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17-Hydroxyprogesterone responses to human chorionic gonadotropin are not associated with serum anti-Mullerian hormone levels among adolescent girls with polycystic ovary syndrome

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Abstract

Background—In adult women with polycystic ovary syndrome (PCOS) 17-OHP responses to human chorionic gonadotropin (hCG) stimulation are highly variable and inversely correlated with serum anti-Mullerian hormone (AMH) levels. The objective of this study was to determine whether adolescents with PCOS exhibit similar variable 17-OHP responsiveness to hCG and whether these responses are correlated to AMH levels.

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Methods—In a prospective study, adolescent PCOS (n=14) and normal controls (n=10) received 25 µg of hCG, intravenously. Blood samples were obtained before and 24 h afterwards for measurement of 17-OHP and basal AMH.

Results—Variable 17-OHP responses to hCG were observed among PCOS girls similar to that observed in adults. There was no correlation between AMH and 17-OHP responses to hCG.

Conclusions—Among adult and adolescent individuals with PCOS variable 17-OHP production appears to be characteristic of the disorder. In adolescent PCOS, 17-OHP responsiveness to hCG is not correlated to AMH.

Keywords

adolescent; anti-Mullerian hormone; 17-hydroxyprogesterone; polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is characterized by excess androgen production, irregular menstrual bleeding and polycystic ovaries [1, 2]. In adult women, the primary source of androgen overproduction is the ovary driven by increased luteinizing hormone (LH) secretion. Because women with PCOS exhibit increased 17-hydroxyprogesterone (17-OHP) responses to gonadotropin stimulation compared to that of normal women, it has been suggested that cytochrome P450 (CYP17) is dysregulated and probably reflects an inherent defect of theca cell androgen production [3, 4].

Despite hyperandrogenemia among women with PCOS, theca cell responses to gonadotropin stimulation vary considerably [5–7]. Previous studies have demonstrated that 17-OHP responses to either human chorionic gonadotropin (hCG) or GnRH agonist are exaggerated in some women (high responder PCOS, HR-PCOS) whereas in others 17-OHP responses are equivalent to those observed in normal women (normal responder PCOS, NR-PCOS) [8, 9]. In a study by Maas et al., increased 17-OHP responses to hCG in HR-PCOS were accompanied by significantly increased serum androgen production compared to minimal increases observed in NR-PCOS [9]. In addition, in women with PCOS, 17-OHP responses were inversely correlated with serum anti-Mullerian hormone (AMH). Recent in vitro studies have shown that AMH inhibits LH-stimulated androgen production and androgen suppresses AMH production which suggests a mechanism for heterogeneous 17-OHP responses to hCG in this disorder [10–12].

Whether hCG-stimulated 17-OHP production is related to AMH levels in adolescent PCOS has not been studied. Ibanez et al., demonstrated that 17-OHP responses to GnRH agonist were elevated in 58% of adolescent PCOS suggesting heterogeneity, although AMH levels were not measured [13]. In a study that included adolescent PCOS women, heightened 17-OHP responses to GnRH agonist were positively associated with serum AMH [5]. However, in subsequent multivariate analysis, this correlation was not observed. In addition, adolescent individuals comprised only 37% of the study population. This study was designed to examine whether variable ovarian responses to gonadotropin stimulation exist in adolescent PCOS and whether these responses are associated with AMH levels.

Materials and methods

Subjects

Fourteen adolescent girls (age range, 12–18 years) with PCOS and 10 age-matched, non-hirsute normal controls with regular menstrual cycles were enrolled in this study. The subjects were recruited from the local community in response to an advertisement. The diagnosis of PCOS was based on hirsutism or biochemical evidence of hyperandrogenemia and irregular menstrual bleeding, according to the 1990 National Institutes of Health Conference on PCOS and consistent with the 2003 Rotterdam PCOS Consensus Workshop. In addition, our criteria met those set forth by the joint statement on the diagnosis of adolescent PCOS recently published [14]. Hyperandrogenism was based on the presence of hirsutism (Ferriman-Gallwey score ≥ 8) and/or elevated serum testosterone (T). Oligomenorrhea was defined as having an average menstrual cycle length between 45 and 90 days, based on a normal menstrual interval of 21–45 days in young females [15]. PCOS subjects were oligomenorrheic except one that was amenorrheic. All subjects were at least 2 years' post-menarche. The mean ($\pm$ SE) ages for the PCOS and normal groups were 14.9 ± 0.5 and 15.4 ± 0.6 years, respectively. The mean body mass index (BMI, kg/m^2) of PCOS subjects was 28.9 ± 1.3 , compared to 22.6 ± 1.6 in control participants ($p < 0.01$). All subjects were euthyroid, without evidence of hyperprolactinemia or adrenal enzyme defects determined by 17-OHP levels < 2 ng/mL at time of serum collection. None of the subjects received any hormone medication or metformin within 2 months of study enrollment. Informed assent and parental permission was obtained from study subjects < 18 years of age. The study was approved by the Human Research Protection Program at the University of California, San Diego and the Institutional Review Board at University of Virginia. All authors complied with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research involving human subjects.

