Treated and Untreated Women With Idiopathic Precocious Puberty: BMI Evolution, Metabolic Outcome, and General Health Between Third and Fifth Decades

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Context: Central precocious puberty (CPP) may have clinical implications in adulthood.

Objective: To assess the prevalence of obesity, metabolic outcome (hyperlipidemia, diabetes, and hypertension), and malignancy rate of former CPP women between the third and fifth decades of life.

Design: This was a case control study of a historical cohort using the computerized database of a health management organization.

Setting: The setting was the Institute for Endocrinology and Diabetes, Schneider Children’s Medical Center of Israel, and Clalit Health Services.

Participants: The study group comprised of 142 CPP women aged 27–50 years [100 GnRH analog (GnRHa) treated; 42 untreated]. The control group comprised of 413 women randomly matched for age, year of birth, and community clinic (283 for the GnRHa treated; 130 for the untreated).

Methods: Extracted from the database were demographic data, medical history, medications dispensed, recorded anthropometric measurements, vital signs, and laboratory data.

Results: At young adulthood, body mass index (percentile and distribution) of treated and untreated former CPP women was comparable to that of their respective controls. Elevated body mass index at presentation was a risk factor for obesity in adulthood in the GnRHa-treated group (r = 0.257; P = .01). The prevalence of metabolic comorbidities (16 vs 13.4%; 21.4 vs 24.6%) and malignancy rate (1.0 vs 1.5%; 4.8 vs 1.5%) were similar in the former CPP women and their controls, with no significant difference between CPP groups.

Conclusion: CPP (treated or untreated) is not associated with increased risk of obesity, metabolic derangements, or cancer morbidities in young adulthood. The finding that the health status of former CPP women is similar to that of the general population is reassuring. (J Clin Endocrinol Metab 100: 1445–1451, 2015)

Central precocious puberty (CPP) in girls, defined as the appearance of secondary sex characteristics before the age of 8 years due to premature activation of the hypothalamic-pituitary-gonadal axis, is considered idiopathic for most girls (1, 2). The goal of treatment in CPP is to prevent the unfavorable physical and emotional man-
ifestations of premature sexual development. Since 1981, depot preparations of GnRH analogs (GnRHa) have been considered the drugs of choice for arresting pubertal progression (3). Numerous clinical trials confirmed the effectiveness and safety of these compounds in suppressing gonadal activation and the reversibility of suppression after discontinuation of treatment (4). Still, there are relatively few data on the implications of CPP on general health of former untreated and treated CPP girls in adulthood. Previous studies showed an association between early puberty or early age of menarche with higher body mass index (BMI), increased metabolic risk factors, and endocrine-related breast and reproductive tract cancers (5–9). However, these studies have limitations: the relatively small number of participants in each study, the lack of controls in most of the studies, and the rather short follow-up.

Recently, we published a prospective study on the reproductive competence, educational achievements, and social adjustment of former CPP women in early and midle adulthood as compared to women with normal puberty (10). In the present study, we expanded our research to assess their present health status using data-mining techniques utilizing the computerized database of the Clalit Health Services (CHS), the largest health management organization in Israel, with a nationwide distribution that includes 53% of the Israeli population.

Our primary end-point was to assess the current BMI and general health status and metabolic outcome of former CPP women between the third and fifth decades of life as compared to women with normal puberty. Our secondary end-point was to determine whether pubertal suppressive therapy significantly affected the long-term medical outcome, by comparison of treated to untreated CPP women.

**Patients and Methods**

**Patients**

Among the medical files of the 186 girls who had sought medical attention due to idiopathic progressive CPP at the Institution for Pediatric Endocrinology at Schneider Children’s Medical Center of Israel between the years 1984 and 2005, we identified 142 women (100 GnRHa treated and 42 untreated) who had fulfilled the criteria for diagnosis, treatment, and follow-up of CPP and who are currently insured by the CHS. These comprised the study cohort. Diagnosis of progressive CPP required that all of the following criteria be met: appearance of secondary pubertal signs (breast Tanner stage 2 with or without sexual hair) (11) before the chronological age (CA) of 8 years, accelerated growth rate, advancement of bone age more than 1 year above CA, and GnRH-stimulated peak LH above 5 IU/L (1). In accordance with our departmental policy at that time, pubertal-suppressive therapy was offered to all girls diagnosed as having progressive CPP after an observation period of up to 6 months to rule out nonsustained or slowly progressive forms of CPP. Among the initial 186 patients identified, therapy was accepted, with parental consent, by 135 girls and refused by 51. Therapy consisted of a depot preparation of GnRHa (Decapeptyl; Ferring Pharmaceuticals Ltd) administered by im injection every 4 weeks at a calculated dose of 1.5–3.0 µg/kg release per day to a maximal dose of 3.75 mg. Treatment was discontinued in most cases at an age when normal puberty could be expected (at CA 11–11.5 y and bone age 12–12.5 y). All girls, treated and untreated, were regularly followed up to the completion of puberty and attainment of final height. Excluded from the study were girls born prematurely or small for gestational age; girls with chronic disease, bone dysplasia, organic brain disease, congenital adrenal hyperplasia, or other endocrinological abnormalities; girls who had undergone radiation therapy and/or chemotherapy; and girls who had been treated for less than 2 years or who were noncompliant.

