The Hormonal Phenotype of Nonclassic 3β-Hydroxysteroid Dehydrogenase (HSD3B) Deficiency in Hyperandrogenic Females Is Associated with Insulin-Resistant Polycystic Ovary Syndrome and Is Not a Variant of Inherited HSD3B2 Deficiency

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To test our hypothesis that the hormonal phenotype of mild 3β-hydroxysteroid dehydrogenase (HSD3B) deficiency in hyperandrogenic females (HF) is related to insulin-resistant polycystic ovary syndrome (PCOS), we compared insulin sensitivity and gonadotropin secretion in HF with compromised (↓) adrenal HSD3B phenotype despite normal HSD3B2 genes (n = 6) to those in HF with classic PCOS (n = 9) of similar ages (14–36 yr). The same was examined in premature pubarche (PP) girls with (n = 4) and without the ↓HSD3B phenotype (n = 5). The ↓HSD3B phenotype was defined by ACTH-stimulated Δ5-precursor steroid levels and Δ5-precursors to Δ4-product steroid ratios higher than those in normal females (n = 30 for adult, n = 12 for pubertal). Classic PCOS HF had elevated testosterone levels and normal ACTH-stimulated hormonal profiles. The insulin sensitivity index determined by the frequently sampled iv glucose-tolbutamide test (FSIVGTT) in all HF with ↓HSD3B phenotype and in all HF with classic PCOS, regardless of body mass index (BMI), was lower than in all eight normal BMI and five high BMI normal females. Integrated incremental insulin determined by FSIVGTT, the area under the curve for insulin, and fasting and 2 h glucose load insulin levels determined by an oral glucose tolerance test in both HF groups were higher (P < 0.01–0.0001) than those in normal females with normal or high BMI. LHRH-stimulated LH levels and LH/FSH ratios in both HF groups were higher (P < 0.01) than those in normal females. No statistical differences were found in the insulin sensitivity and gonadotropin parameter between the two PP girl groups. The insulin sensitivity index in each half of PP girls with the ↓HSD3B phenotype was lower than or similar to that in control PP girls with a similar weight length index. The fasting glucose to insulin ratio in three of four PP girls with the ↓HSD3B phenotype was lower than that in control PP girls, but one of four with the ↓HSD3B phenotype had a higher fasting glucose to insulin ratio than the control PP girls. The findings of insulin sensitivity and gonadotropin data in both HF with the ↓HSD3B phenotype and classic PCOS indicate significant insulin resistance and LH hypersecretion in both. These suggest that the ↓HSD3B phenotype in HF is associated with a variant of insulin-resistant PCOS. The variable insulin sensitivity parameter in the small number of PP girls with the ↓HSD3B phenotype warrants a further large scale study to examine this phenotype association with childhood insulin resistance. (J Clin Endocrinol Metab 89: 783–794, 2004)

IN HUMANS, THE type II 3β-hydroxysteroid dehydrogenase/Δ5-Δ4-isomerase (HSD3B2) gene encodes the adrenal and gonadal HSD3B enzyme, which catalyzes the conversion of Δ5-3β-hydroxysteroids to Δ4-3β-ketosteroids in the adrenals and gonads (1, 2). Thus, inherited HSD3B2 deficiency results from a deleterious mutation in the HSD3B2 gene (3, 4). The clinical spectrum of inherited HSD3B deficiency ranges from the classic salt wasting, genital ambiguity, and hypogonadism in males and females (3–7) to nonclassic hyperandrogenic symptoms in children (8–10) and young women (3, 4, 11, 12) with proven HSD3B2 gene mutation. In the last 2 decades, mild nonclassic HSD3B deficiency has been diagnosed without any genotypic proof in many children with premature pubarche (PP) (13, 14) and in women with hirsutism and menstrual disorders (14–18) based on the criteria of greater than 2 sd above normal mean value of ACTH-stimulated Δ5 precursor steroid levels in-
including 17-hydroxyprogrenolone (Δ5-17P) and dehydroepiandrosterone (DHEA) levels, and increased Δ5-precursor to Δ4-product steroid ratios, including Δ5-17P to 17-hydroxyprogesterone (17-OHP), Δ4-17P to cortisol (F), and DHEA to androstenedione (Δ4-A) ratios.

Our recent HSD3B2 genotype and hormonal phenotype study in more than 70 patients with clinical and hormonal indication of adrenal HSD3B deficiency revealed two distinct groups of patients, including the HSD3B2 gene-mutated, severe HSD3B2 deficiency group and the HSD3B2 gene-normal, mildly compromised adrenal HSD3B activity group (19–21). In the latter group of patients, nevertheless, ACTH-stimulated Δ5-17P and Δ4-17P to F ratios were as high as 11 and 5 sd above the normal mean value, respectively, in children with PP and up to 12 and 10 sd above the normal mean value, respectively, in hyperandrogenic females (HF) (19). In addition, ACTH-stimulated DHEA levels and ratios of Δ5-17P to 17-OHP, and DHEA to Δ4-A ratios in the HSD3B2 gene-normal patients were often indistinguishable from those in the HSD3B2 gene-mutated patients (19–21). These elevated ACTH-stimulated Δ5-17P and DHEA levels with elevated ratios of Δ4-17P to 17-OHP, Δ5-17P to F, and DHEA to Δ4-A in the HSD3B2 gene-normal HF and children with PP indicate compromised adrenal HSD3B activity regardless of or in addition to the postulated CYP17 dysregulation (22). CYP17 dysregulation alone is unlikely to cause the increased ratio of Δ5 precursor to Δ4 product steroids upon ACTH stimulation. Thus, the hormonal phenotype of mildly compromised adrenal HSD3B activity in HF and PP children with normal HSD3B2 gene suggests compromised adrenal HSD3B2 expression (19–21, 23). The HSD3B2 genotype-normal HF with the phenotype of compromised adrenal HSD3B activity have an equally high frequency of menstrual disorders as in HF with classic polycystic ovary syndrome (PCOS) regardless of normal or high body mass index (BMI) (19, 24). Thus, we hypothesize that the phenotype indicating compromised adrenal HSD3B activity in HF may be related to a variant of classic PCOS. If so, HF with hormonal phenotype of compromised adrenal HSD3B activity would manifest insulin resistance (25, 26) and LH hypersecretion (27, 28), characteristics of PCOS. We thus investigated and compared insulin sensitivity and gonadotropin secretion in HSD3B2 genotype-normal HF with hormonal abnormalities of compromised adrenal HSD3B activity to those in HF with classic PCOS. In addition, we studied insulin sensitivity and gonadotropin secretion in young PP girls with and without the hormonal phenotype of compromised adrenal HSD3B activity to determine whether this phenotype during childhood is associated with insulin resistance and altered gonadotropin secretion.