Procedures

Subjects were admitted to the Clinical and Translational Research Institute (CTRI) at the University of California, San Diego or the University of Virginia on the days of testing. Normal subjects were studied during the midfollicular phase (cycle days 5–8), while in adolescent PCOS women blood samples were drawn on a random day. Each subject received intravenous (iv) administration of recombinant hCG (r-hCG) as a 25 μg bolus. Blood samples were collected prior to and 24 h following r-hCG injection. None of the PCOS subjects experienced recent ovulation as evidenced by absence of recent menstrual bleeding for 2 months before study and serum progesterone (P4) < 1.0 ng/mL at a baseline sample.

Assays

Blood samples were collected, processed, and stored at -20°C until ready for analysis. Each sample was measured in duplicate. Serum concentrations of LH and follicle-stimulating hormone (FSH) were measured by radioimmunoassay (RIA) with intra- and inter-assay coefficients of variation (CV) of 5.4% and 8.0%, respectively, for LH and 3.0% and 4.6%, respectively, for FSH (Diagnostic Products Corp., Los Angeles, CA, USA). Serum concentrations of androstenedione (A4), T and dehydroepiandrosterone (DHEA) were measured by well-established RIA with intra-assay CV $< 7\%$. Serum levels of 17-OHP and

P4, were measured by RIA with intra-assay CV <7% (Diagnostic Systems Laboratories, Inc., Webster, TX, USA). Serum AMH was measured by an enzyme-linked immunosorbent assay (US AMH ELISA, Ansh Labs, Webster, TX, USA); total imprecision calculated on three samples over 12 runs, 4 replicates per run was 5.1% at 0.35 ng/mL, 6.03% at 0.715 ng/mL and 4.46% at 1.85 ng/mL.

Statistical analysis

Statistical analysis was performed using JMP 10.0 (SAS, Cary, NC, USA). Based on the categorization scheme described in Maas et al. [9], the cutoff value to categorize adolescents with PCOS as NR- and HR-PCOS subgroups was calculated using the mean +1.96 SD of 17-OHP levels in normal controls 24 h after iv r-hCG. Using this algorithm, five adolescent women were categorized as HR-PCOS and nine as NR-PCOS.

As the data were normally distributed age and BMI were compared between all groups using ANOVA followed by pairwise post-hoc analysis with the Tukey-Kramer test. Hormone responses to r-HCG stimulation were calculated as fold changes of 24-h vs. baseline values. Because of a significantly different BMI, comparisons between PCOS groups and normal-weight controls were performed after adjusting for BMI values. Correlations were examined by Pearson's correlation. All data are expressed as mean±SE. p-Values <0.05 were regarded as statistically significant.

Results

Determination of adolescent PCOS subgroups based on 17-OHP responses to r-hCG

In normal controls the mean (±SE) serum 17-OHP, 0.52±0.9 ng/mL, increased significantly following hCG to achieve a peak level of 1.32±0.33 ng/mL. In this group the mean+1.96 SD 17-OHP response was 3.3 ng/mL which was designated as the upper limit for normal controls. In the entire PCOS group hCG administration resulted in an increase of 17-OHP levels from 0.95±0.10 ng/mL to 3.20±0.52 ng/mL. There was considerable variability of response among PCOS adolescents (Figure 1). Notably, five of 14 PCOS subjects exhibited high 17-OHP responses (high responder PCOS or HR-PCOS) that exceeded the upper limit of normal controls (>3.3 ng/mL). By comparison, in nine of 14 PCOS subjects, 17-OHP responses were equivalent to those of normal controls (normal responder PCOS or NR-PCOS). Accordingly, the fold change of serum 17-OHP in HR-PCOS following r-hCG administration was significantly greater than that of either NR-PCOS or normal women (Figure 1).

Basal clinical features and hormone levels in PCOS subgroups and normal controls

The mean (±SE) ages of HR-PCOS and NR-PCOS subgroups (14.8±0.8 and 14.9±0.6, respectively) were not different from that of normal controls (15.4±0.4). Mean BMI values between HR-PCOS (28.6±2.3) and NR-PCOS (29.1±1.7) were similar. The mean BMI of HR-PCOS was significantly greater than that of normal controls (22.6±1.6; p=0.03). However, a statistical difference in BMI was not detected between NR-PCOS and normal adolescents.