The medical information of the eligible CPP women was queried down from the CHS computerized data warehouse by using their unique personal identification numbers. The control group was randomly selected from among the CHS-insured females listed in the computerized database, matched for age, year of birth, and community clinic. According to the size of the cohort, the control group comprised 413 women: 283 for the GnRHa-treated group, and 130 for the untreated group.

**Methods**

**Collection of data from the CHS computerized database**

The CHS database is a comprehensive state-of-the-art computerized data warehouse that stores demographic and medical data. Data are aggregated by continuous real-time input from physicians and health service providers and include anthropometric measurements, vital signs, laboratory data, and pharmaceutical information. Data can be queried to the level of an individual member. The diagnoses of chronic diseases—hyperlipidemia, diabetes, hypertension, and malignancy—in the CHS database are validated by systematic methodology based on the diagnosis of the primary care physician, chronic medication use, laboratory results, hospitalization diagnosis, and malignancy registry (12).

The CHS performs logistic checks by comparing diagnoses from various sources and by direct validation of the diagnoses by the treating physicians of each patient.

For the purpose of our study, we queried current demographic data (age), anthropometric measures (height, weight), blood pressure, and diagnosis of chronic diseases (ie, diabetes, hypertension, and malignancy).

**Data collection of the CPP group through childhood and adolescence**

Extracted from the medical files of all the CPP girls (treated and untreated) were age, height, and weight at onset of puberty, at menarche, and at last visit; the data obtained from the files of the treated girls included these data at initiation and cessation of therapy with GnRHa.
BMI assessment

In all participants (former CPP and their controls) BMI (weight in kilograms/square of height in meters) was calculated using the most recent anthropometric measurements documented in the CHS database. BMI was used as the index of body weight according to the World Health Organization criteria: underweight, <18.5 kg/m²; normal weight, 18.5–24.9 kg/m²; overweight, 25.0–29.9 kg/m²; and obese, ≥30 kg/m² (13).

In childhood and adolescence, the BMI of all the CPP girls was calculated at diagnosis and at the last clinic visit, and BMI of the treated girls was also calculated at the discontinuation of GnRHa treatment. The evolution of BMI of the former CPP cohort from childhood through adolescence to adulthood was assessed by using BMI percentiles. In childhood and adolescence, BMI values were converted to age- and gender-specific percentiles according to the CDC 2000 (14); in adulthood, BMI values were converted according to the anthropometric reference data for all ages of the US population in 2003–2006 found in the latest National Health and Nutrition Examination Survey and National Center for Health Statistics (15). BMI percentiles were used as the index of body weight through childhood and adolescence: underweight, < fifth percentile; normal weight, fifth to 84th percentiles; overweight, 85th to 94th percentiles; and obese, ≥95th percentile (16).

This study was approved by our institutional ethics committee. Because there was no identification of the patients for whom data was retrieved, informed consent by the patients was waived.

Statistics

All analyses were done using SPSS version 19 for Windows (SPSS Inc).

Numerical data are expressed as mean ± SD, and categorical data are expressed as number (percentage). The two-tailed Pearson’s χ² test and Fisher exact test were used to compare categorical variables. The t test was used to compare numerical variables. Spearman’s correlation test was used to analyze correlations between the BMI percentiles at different time points. The changes in BMI over time were tested with ANOVA with repeated measures and with general linear model to identify statistical significance over the follow-up period. Forward-stepwise logistic regression analyses were used to evaluate variables associated with adverse metabolic outcomes (hyperlipidemia, diabetes, and hypertension) and malignancy. All tests were two-tailed, with a P value of ≤.05 considered significant.

Results

The present study was carried out at a median time of 17.3 years after the last follow-up visit in our clinic. The mean current age of the former CPP women (GnRHa treated and untreated) was 33.4 ± 4.2 years, with ages ranging from 27 to 50 years.