**Subjects and Methods**

This study was approved by the institutional review board of University of Illinois (Chicago, IL) and was performed after informed consent was obtained from the subjects and from legal guardians or parents of minor subjects, and informed assent was obtained from the minor subjects when appropriate.

**Patient population**

Fifteen HF (aged 14.2–36 yr) were recruited for studies of insulin sensitivity and gonadotropin secretion (Table 1). All HF had random testosterone (T) levels and baseline and ACTH-stimulated hormonal evaluation. Those with 21-hydroxylase or 11β-hydroxylase deficiency were excluded from the study.

Six of these HF (aged 14.2–22 yr; mean, 18 yr) had the hormonal abnormalities of compromised adrenal HSD3B activity by increased ACTH-stimulated Δ5-17P and DHEA levels and ratios of Δ5-17P to 17-OHP. Δ4-17P to F. and DHEA to Δ4-A all greater than 2 sd of the normal female mean value (Table 1). The baseline hormonal parameters in these HF were either significantly higher than in normal females or males with normal adrenal HSD3B activity and DHEA to androstenedione (Δ4-A) ratios.

**Table 1. Clinical and hormonal data of HF with hormonal phenotype of decreased adrenal HSD3B activity and HF with classic PCOS**

<table>
<thead>
<tr>
<th>ID no</th>
<th>Race</th>
<th>Age at study (yr)</th>
<th>Age at pubarche (yr)</th>
<th>Age at menarche (yr)</th>
<th>Hyperandrogenic symptoms</th>
<th>Random T (nmol/l)</th>
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<td></td>
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<td></td>
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<tr>
<td>Normal females (mean ± sd, n = 30)</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>W</td>
<td>28 ± 7</td>
<td>&lt;11</td>
<td>14</td>
<td>16, H</td>
<td>1.6 ± 0.4</td>
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<tr>
<td>2</td>
<td>W</td>
<td>14.2</td>
<td>9</td>
<td>12</td>
<td>15, A</td>
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</tr>
<tr>
<td>3</td>
<td>W</td>
<td>18</td>
<td>8</td>
<td>9</td>
<td>9, H</td>
<td>2.67</td>
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<tr>
<td>4</td>
<td>W</td>
<td>17</td>
<td>10</td>
<td>11</td>
<td>14, H, A</td>
<td>2.1</td>
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<tr>
<td>5</td>
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<td>15</td>
<td>4</td>
<td>9</td>
<td>10, H, A</td>
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</tr>
<tr>
<td>6</td>
<td>HW</td>
<td>22</td>
<td>7</td>
<td>9</td>
<td>15, H</td>
<td>2.35</td>
</tr>
</tbody>
</table>

**Group mean ± sd (n = 9): 18 ± 3**

| HF with classic PCOS |       |                  |                     |                     |                         |                  |
| 1     | HW   | 16               | 13                  | 15                  | 15, H                   | 1.8 ± 0.60       |
| 2     | AA   | 16               | 15.5                | 14                  | 12, H                   | 2.5              |
| 3     | AA   | 25               | 15                  | 14                  | 18, H                   | 4.1              |
| 4     | HW   | 19               | 8                   | 17                  | 11, H                   | 2.6              |
| 5     | W    | 31               | 9                   | 11                  | 10, H                   | 4.0              |
| 6     | HW   | 25               | <12                 | 12                  | 15, H                   | 4.8              |
| 7     | W    | 36               | 10                  | 12                  | 13, H                   | 4.0              |
| 8     | W    | 24               | 10.5                | 12                  | 18, H                   | 2.4              |
| 9     | AA   | 17               | 7.5                 | 14                  | 13, H                   | 2.3              |

**Group mean ± sd (n = 9): 23 ± 7**

784 J Clin Endocrinol Metab, February 2004, 89(2):783–794

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random T levels compared with normal females or HF with compro-
mise test (OGTT), and LHRH stimulation test. Both groups of HF had a frequently sampled iv glucose and tolbutamide tolerance test (FSIVGTT), oral glucose tolerance test (OGTT), and LHRH stimulation test.

Nine young girls, aged 6.8–9 yr, had PP at 3–7 yr of age (Table 2). All had Tanner stage II–III pubic hair at evaluation, and all except one had Tanner stage II breasts (Table 2). The race and ethnicity of the PP girls were varied. All PP had baseline and ACTH-stimulated hormonal evaluation. Four girls with PP had the hormonal abnormalities of compromised adrenal HSD3B activity by increased ACTH-stimulated Δ4-17P and DHEA levels, and ratios of Δ4-17P to 17-OHP, Δ4-17P to F, and DHEA to Δ4-A all above 2 sp of the mean values of control girls with Tanner stage II–III pubic hair (Table 2). The baseline hormonal values in these PP girls were generally higher than those in control girls (Table 2). The HSD3B2 gene sequence in these PP girls was normal. These PP girls did not have acanthosis nigricans. Five other girls with PP had apparently normal adrenal HSD3B activity by the baseline and ACTH-stimulated steroid values comparable to or insignificantly different from those in the control girls, although the DHEA to Δ4-A ratio was statistically higher than that in the control girls. One PP girl from this group had acanthosis nigricans (Table 2).

