contraception was comparable in all 3 groups. Two girls of group 1 reported pregnancies (at age 17 and 17.5 years, respectively), both of which were terminated by elective abortion.

### DISCUSSION

The few studies in the literature on the long-term outcome of patients with CPP involve adolescent girls or young women with both neurologic and idiopathic forms of CPP studied for an average of 1.5 to 3 years postmenarche.\(^*\) The present long-term study takes into account a homogeneous sample of young women previously affected by idiopathic early puberty who were all examined more than 6 years after menarche as a reliable index of a complete maturation of the female reproductive function.\(^\dagger\) Moreover, the previous randomized trial allowed us to compare treated and untreated subjects with a control group to determine the influence of early puberty itself or treatment on future endocrine function.

Although the size of the sample examined does not allow us to reach conclusive results, our data seem to demonstrate that neither early puberty nor its treatment significantly affects normal adult function of the pituitary-gonadal axis. We also must point out that the original sample of patients examined showed a slowly progressive variant of pubertal precocity in which height prognosis was not significantly improved by GnRH treatment. Our current results seem to confirm that the patients with early puberty exhibit a variant of normal puberty also in terms of menstrual pattern and reproductive outcome, and that GnRH treatment, at least for a few years, does not seem to affect this outcome adversely.

Hormonal suppression achieved with GnRH analogues proved to be fully reversible in all cases, although the time of onset of menarche after the suspension of treatment varied widely. Because the type and duration of therapy were comparable in all cases examined, it is likely that this pattern simply indicates the natural variability of the phenomenon itself.

To the best of our knowledge, the lower incidence of dysmenorrhea in treated subjects has not been reported in the literature, and the explanation appears questionable at present. Despite the restrictive criteria that we used to define dysmenorrhea, this symptom remains at least partially subjective, and its frequency may be overestimated due to the medical background of controls. Nonetheless, we must point out that the untreated patients reported the same frequency as controls and that a similar incidence of dysmenorrhea was found in a young population examined in a large study in postgraduate schools of Northern Italy.\(^\ddagger\) Further studies with

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**Table I. Menstrual function in subjects examined**

<table>
<thead>
<tr>
<th>Age at menarche, (mean ± SD) years</th>
<th>Years after menarche, (mean ± SD) years</th>
<th>Girls reporting regular menses</th>
<th>Girls reporting oligomenorrhea</th>
<th>Girls reporting dysmenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Group 1 12.0 ± 1.0</td>
<td>8.3 ± 2.8</td>
<td>13/22</td>
<td>60%</td>
<td>1/22</td>
</tr>
<tr>
<td>Group 2 10.8 ± 0.7*</td>
<td>8.9 ± 2.2</td>
<td>11/18</td>
<td>61%</td>
<td>1/18</td>
</tr>
<tr>
<td>Controls 12.6 ± 1.5</td>
<td>8.4 ± 2.4</td>
<td>14/22</td>
<td>63%</td>
<td>1/22</td>
</tr>
</tbody>
</table>

*\(P < .005\) versus controls.
**\(P < .01\) versus controls.

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**Table II. Clinical, ultrasound, and hormonal findings in subjects examined**

<table>
<thead>
<tr>
<th></th>
<th>BMI</th>
<th>Uterine volume (mL)</th>
<th>Mean ovarian volume (MOV) (mL)</th>
<th>LH (mU/mL)</th>
<th>FSH (mU/mL)</th>
<th>Estradiol (pg/mL)</th>
<th>Progesterone (ng/mL)</th>
<th>Androstenedion (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>22.5 ± 3</td>
<td>55.7 ± 17.7</td>
<td>7.1 ± 2.3</td>
<td>9.8 ± 7.8</td>
<td>4.1 ± 3.4</td>
<td>130.8 ± 54.7</td>
<td>8.2 ± 6.2</td>
<td>234.5 ± 82.5</td>
</tr>
<tr>
<td>Group 2</td>
<td>21.6 ± 2.8</td>
<td>60.0 ± 11.9</td>
<td>8.8 ± 4.4</td>
<td>7.5 ± 4.9</td>
<td>3.4 ± 1.8</td>
<td>118.5 ± 50.8</td>
<td>10.7 ± 8.1</td>
<td>278.3 ± 100.9</td>
</tr>
<tr>
<td>Controls</td>
<td>22.5 ± 3.2</td>
<td>49.8 ± 11.2</td>
<td>7.3 ± 3.9</td>
<td>9.6 ± 6.6</td>
<td>4.2 ± 2.7</td>
<td>136.7 ± 87.5</td>
<td>8.9 ± 7.3</td>
<td>241.8 ± 88.6</td>
</tr>
</tbody>
</table>

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\(H_{11006}\)
more patients are needed to confirm this possible “analgesic” effect of GnRH analogue (GnRHa) treatment.

Regarding the BMI changes in subjects with CPP, some authors have noted a progression toward marked obesity, especially in patients with hypothalamic hamartoma.5,19 A recent study did not confirm this finding, however; on the contrary, it showed a favorable effect of GnRHa therapy on BMI decrease.22 In agreement with those results, we found no cases of marked obesity in our study, and the incidence of borderline excess weight was comparable in patients and controls.

The prevalence of enlarged oocytes in our patients was not significantly different from that in the controls and was comparable to that reported in previous studies.8 The data in the literature concerning the occurrence of polycystic ovary (PCO) syndrome in CPP patients are controversial, but a very high incidence of PCO has been reported only in patients treated with a combination of GH and GnRHa, which is not a conventional therapy.6,9,10 The characteristics of our protocol did not allow us to perform a diagnosis of PCO syndrome, defined according to Franks23 as the association of hyperandrogenism with chronic anovulatory cycles in women without specific underlying disease of the adrenal or pituitary glands. Single symptoms of PCO syndrome were observed in both patients and controls, and our results confirm a previous report of a PCO prevalence of 23% in asymptomatic healthy women.17

The pregnancies that occurred in our patients confirm the normal reproductive outcome in subjects with previous CPP; however, many report pregnancies occurring in young patients (as young as 13.8 and 15.9 years old) and often terminated with elective abortion as in our 2 cases.4,5 These data, together with the apparent precocious sexual activity reported by our patients, warrant further investigation to evaluate the psychosocial impact on sexual behavior of early sexual maturation.

Finally, in this study we were unable to use a standard-ized quality-of-life questionnaire to evaluate the psychosocial impact of treatment (or no treatment) on the patients and their families. This information would simplify therapeutic decision making by the pediatrician, particularly in subjects with mild forms of precocious puberty.

REFERENCES