Characteristics of CPP girls from diagnosis to late adolescence

The characteristics of the CPP girls at diagnosis and throughout follow-up in our clinic are presented in Table 1. Age at onset of puberty and at last visit were similar in the GnRHa-treated and untreated CPP girls. As expected, the age of menarche was significantly younger in untreated CPP girls (P < .001).

BMI changes of former CPP patients from diagnosis to young adulthood

At diagnosis, the mean BMI percentile of the GnRHa-treated CPP girls was significantly higher than that of the untreated CPP girls (P = .001) (Table 1 and Figure 1). In the treated girls, longitudinal analysis of BMI percentile at follow-up time points yielded a significant change in BMI over time—a slight increase during GnRHa therapy, followed by a progressive decrease from cessation of treatment to late adolescence and to young adulthood (P < .001). In contrast, longitudinal analysis of the BMI percentile of the untreated girls yielded a stable BMI from onset of puberty to young adulthood. At late adolescence and young adulthood, the mean BMI percentile was similar in the treated and untreated girls (Figure 1).

A positive correlation between BMI percentile at presentation and at young adulthood was found only for the treated group (r = 0.257; P = .01).
Demographic data, anthropometric measurements, and medical history of the study cohort, categorized into two groups (treated and untreated former CPP patients), and their respective controls are shown in Table 2.

Anthropometric measurements of former CPP women compared to their controls

**Adult height**

Although the mean adult height of the GnRHa-treated and untreated former CPP women was within the normal range, it was significantly shorter than that of their respective controls ($P < .001$ for both groups). The mean adult height of the GnRHa-treated women was significantly higher than that of the untreated women ($P < .001$).

**Body mass index**

At young adulthood, the mean BMI of the treated women was significantly higher than that of their respective controls ($P < .001$), whereas the BMI of the untreated patients was similar to that of their controls. However, BMI distribution (underweight, normal weight, overweight, and obese) of the former CPP women did not differ significantly from that of their respective controls. BMI distribution was also comparable, with a similar percentage of overweight and obese subjects in the treated and untreated groups (Table 2). The mean BMI and BMI distribution of the GnRHa-treated women were similar to those of the untreated women.

**Metabolic outcome and general health status of former CPP women compared to those of controls**

**Metabolic outcome and blood pressure**

In the former CPP women, whether treated or untreated, the percentage of hyperlipidemia, diabetes, and hypertension was relatively low, with no significant difference between the former CPP patients and their respective controls and between treated and untreated former CPP women.

**Malignancy**

At young adulthood, the rate of malignant diseases was low in both the former CPP women and their controls. Malignant diseases were only documented in three former CPP women, with no report of breast or ovarian cancer.

In a multivariate analysis of the entire cohort with current age, BMI, and “group” (treated and untreated CPP women, and their respective controls) as potential explanatory variables, current age alone was significant for adverse metabolic outcomes (hyperlipidemia, diabetes) and...
hypothesis of obesity in former CPP patients from late adolescence to young adulthood and the prevalence of obesity and its related comorbidities have not been thoroughly assessed. In this prospective study of a historical cohort of former CPP girls, we found that the BMI distribution of both the GnRHa-treated and untreated women in their third to fifth decades was similar to that in the normal population, without a higher rate of overweight and obesity. No increased risk for metabolic and cardiovascular diseases or incidence of malignancy was observed.

Girls with idiopathic CPP are frequently overweight at presentation, probably due to the changes in hormonal and metabolic regulatory factors that accompany the start of puberty (1, 2). Consistent with previous studies, the prevalence of increased BMI and the rate of overweight at diagnosis were relatively high among our treated CPP girls (4, 5, 7, 17–22). It has been suggested that the increased BMI may be attributed to the GnRHa therapy. Our findings demonstrating a stable BMI throughout the treatment period make this assumption unlikely. Indeed, the data available in the literature on the effects of GnRHa on BMI in CPP girls are controversial. Similar to our findings, several reported studies found that GnRHa did not induce significant changes in BMI and the percentage of fat mass (5, 7, 18), whereas other studies demonstrated an increase in BMI during treatment (19–21), and in one study a reduction in BMI was reported (22). Hence, the increased weight among CPP girls cannot be causally related to the GnRHa treatment.