The weight-length index (WLI) was determined as reported [actual weight in kilograms ÷ actual height in centimeters/50th percentile expected weight in kilograms for age ÷ 50th percentile expected height in height for age] (30). The PP girls had a modified FSIVGTT and LHRH stimulation test.

Control population

The reference baseline and ACTH-stimulated hormonal data in normal adult females were previously reported (24, 31). The reference baseline and ACTH-stimulated hormonal data for the control girls with Tanner stage II–III pubic hair were previously reported (32). Fourteen healthy normal females (mean age, 25 yr; range, 18–35 yr) with no androgen excess symptoms or acanthosis nigricans, regular menstrual cycles, and no family history of diabetes mellitus were recruited as control subjects. Nine had normal BMI (mean ± SE, 21 ± 0.4) and five had a higher BMI (mean ± SE, 28 ± 0.6). These females had an FSIVGTT and OGTT performed. Eight normal BMI and three high BMI normal females had an LHRH stimulation test performed.

Study procedures and laboratory methods

ACTH stimulation test and hormonal assay. The test was performed between 0830–1100 h in HF and girls with PP. Blood samples were obtained before and 60 min after iv bolus administration of a synthetic ACTH (250 μg; Cortrosyn, Ben Venue Laboratories, Inc., Bedford, OH). Serum steroid levels were determined by a reported RIA after Celite chromatographic purification (34, 31, 32). The inter- and in assay vari-

### Table 1. Continued

<table>
<thead>
<tr>
<th></th>
<th>Δ4-17P (nm/liter)</th>
<th>17-OHP (nm/liter)</th>
<th>P (nm/liter)</th>
<th>DHEA (nm/liter)</th>
<th>Δ4-A (nm/liter)</th>
<th>Δ4-17P/17-OHP</th>
<th>Δ4-17P/F</th>
<th>DHEA/Δ4-A</th>
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<tr>
<td></td>
<td>0</td>
<td>60</td>
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<td>60</td>
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<tr>
<td>Δ4-17P</td>
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<td>6.3</td>
<td>4.3</td>
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<td>4.3</td>
<td>1.7</td>
<td>4.3</td>
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<td>17-OHP</td>
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<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>P</td>
<td>0.6</td>
<td>6.3</td>
<td>4.3</td>
<td>1.7</td>
<td>4.3</td>
<td>1.7</td>
<td>4.3</td>
<td>1.7</td>
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<td>DHEA</td>
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<td>1</td>
<td>0.1</td>
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<td>0.1</td>
<td>0.1</td>
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<tr>
<td>Δ4-A</td>
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<td>6.3</td>
<td>4.3</td>
<td>1.7</td>
<td>4.3</td>
<td>1.7</td>
<td>4.3</td>
<td>1.7</td>
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<tr>
<td>Δ4-17P/17-OHP</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
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<td>0.1</td>
<td>0.1</td>
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<tr>
<td>Δ4-17P/F</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>DHEA/Δ4-A</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
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</tr>
</tbody>
</table>

AA, African-American; W, white; HW, Hispanic white; H, hirsutism; A, acne; R, regular; IR, irregular; AM, amenorrhea. To convert to DHEA, multiply by 33.3 for Δ4-17P and 17-OHP; multiply by 28.6 for DHEA and Δ4-A; multiply by 28.8 for T. To convert to micrograms per deciliter, multiply by 33.3 for F.

a Up at P < 0.05–0.0001 in each HF group compared to normal females.

b At P < 0.05 in HF with ↑ HSD3B phenotype compared to HF with classic PCOS.
apparently normal adrenal HSD3B activity

breast development had an LHRH stimulation test using an LHRH dose

samples were drawn at 30, 45, and 90 min. In girls with PP, those with

Laboratories, Inc., Philadelphia, PA) was given by a bolus, and blood

/H9262

Synthetic LHRH (100 μg; Factrel, gonadotropin hydrochloride, Ayerst

lished, and blood samples were drawn at

after a negative pregnancy test. One to 2 h after breakfast, an iv line was estab-