Baseline serum LH levels were significantly higher in NR-PCOS (7.8 ± 1.2 mIU/mL; $p < 0.05$) and HR-PCOS (6.8 ± 0.9 mIU/mL; $p < 0.01$) compared to that of normal controls (4.0 ± 0.8 mIU/mL). Circulating FSH levels were similar among NR-PCOS (6.7 ± 0.6 mIU/mL), HR-PCOS (5.9 ± 0.9 mIU/mL), and normal women (8.0 ± 0.8 mIU/mL).

Basal androgen levels among adolescent PCOS subgroups and normal controls are shown in Table 1. In HR-PCOS and NR-PCOS women, serum T and A4 values were significantly higher than those observed in controls. In addition, baseline DHEA levels in both PCOS subgroups were higher compared to values in the control group. After adjusting for BMI, these differences in basal androgen levels among subgroups remained except for DHEA which was similar between the NR-PCOS and normal controls.

Androgen responses to r-hCG in adolescent PCOS subgroups and normal controls

Twenty-four hours after r-hCG stimulation, serum levels of T and A4 in NR-PCOS and A4 and DHEA in HR-PCOS subjects were significantly higher compared to that observed in normal control subjects (Table 1). However, due to elevated basal serum androgens in PCOS the relative magnitude of androgen responsiveness among all groups was modest and not significantly different. The incremental changes for T and A4 were approximately 1–1.6-fold and that of DHEA about 0.7–0.9-fold (Figure 2) among all groups.

AMH levels in adolescent PCOS subgroups and normal controls

As expected, in all adolescent PCOS girls mean serum AMH levels (6.0 ± 0.9 ng/mL) were significantly higher than that observed for normal controls (4.1 ± 1.1 ng/mL; $p = 0.02$), although there was considerable overlap (Figure 3). Among PCOS subgroups, the mean AMH level in HR-PCOS, 6.7 ± 1.9 ng/mL, was significantly greater than that of controls ($p < 0.03$) whereas no difference was observed between NR-PCOS, 5.5 ± 1.4 ng/mL, and controls. No significant correlation was found between AMH and basal or stimulated levels of 17-OHP, A4, T and DHEA in PCOS subjects.

Discussion

This study has demonstrated that in adolescent girls with PCOS 17-OHP responses to hCG are variable much like that of their adult counterparts. This suggests that the mechanism underlying variable 17-OHP responsiveness is inherent in this disorder. However, unlike adult women, androgen responses to hCG in adolescent PCOS subgroups were similar and not different from those of normal controls. In adolescent HR-PCOS, serum AMH levels were significantly higher than that of normal controls, but not different from NR-PCOS. Correlations between AMH and 17-OHP responses to hCG in PCOS were not observed.

The observed variable 17-OHP responsiveness to hCG in PCOS girls suggests that dysregulated CYP17 expression is present early in the onset of this disorder. However, the severity of dysregulation was insufficient to promote excessive ovarian androgen production as manifested by absence of hyperresponsiveness to hCG. In adolescent HR-PCOS girls, increased 17-OHP responses to hCG were not accompanied by corresponding increases of T, A4 or DHEA. Rather, androgen responses to hCG were similar between subgroups and indistinguishable from normal controls. The reason for a commensurate lack of androgen

hyperresponsiveness to hCG in adolescent HR-PCOS compared to that observed in adult HR-PCOS is unclear [9]. This discordance may be related to differences in the severity and/or duration of theca cell dysfunction between adolescent and adult women with PCOS. This possibility is suggested by the observation that adolescent PCOS girls with prolonged exposure to androgen excess by virtue of having premature pubarche exhibited hyperresponsive 17-OHP production following GnRH agonist which was associated with modest increases of A4 and DHEA [16]. Whether greater A4 and DHEA responses to GnRH agonist were primarily related to the onset of premature pubarche is not obvious although girls with this diagnosis appear to demonstrate exaggerated androgen synthesis from the early stages of puberty onward, thus, increasing their duration of exposure to androgen excess. To our knowledge, a comparison of androgen responses to gonadotropin stimulation between adolescent PCOS girls with and without a history of premature pubarche has not been reported. Notably, none of our adolescent subjects had premature pubarche.

The absence of increased androgen production by hCG in adolescent PCOS may have contributed to the lack of correlation between hCG-stimulated 17-OHP responses and serum AMH as seen in adult PCOS women [9]. It has been previously reported that testosterone reduced AMH mRNA expression in bovine granulosa cells from small antral follicles [11]. This suggests a regulatory role for androgen in the production of AMH. It is possible that in adolescents with PCOS a limited amount of intraovarian androgen excess was unable to effect a reduction in serum AMH. Perhaps a more prolonged exposure of the ovarian follicle to hyperandrogenemia is necessary to influence AMH production. Alternatively, the lack of correlation may have been due to the wide variation of AMH values in both PCOS and normal girls combined with a limited number of subjects studied.