One of the concerns of precocious puberty in early childhood is well established (17, 18), yet the natural history of weight gain in former CPP patients from late adolescence to young adulthood and the prevalence of obesity and its related comorbidities have not been thoroughly assessed. In this prospective study of a historical cohort of former CPP girls, we found that the BMI distribution of both the GnRHa-treated and untreated women in their third to fifth decades was similar to that in the normal population, without a higher rate of overweight and obesity. No increased risk for metabolic and cardiovascular diseases or incidence of malignancy was observed.

The impact of sexual precocity on the long-term general health status of former CPP women is inconclusive. Previous studies have reported that girls with CPP or early age at menarche who became obese in adulthood were prone to developing metabolic derangements (dyslipidemia, hypertension, and diabetes) and cardiovascular disease (9, 26–31). The adverse health outcomes were related to excessive adult adiposity and hyperinsulinism. These associations were identified across a large number of studies. In a report from the Bogalusa Heart Study, a positive relationship was demonstrated between early menarche and obesity, and increased insulin and homeostasis model of assessment for insulin resistance (HOMA-IR) levels (26). He et al (29) and Lakshman et al (27, 28) found that early menarche, type 2 diabetes, and cardiovascular disease were mediated by increased adult BMI and childhood obesity.

Yet Elks et al (30) found a higher adult BMI as a risk factor for type 2 diabetes in less than half of women with a history of early menarche. Indeed, the BMI percentile of our CPP patients was increased at the start of and during early treatment, but similarly to other studies, it normalized thereafter (4, 19–21). Therefore, it is not surprising that the occurrence of obesity-related comorbidities was relatively low among our former CPP women and resembled that of their age-related normal controls.
Early pubertal maturation also carries with it higher risk for estrogen-dependent malignancy in later life (breast and reproductive tract cancers), especially among women with abdominal type obesity, insulin resistance, and elevated insulin levels (31, 32). It has been suggested that prolonged exposure of the developing breast tissue to estrogens may be the underlying link between breast cancer and early onset of puberty, whereas a greater number of ovulatory cycles may increase the risk for ovarian cancer (33). In this study, the diagnosis of breast or ovarian cancer was not documented in any of our treated and untreated former CPP women. This finding is in agreement with previous studies reporting that the relative risk for development of breast cancer among women with a history of an early pubertal spurt (34) or early menarche (before age 12 y) (35) was only slightly greater than in women with a history of normal puberty. Moreover, the association between age at first menstruation and ovarian cancer was also found to be weak (33). Still, the paucity of malignant diseases in our studied cohort may also be partly explained by the relatively young age of the participants.

Strength and limitations

The major strength of our study is that it is based on data on a large cohort of former CPP women and their age-matched controls from the general population, extracted from a very large comprehensive health information system. The analysis, carried out one to three decades after the last follow-up in our clinic, allowed assessment of the influence of precocious puberty itself and of its treatment on height and weight status, metabolic outcome, and general health in early and middle adulthood, through a wide age range (27–50 y). The present study was strengthened by the fact that the longitudinal BMI data of the former CPP subjects was based on the actual weight and height measurements recorded in their medical files, in contrast to other studies based on self-reported data with its increased bias because participants tend to under-report weight and over-report height (36). Although analysis of height in former CPP women is beyond the scope of this study, it is noteworthy that, in accordance with previous studies, the adult height of our treated CPP women was taller than that of the untreated women (7) but relatively shorter than that of the normal population.

The main limitation of our study is the lack of clinical measures of body adiposity such as skinfold thickness, waist circumference, bioelectrical impedance, or dual-energy x-ray absorptiometry. Nevertheless, the BMI is considered a reliable and clinically valid screening tool for obesity. Furthermore, there are no data on markers of impaired glucose metabolism such as fasting insulin, and measures of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) are lacking. This is a point worth addressing in future studies.

Conclusion

Our longitudinal follow-up study provides unique insights into the evolution of weight gain from childhood to young and middle adulthood in former CPP women. The course of weight gain is reassuring because weight status of both GnRHα-treated and untreated former CPP women resembled that of the general population from late adolescence to early-mid adulthood despite their above-average BMI at the onset of puberty. The risk of permanent obesity was found only among women who were already obese in early childhood. Moreover, weight gain of the treated CPP girls was not aggravated by GnRHα therapy. Our study also adds to the accumulating evidence that the incidence of obesity-related complications, such as metabolic dysfunctions and cancer comorbidities, is not increased in former CPP women. Our study would appear to lay to rest any question as to the relation of idiopathic CPP to adult obesity and metabolic outcome. It also emphasizes the need for continued follow-up to determine whether sexual precocity increases the risk for adverse health consequences in later life.

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