7 d) if the cycle was known and regular,

OGTT was performed after overnight fasting. Subjects

contraceptives for 1–3 months and had a negative pregnancy test before

OGTT and modified FSIVGTT. The subjects first completed a 300-g car-

bohydrate diet for 3 d. No subjects received any medication or oral

contraceptives for 1–3 months and had a negative pregnancy test before

OGTT was performed after overnight fasting. Subjects

had an iv line established and rested for 30 min. Blood samples were
drawn at −30, −15, and −1 min, glucose solution (40 g/m² to a max-
imum of 75 g) was given orally, and the samples were drawn at 30, 60,
and 180 min for determination of glucose and insulin concentra-
tions. The areas under the curve for glucose (AUCg) and insulin (AUCi)
from the OGTT were determined by the trapezoidal rule. The FSIVGTT
was performed as previously reported (33) after overnight fasting. Each
subject had two iv lines, one in each arm, and rested for 30 min. At time
zero, a glucose solution (0.3 g/kg) was administered iv over 1 min, and
at 20 min, tolbutamide (500 mg; Upjohn Co., Kalamazoo, MI) was ad-
ministered iv over 15–20 sec. Blood samples were drawn from the
contralateral arm at −15, −10, −5, −1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22,
23, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, and 180 min for
determination of glucose and insulin. The FSIVGTT in girls with PP was
performed by an identical method, except a tolbutamide dose of 5
mg/kg was given, and the procedure ended at 90 min (34, 35). Physician
attendance throughout the procedure ensured the subject’s safety. No ill
effects from the procedure occurred in any subject. The insulin sensi-
tivity index (S_I) was calculated from glucose and insulin data by the
minimal model computer program (from Dr. L. Quinn, University of
Illinois, using the MINMOD program version). The modified S_I, from the
90-min FSIVGTT in girls with PP was calculated as previously reported
(34, 35). Integrated incremental insulin was calculated by the magnitude
of insulin above the basal level using the computer program. The glucose
concentration was determined by a glucose oxidase method (YSI, Inc.,
Yellow Springs, OH), and the insulin concentration was determined by a
chemiluminescent immunoassay with inter- and intraassay coeffi-
cients of variation of 4% and 5% respectively.

LHRR stimulation test. The test was performed during the early follicular
phase of the menstrual cycle (1–7 d) if the cycle was known and regular,
after a negative pregnancy test. For those with very irregular menses and
first or second degree amenorrhea, the test was performed after a nega-
tive pregnancy test. One to 2 h after breakfast, an iv line was estab-
lished, and blood samples were drawn at −60, −40, −20, and −1 min.
Synthetic LHRR (100 μg; Factrel, gonadotropin hydrochloride, Ayerst
Laboratories, Inc., Philadelphia, PA) was given by a bolus, and blood
samples were drawn at 30, 45, and 90 min. In girls with PP, those with
breast development had an LHRR stimulation test using an LHRR dose
of 100 μg/m². PP girls with no breast development had only the basal
level study. All samples were determined for LH and FSH levels by two-
site fluorimmunometric assay (Wallac, Turku, Finland), with inter-
and intraassay coefficients of variation of 1.8% and 2.5%, respectively.

Statistical analysis. A two-sample Wilcoxon and rank-sum (Mann-
Whitney) test was used to determine the differences in all steroid values,
insulin sensitivity, and gonadotropin parameters between each HF
group and normal females, between the two groups of HF, or between
PP girls with and without the phenotype of compromised adrenal
HSD3B activity. P < 0.05 between the groups was considered significant.

Results

S_I and integrated incremental insulin (IIIns) from
FSIVGTT (Tables 3 and 4, Fig. 1, A and B, and
Fig. 2, A and B)

The S_I in all six HF with the phenotype of compromised
adrenal HSD3B activity (↓ HSD3B phenotype), regardless of
BMI, was lower than the S_I in normal females with normal and
high BMI (Fig. 1A and Table 3); the S_I in HF with normal or
high BMI was equally low (Fig. 1A and Table 3). The S_I in
all HF with classic PCOS, regardless of BMI, was also lower
than that in normal females with normal or high BMI; the S_I
in the classic PCOS HF was higher than or
 overlapped with IIIns in normal females with normal or high BMI (Fig. 1A and Table 3). There was no significant difference in the S_I between HF with the ↓ HSD3B phenotype and HF
with classic PCOS (Table 3).

IIIns in HF with the ↓ HSD3B phenotype was significantly
higher than IIIns in normal females with normal or high BMI
(Table 3); IIIns in HF with normal or high BMI was higher than
IIIns in normal females with comparable BMI (Fig. 1B and
Table 3). IIIns in HF with classic PCOS was also signifi-
cantly higher than IIIns in normal females with normal or
high BMI; IIIns in classic PCOS HF were higher than or
overlapped with IIIns in the high BMI normal females (Fig.
1B and Table 3). There was no significant difference in IIIns
between HF with the ↓ HSD3B phenotype and HF
with classic PCOS (Fig. 1B and Table 3).

In girls with PP, there were no statistical differences in S_I
and IIIns values between four PP girls with the ↓ HSD3B
phenotype and five PP girls with normal HSD3B activity. The
S_I in half of the PP girls (two of four) with the ↓ HSD3B
phenotype was lower than the S_I in control PP girls of similar
WLI with normal HSD3B activity, whereas the S_I in the other

TABLE 2. Clinical and hormonal data of girls with PP with hormonal phenotype of ↓ adrenal HSD3B activity and girls with PP with apparently normal adrenal HSD3B activity

<table>
<thead>
<tr>
<th>Group ID</th>
<th>Group no.</th>
<th>Race</th>
<th>Age at onset of puberty (yr)</th>
<th>Age at test (yr)</th>
<th>Tanner stages at test</th>
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<td>Control normal girls (n = 12)</td>
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<td>PPG with ↓ phenotype of adrenal HSD3B activity</td>
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<td>9–13</td>
<td>I–II</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>HW</td>
<td>3</td>
<td>8.58</td>
<td>II</td>
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<td>AA</td>
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<td>9.33</td>
<td>III</td>
</tr>
<tr>
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<td>5</td>
<td>7.83</td>
<td>III</td>
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<tr>
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<td>5</td>
<td>AA</td>
<td>5</td>
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<td>II</td>
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<tr>
<td>Group mean ± SD (n = 4)</td>
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<td>8.4 ± 0.8</td>
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<td>PPG with apparently normal adrenal HSD3B activity</td>
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<td>5</td>
<td>7</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>W</td>
<td>7</td>
<td>8.9</td>
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<tr>
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<td>9</td>
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<tr>
<td>Group mean ± SD (n = 5)</td>
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<td>7.96 ± 0.5</td>
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<th>Δ²-17P (nm/liter)</th>
<th>17-OHP (nm/liter)</th>
<th>P (μg/liter)</th>
<th>DHEA (μg/dl)</th>
<th>Δ²A (nm/liter)</th>
<th>Δ²-17P/17-OHP</th>
<th>Δ²-17P/P</th>
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<tr>
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<td>0.22±0.6</td>
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<td>14±4.9</td>
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<tr>
<td>0.8±1.2</td>
<td>3.9±1.2</td>
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<td>0.22±0.6</td>
<td>0.9±0.9</td>
<td>21.4±5.5</td>
<td>14±4.9</td>
<td>1.9±0.8</td>
</tr>
</tbody>
</table>