Compared to divergent mean AMH values observed in adult HR-PCOS and NR-PCOS despite equivalent antral follicle number, other factors may be considered to account for similar AMH levels in adolescents. In vitro studies have suggested that LH may stimulate AMH production. Pellatt et al. showed that granulosa cells from unstimulated PCOS antral follicles produced substantial AMH in response to LH [17]. In addition, AMH expression in granulosa cells harvested at the time of egg retrieval from women with PCOS was upregulated by LH [18]. In the same study, FSH was also shown to upregulate AMH expression in granulosa cells from both normal and PCOS women. In contrast, it has recently been reported that in adult women with PCOS, serum AMH levels were not altered following iv administration of hCG [19]. In our adolescent PCOS girls, there was no distinction between basal LH or FSH levels in PCOS subgroups. Another consideration is an inhibitory effect of estrogen on AMH as suggested from in vitro studies in IVF patients [20]. In the current study, basal E₂ levels were equivalent between HR-PCOS and NR-PCOS subgroups.

In our adolescent PCOS subjects, 36% exhibited high 17-OHP responses to hCG (5 of 14) whereas an earlier study of adolescent girls with androgen excess reported a higher rate of supranormal responses, 58%, following administration of a GnRH agonist [13]. The lower rate of response in our subjects may have been due to differences in stimulatory agents, doses employed and/or the route of administration. In adult women with PCOS, the frequency of exaggerated 17-OHP responses to either hCG or GnRH agonist has generally

been slightly higher, 47%–58%, than that observed in our adolescent PCOS girls [7, 8, 21]. Recently, we employed the same hCG stimulation protocol in adult women with PCOS and showed an exaggerated 17-OHP response in 44% which is consistent with response rates as described for adults in earlier studies [9]. Collectively, our results suggest that the frequency of higher responders in adolescent girls with PCOS is probably similar to that observed in adult women, although further investigation is necessary to confirm this.

There are several limitations of our study. First, pelvic ultrasonography was not performed to assess ovarian morphology and antral follicle number. Most of our subjects were virginal and it was elected not to pursue ultrasound imaging studies. Second, the number of normal controls and PCOS subjects was limited; therefore, the results must be interpreted with extreme caution. Third, we did not assess insulin secretion, although both PCOS subgroups were heavier than controls. It has been shown previously that in women with PCOS insulin may enhance androgen responses to gonadotropin stimulation. Despite this finding, androgen responses among all groups were not different.

In summary, our results have demonstrated that adolescent girls with PCOS exhibit heterogeneous 17-OHP responses to hCG stimulation which is consistent with our previously reported findings in adult women. This finding suggests that variable 17-OHP responsiveness is present in all individuals with this disorder. However, subgroup analysis of adolescent HR-PCOS and NR-PCOS girls failed to detect differences in corresponding androgen responses to hCG or basal serum AMH levels unlike that of adults. Whether this discordance is related to differences in the severity and/or duration of theca cell dysfunction relative to AMH production between adolescent and adult women with PCOS is uncertain and warrants further investigation.

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Figure 1.

Scatterplot of individual serum 17-OHP levels at baseline and 24 h after r-hCG, 25 µg iv, in normal adolescent controls and adolescent NR-PCOS and HR-PCOS subgroups. Inset depicts mean fold change ($\pm$ SE) for 17-OHP responses to r-hCG in each group.

Figure 2. Mean fold-change ($\pm$ SE) for A4, T, and DHEA at 24 h following administration of r-hCG, 25 μ g iv, in normal controls, NR-PCOS and HR-PCOS subjects.

Figure 3.

Relationship between serum AMH and 17-OHP responses (fold-change) among individual adolescent PCOS and control subjects.

Regression lines drawn for all PCOS (dashed line) and controls (dotted line).

Table 1

Steroid hormone values at baseline and 24 h after r-hCG stimulation.

	Controls (n =10)		NR-PCOS (n =9)		HR-PCOS (n =5)	
	t =0	t =24 h	t =0	t =24 h	t =0	t =24 h
T, ng/mL	0.2±0.1	1.0±0.2	0.4±0.1 ^a	1.6±0.2 ^a	0.5±0.1 ^b	1.5±0.2
A4, ng/mL	0.6±0.2	0.9±0.2	1.7±0.2 ^a	2.1±0.2 ^a	1.4±0.2 ^c	2.3±0.3 ^b
DHEA, ng/mL	1.2±0.4	1.0±0.2	2.7±0.4	1.6±0.2	1.9±0.6 ^c	1.5±0.2 ^c

^aNR-PCOS vs. control, p<0.05;
^bHR-PCOS vs. control, p<0.05;
^cHR-PCOS vs. control, p<0.01.

To convert to SI units multiply by the following conversion factors: T (3.47); A4 (3.49); DHEA (3.47).