AA, African-American; W, white; HW, Hispanic white; AA/W, mixed African-American and white. To convert to nanograms per deciliter, multiply by 33.3 for Δ²-17P and 17-OHP; multiply by 28.6 for DHEA and Δ²A; multiply by 28.8 for T. To convert to micrograms per deciliter, multiply by 33.3 for F.

- **AUCi** and **AUCg** from OGTT (Table 3)

Both AUCi and AUCg in HF with the ↓ HSD3B phenotype were significantly higher than those in normal females with normal or high BMI (Table 3); AUCi in these HF with normal or high BMI were higher than or comparable to normal females with comparable BMI. AUCi in HF with classic PCOS was also significantly higher than AUCi in normal females with normal or high BMI (Table 3); AUCi in these HF with normal or high BMI were higher than or comparable to normal females with normal or high BMI, but not significantly (Table 3). There was no significant difference in AUCi and AUCg between HF with the ↓ HSD3B phenotype and HF with classic PCOS (Table 3).

**Fasting glucose and insulin levels and glucose to insulin ratios**

The fasting glucose level (mean of three values in 30 min) in HF with the ↓ HSD3B phenotype [n = 6; mean ± se, 90 ± 2.3 mg/100 ml (5 ± 0.13 mmol/liter)] was different from that in normal BMI females [n = 9; 83 ± 2.8 mg/100 ml (4.6 ± 0.16 mmol/liter)], but was higher (P < 0.05) than that in high BMI normal females [n = 5; 75 ± 2.5 mg/100 ml (4.2 ± 0.14 mmol/liter)]. The fasting insulin level in this HF group (mean ± se, 25 ± 4.3 μU/ml) was higher (P < 0.001) than that in normal females with normal BMI (4.8 ± 0.8 μU/ml) or high BMI (6.5 ± 1.6 μU/ml). The fasting glucose (milligrams per 100 ml) to insulin (microunits per milliliter) ratios in this HF (mean ± se, 4.3 ± 0.77), regardless of BMI, was lower (P < 0.05–0.001) than that in normal females with normal BMI (23 ± 5) or high BMI (17 ± 6). In HF with classic PCOS, the fasting glucose level [mean ± se, 94.8 ± 0.72 mg/100 ml (5.27 ± 0.04 mmol/liter)] was higher (P < 0.05–0.001) than that in normal females with normal or high BMI. The fasting insulin level in classic PCOS HF (51 ± 35 μU/ml), regardless of BMI, was higher (P < 0.05–0.001) than that in normal females with normal or high BMI. The fasting glucose (milligrams per 100 ml) to insulin (microunits per milliliter) ratios in classic PCOS HF (6.3 ± 1.1), regardless of BMI, was lower (P > 0.05) than that in normal females with normal or high BMI. There were no significant differences in fasting glucose and insulin levels and glucose to insulin ratios between HF with the ↓ HSD3B phenotype and HF with classic PCOS.

In girls with PP, there was no statistical difference in fasting glucose, insulin, and glucose to insulin ratio between four PP girls with the ↓ HSD3B phenotype and five PP girls with normal HSD3B activity. However, regardless of WLI, fasting insulin levels in three of four PP girls with the ↓ HSD3B phenotype were higher and the fasting glucose to insulin ratio in the same PP girls was lower than those in five PP girls with normal HSD3B activity, but one of four PP girls with the ↓ HSD3B phenotype had a higher ratio than the control PP girls (Table 4).

**Two-hour glucose and insulin levels after glucose load via OGTT**

The 2 h glucose level in HF with the ↓ HSD3B phenotype [n = 5; mean ± se, 138 ± 10.2 mg/100 ml (7.7 ± 0.5 mmol/liter)] was higher (P < 0.05–0.001) than that in normal females with normal BMI [n = 8; 101 ± 6.3 mg/100 ml (5.6 ± 0.35 mmol/liter)] or high BMI [n = 5; 99 ± 10.8 mg/100 ml (5.5 ± 0.6 mmol/liter)]. Three of five HF with the ↓ HSD3B phenotype had glucose impairment (>140 mg/100 ml). The 2 h
TABLE 3. Insulin sensitivity and gonadotropin parameters (mean ± SE) in HF and in control normal (NL) females

<table>
<thead>
<tr>
<th>Group</th>
<th>Age at study (yr)</th>
<th>BMI (kg/m²)</th>
<th><strong>SI</strong> (µU/ml)</th>
<th><strong>IIins</strong> (µU/ml × min)</th>
<th><strong>AUCl</strong> (min × µU/ml)</th>
<th><strong>AUCh</strong> (min × µU/ml)</th>
<th>Baseline LH (mU/ml)</th>
<th>Baseline FSH (mU/ml)</th>
<th>Baseline LH/FSH</th>
<th>Peak LHRH stimulated LH (mU/ml)</th>
<th>Peak LHRH stimulated FSH (mU/ml)</th>
<th>Peak LHRH stimulated LH/FSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control NL BMI females (n = 8–9)</td>
<td>24 ± 3.5</td>
<td>21 ± 0.4</td>
<td>16 ± 5.9</td>
<td>1,909 ± 433</td>
<td>4,323 ± 969</td>
<td>4,650 ± 701</td>
<td>3.8 ± 0.46</td>
<td>8.8 ± 1.6</td>
<td>0.48 ± 0.06</td>
<td>15 ± 1.7</td>
<td>12.4 ± 1.9</td>
<td>1.3 ± 0.17</td>
</tr>
<tr>
<td>[mean ± SE (range)]</td>
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<td></td>
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</tr>
<tr>
<td>Control high BMI NL females (n = 5)</td>
<td>27 ± 3.2</td>
<td>28 ± 0.6</td>
<td>10.5 ± 6.3</td>
<td>4,003 ± 1,319</td>
<td>7,489 ± 2,479</td>
<td>3,735 ± 979</td>
<td>433 ± 163</td>
<td>1,323 ± 1,110</td>
<td>0.48 ± 0.06</td>
<td>15 ± 0.95</td>
<td>2.3 ± 0.63</td>
<td>0.92 ± 0.07</td>
</tr>
<tr>
<td>[mean ± SE (range)]</td>
<td></td>
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<td></td>
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<tr>
<td>HF with phenotype of adrenal HSD3B activity (n = 5–6)</td>
<td>18 ± 1.2</td>
<td>32 ± 2.2a</td>
<td>0.68 ± 0.23</td>
<td>17,637 ± 5,306</td>
<td>27,282 ± 5,316</td>
<td>8,773 ± 634</td>
<td>5.2 ± 1.2</td>
<td>4.9 ± 0.44</td>
<td>1.1 ± 0.24</td>
<td>27 ± 5.9c</td>
<td>8.4 ± 0.83</td>
<td>3.2 ± 0.6c</td>
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<tr>
<td>[mean ± SE (range)]</td>
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<td></td>
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<tr>
<td>HF with classic PCOS (n = 7–8)</td>
<td>23 ± 2.3</td>
<td>34 ± 2.1a</td>
<td>0.94 ± 0.36</td>
<td>14,848 ± 3,078</td>
<td>18,332 ± 5,889</td>
<td>8,095 ± 2,725.4</td>
<td>7.2 ± 0.92</td>
<td>4 ± 0.42</td>
<td>1.7 ± 0.17</td>
<td>36.1 ± 9.4c</td>
<td>6.8 ± 1.0c</td>
<td>4.7 ± 0.6c</td>
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<td>[mean ± SE (range)]</td>
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</tr>
</tbody>
</table>

No significant differences in all parameters between HF with ↓ HSD3B phenotype vs. HF with classic PCOS.

* a at P < 0.05–0.0001 in the HF group compared to each normal BMI and high BMI normal females.
* b at P < 0.05 in the HF group compared to only normal BMI normal females.
* c at P < 0.05–0.0001 in the HF group to the combined normal BMI (n = 8) and high BMI (n = 3) normal females (n = 11).
* d at P < 0.05–0.0001 in the HF compared to combined normal BMI and high BMI normal females.
<table>
<thead>
<tr>
<th>Control Group</th>
<th>ID no.</th>
<th>Age at test (yr)</th>
<th>WLI</th>
<th>AN</th>
<th>Breast</th>
<th>Pubic hair</th>
<th>SI (× 10^{-4} \text{ min}^{-1}/\mu \text{U/ml})</th>
<th>III (\mu \text{U/ml} × \text{ min})</th>
<th>Fasting levels</th>
<th>Baseline</th>
<th>Peak LH/LHFSH</th>
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<tr>
<td>PGG with phe-</td>
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<td>8.58</td>
<td>105</td>
<td>No</td>
<td>II</td>
<td>III</td>
<td>9.75</td>
<td>124</td>
<td>77.4 (2.4)</td>
<td>3.5</td>
<td>0.25</td>
</tr>
<tr>
<td>notype of adrenal</td>
<td>2</td>
<td>9.33</td>
<td>122</td>
<td>No</td>
<td>II</td>
<td>III</td>
<td>2.44</td>
<td>4963</td>
<td>84.7 (4.7)</td>
<td>24.5</td>
<td>2.28</td>
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<tr>
<td></td>
<td>3</td>
<td>7.83</td>
<td>133</td>
<td>No</td>
<td>II</td>
<td>III</td>
<td>5.06</td>
<td>2951</td>
<td>75.4 (4.2)</td>
<td>15.4</td>
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<td></td>
<td>4</td>
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<td>146</td>
<td>No</td>
<td>II</td>
<td>III</td>
<td>2.35</td>
<td>7569</td>
<td>75.4 (4.1)</td>
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<td>Group mean ± SE (n = 4)</td>
<td>8.4 ± 0.8</td>
<td>126 ± 8.6</td>
<td></td>
<td></td>
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<td></td>
<td>4.9 ± 1.7</td>
<td>4052 ± 1457</td>
<td>77.8 ± 2.1 (4.3 ± 0.14)</td>
<td>14.7 ± 4.3</td>
<td>8.8 ± 4.4 (4.3 ± 0.14)</td>
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<tr>
<td>PGG with apparent NL</td>
<td>1</td>
<td>7</td>
<td>99</td>
<td>No</td>
<td>II</td>
<td>III</td>
<td>7.65</td>
<td>2956</td>
<td>79.4 (4.4)</td>
<td>8.4</td>
<td>0.33</td>
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<td>8.9</td>
<td>99</td>
<td>No</td>
<td>II</td>
<td>III</td>
<td>10.53</td>
<td>609</td>
<td>79.4 (4.4)</td>
<td>5.2</td>
<td>0.03</td>
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<tr>
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<td>132</td>
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<td>I</td>
<td>III</td>
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<td>III</td>
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<tr>
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<td>9</td>
<td>163</td>
<td>Yes</td>
<td>II</td>
<td>III</td>
<td>3.06</td>
<td>5157</td>
<td>80.4 (4.4)</td>
<td>9.2</td>
<td>0.07</td>
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<tr>
<td>Group mean ± SE (n = 5)</td>
<td>7.95 ± 0.5</td>
<td>129 ± 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.95 ± 3.12</td>
<td>2906 ± 772</td>
<td>81.2 ± 2.6 (4.5 ± 0.19)</td>
<td>8.6 ± 0.98</td>
<td>10.4 ± 1.4</td>
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</table>

ID no. of subjects corresponds to ID no. on Table 2. AN, Acanthosis nigricans; Yes, present; No, absent on physical examination. Fasting glucose to insulin ratio was based on glucose in mg% and insulin in \mu \text{U/ml} compared with the published ratio (Refs. 44 and 45). No statistical significance was noted in all parameters of insulin sensitivity and gonadotropins between the groups of PP girls.
insulin level in these HF (mean ± se, 201 ± 34 μU/ml), regardless of BMI, was higher than that in normal females with normal BMI (34 ± 7 μU/ml) or high BMI (50 ± 16 μU/ml). The 2-h glucose level [145 ± 19.8 mg/100 ml (8.1 ± 1.1 mmol/liter)] and insulin level (170 ± 54 μIU/ml) in HF with classic PCOS (n = 8) were higher (P < 0.01–0.05) than those in normal females with normal or high BMI. Two of eight HF with classic PCOS had glucose impairment, and one subject had diabetes mellitus (>200 mg/100 ml). There were no significant differences in the 2-h glucose and insulin levels between HF with the ↓ HSD3B phenotype and HF with classic PCOS.

Baseline and LHRH-stimulated gonadotropin profile

The basal LH to FSH ratios (mean of four basal values in 1 h) and LHRH-stimulated peak LH levels and LH to FSH ratio in HF with the ↓ HSD3B phenotype were significantly higher than those in normal females, comprised of overlapping values of eight normal BMI and three high BMI females (Table 3 and Fig. 3). In HF with classic PCOS, the basal and LHRH-stimulated peak LH levels and LH to FSH ratios were significantly higher than those in normal females, and the FSH levels were significantly lower than those in normal females (Table 3 and Fig. 3). In HF with the ↓ HSD3B phenotype, LHRH-stimulated LH levels and LH to FSH ratios tended to be lower in the two lower BMI subjects, but the parameters in the classic PCOS female with lower BMI were indistinguishable from those in the high BMI HF. There were no significant differences between basal and LHRH-stimulated peak LH and FSH levels and LH to FSH ratios between HF with the ↓ HSD3B phenotype and HF with classic PCOS (Table 3 and Fig. 3). In girls with PP, basal and LHRH-stimulated gonadotropin profiles overlapped and were not significantly different between the two groups (Table 4).

Discussion

In the last two decades, many HF and children with PP have been diagnosed with mild nonclassic HSD3B2 deficiency based on moderately elevated levels of ACTH-stimulated Δ⁵-17P and DHEA levels and elevated ratios of
These hormonal abnormalities indicate compromised adrenal HSD3B activity. The etiology or causative factor(s) related to this hormonal phenotype of mildly compromised adrenal HSD3B activity in HF and young children with PP (13–18) has been uncertain. Studies of HSD3B2 and HSD3B1 genes in the patients with the hormonal phenotype of compromised adrenal HSD3B activity, including our work (19–21) and that of others (23), showed no demonstrable mutation in the genes. This indicates that the causative factor is not within the HSD3B2 gene, but is probably related to altered gene expression, possibly due to a systemic or intraadrenal factor(s).

Our previous work and that of others, as well as the present work, have noted that HF with the hormonal phenotype of compromised adrenal HSD3B activity have a very high frequency of menstrual disorders (19, 22, 24), increased BMI as a group, although BMI varied from normal to high (24), and evidence of possibly increased ovarian androgen secretion (22, 24). These presentations in HF with the compromised adrenal HSD3B phenotype are similar to the clinical, physical, and hormonal presentations of HF with classic PCOS. PCOS is often associated with significant insulin resistance (25, 26, 33–38). Recent studies suggest that hyperinsulinemia due to insulin resistance of PCOS results in augmented adrenal and/or ovarian steroidogenesis based on in vivo (33) and in vitro findings (39). We hypothesized that the hormonal phenotype of compromised adrenal HSD3B activity associated with primarily adrenal hyperandrogenism in HF might be related to a variant of PCOS. If so,
insulin resistance and altered LH secretion characteristic of PCOS might be manifested in HF with compromised HSD3B phenotype (27, 28).

The present study demonstrates that marked insulin resistance is present in both HF with the hormonal phenotype of compromised adrenal HSD3B activity and HF with classic PCOS, regardless of BMI. The strongest evidence of insulin resistance in both groups of HF was low SI and high IIIns in a few HF of both groups with normal or only modestly high BMI comparable to the control females. The low SI and high or higher IIIns in the majority of HF with high BMI in both groups also indicate the presence of marked degree of insulin resistance. However, in the high BMI HF with both the ↓ HSD3B phenotype and classic PCOS, a possibility that the marked insulin resistance might in part have been influenced by the obesity effect could not be excluded due to the absence of comparative high BMI control data in the present study or in the literature. However, it is known that insulin resistance of PCOS females is independent of adiposity or obesity (25, 36, 37). Furthermore, the low SI values in HF of both groups in our study are similar to the reported low SI values in HF with PCOS (33, 38). Additional parameters of insulin sensitivity, including increased AUCi, fasting and 2-h glucose load insulin levels, and increased fasting glucose to insulin ratios in HF with the ↓ HSD3B phenotype, regardless of BMI, were similar to those of classic PCOS with comparable BMI in the present study. These findings support the conclusion that insulin resistance in HF with the ↓ HSD3B phenotype is unlikely to be due to obesity, but is probably related to underlying PCOS. Furthermore, significantly increased LHRH stimulated LH levels and LH to FSH ratios in the group of HF with the ↓ HSD3B phenotype compared with those in normal females, and a similar pattern of LHRH-stimulated gonadotropin parameters between HF with the ↓ HSD3B phenotype and HF with classic PCOS suggest LH hypersecretion, a characteristic of PCOS (27, 28), in these HF. These findings suggest that HF with the biochemical phenotype of compromised adrenal HSD3B activity not only exhibit clinical features of PCOS, but also manifest with insulin resistance and LH hypersecretion characteristic of PCOS. Thus, the hormonal phenotype of compromised adrenal HSD3B activity is associated with a variant of insulin-resistant PCOS.

The puzzling observation from this study is that both groups of HF have a significant degree of insulin resistance, but HF with classic PCOS have normal adrenal HSD3B activity and markedly increased ovarian androgen secretion. HF with the ↓ HSD3B phenotype and adrenal hyperandrogenism have significantly lower T levels than HF with classic PCOS, indicating a lesser degree of ovarian androgen secretion. If insulin is a common systemic factor for PCOS in both groups of HF, such a disparity in the adrenal hormonal profile related to HSD3B activity between the two groups of HF with marked insulin resistance is puzzling. It has been suggested that patients exhibiting mild adrenal HSD3B deficiency have PCOS with dysregulation of P450 c17 in adrenals and ovaries (22), but CYP17 dysregulation alone is unlikely to cause the phenotype of increased Δ^2-precursor to Δ^4-product ratios. It is, however, possible that a common factor may affect both adrenal HSD3B activity and CYP17 activity. This postulation is supported by the findings of simultaneous control of both the expression level of HSD3B and CYP17 in a human adrenocortical tumor cell line (40) and the complexity of human adrenal HSD3B expression through
multiple signaling pathways (41–43). The disparity in the adrenal hormonal profiles between the two groups of HF with marked insulin resistance suggests the existence of another factor besides, or in addition to, insulin resulting in the disparity of the adrenal HSD3B phenotype in HF. Conversely, it is possible that hyperandrogenism of a differing etiology in the two groups of HF may cause insulin resistance. Further examination of adrenal HSD3B activity after improvement of hyperinsulinemia in HF with the ↓ HSD3B hormonal phenotype should help in clarifying the relationship of cause and effect between the hormonal phenotype of compromised adrenal HSD3B activity and insulin resistance.

The fact that both young girls with premature androgen symptoms of PP and older females with hyperandrogenic symptoms exhibit the same hormonal phenotype of compromised adrenal HSD3B activity suggests that this phenotype represents a common etiology from childhood to adulthood (13–18). Our findings of insulin resistance and LH hypersecretion in HF with the ↓ HSD3B phenotype suggest that PP girls with the same hormonal phenotype may be at risk of insulin resistance and LH hypersecretion as they mature. Insulin sensitivity and gonadotropin secretion in our small scale study of PP girls with and without the ↓ HSD3B phenotype did not reveal statistical differences. The \( S_I \) value in the small number of PP girls with the ↓ HSD3B phenotype was variable, as the value was lower than or similar to that of PP girls with normal adrenal HSD3B activity with similar WLI. The lower \( S_I \) value in two of four PP girls with the ↓ HSD3B phenotype in this study was lower than or similar to the reported \( S_I \) values in WLI-matched PP girls with decreased insulin sensitivity associated with acanthosis nigricans (34). The \( S_I \) values in girls with PP in our study were within the reported \( S_I \) value in prepubertal or pubertal subjects (35). The fasting glucose to insulin ratio is a useful measure of insulin resistance in girls with premature adrenarche, and a ratio less than 7 has been reported to indicate insulin resistance in PP children (44, 45). The ratios (4<.48) in three of four PP girls with the ↓ adrenal HSD3B phenotype in our study were lower than those in all five PP girls with normal adrenal HSD3B activity (>6.7), regardless of WLI, but one subject with the ↓ HSD3B phenotype had a higher ratio than the control PP girls. These findings suggest variable insulin sensitivity in PP girls with the ↓ adrenal HSD3B phenotype. Reduced insulin sensitivity in less than half of the girls with PP and adrenal hormonal hyperresponse (46, 47) as well as postpubertal hyperandrogenism and insulin resistance in girls with history of PP (47–49) have been reported. The variable findings of insulin sensitivity in this small scale study of PP girls with the ↓ HSD3B phenotype warrants further examination in a greater population study of PP girls with and without the phenotype to determine whether this phenotype is a risk factor for childhood-onset insulin resistance.

In conclusion, our study demonstrates that the hormonal phenotype of compromised adrenal HSD3B activity that has led to an incorrect diagnosis of mild nonclassic variant of HSD3B deficiency congenital adrenal hyperplasia in hyperandrogenic females in the past is associated with the insulin resistance and LH hypersecretion characteristic of PCOS. The relationship between insulin resistance and the compromised adrenal HSD3B phenotype in HF, however, needs further elucidation. The link between the possible childhood decreased insulin sensitivity and adulthood insulin-resistant PCOS with the ↓ HSD3B hormonal phenotype is yet to be proven.

Acknowledgments

Received May 29, 2003. Accepted October 31, 2003.

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This work was supported by USPHS Grant R01-HD-36399 (to S.P.) and in part by a USPHS grant for the General Clinical Research Center at University of Illinois (Chicago, IL).

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