CLINICAL STUDY

Metabolic and endocrine effects of treatment with peroral or transdermal oestrogens in conjunction with peroral cyproterone acetate in women with polycystic ovary syndrome

J Vrbíková, S Stanická, K Dvořáková, M Hill, K Vondra, B Bendlova and L Stárka

Institute of Endocrinology, Prague, Czech Republic

(Correspondence should be addressed to Jana Vrbíková, Institute of Endocrinology, Národní 8, Prague 1, 116 94, Czech Republic; Email: jvrbikova@endo.cz)

Abstract

Objective: To compare the influence of transdermal and peroral oestrogen treatments in conjunction with cyproterone acetate (CPA) on metabolic and hormonal parameters in women with polycystic ovary syndrome (PCOS).

Patients and methods: Twenty-four women with PCOS, aged 25.4 ± 4.3 (mean ± S.D.) years, body mass index 24.5 ± 3.9 kg/m² were randomly assigned to receive either transdermal oestradiol plus CPA (n = 12) or a peroral oestradiol – CPA combination (n = 12). Before and after 3 months of treatment, basal blood samples, euglycaemic hyperinsulinaemic clamp combined with indirect calorimetry and arginine tests were performed. ANOVA and Student’s t-test or Wilcoxon’s test were used for statistical analyses.

Results: After peroral oestradiol – CPA, insulin sensitivity (P < 0.004) and the disposition index as the function of insulin sensitivity and secretion (P < 0.0001) decreased significantly. Fasting insulin (P < 0.05), cholesterol (P < 0.05), high-density lipoprotein cholesterol (P < 0.05) and sex-hormone binding globulin (P < 0.0001) increased significantly. Dehydroepiandrosterone (P < 0.05) and 17-OH progesterone (P < 0.01) decreased significantly. After transdermal oestradiol + CPA, no significant changes were observed in sex-hormone binding globulin and androgen concentrations, insulin sensitivity or disposition index.

Conclusions: In women with PCOS, peroral oestrogens (at doses common in combined oral contraceptives) led to a significant impairment in insulin secretion and action. In contrast, the transdermal application of oestrogens did not significantly influence insulin sensitivity.

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting about 5–10% of women of fertile age (1, 2). In recent decades, insulin resistance has been found to be an integral part of PCOS (3, 4): women with PCOS are at increased risk of the development of either impaired glucose tolerance or type II (non-insulin-dependent) diabetes mellitus (NIDDM) (5–8).

Combined oral contraceptives remain the first-line therapy for women with PCOS who do not wish to become pregnant. They ameliorate dermatological manifestations of hyperandrogenism, improve menstrual cycle disturbances and may prevent endometrial and ovarian cancer. To date, however, little attention has been given to the metabolic effects of combined oral contraceptives. There is some evidence that they could worsen glucose tolerance (9) and insulin sensitivity in both healthy women and those with PCOS (10, 11).

In contrast, most studies conducted in another age group – postmenopausal women – have detected no harmful effects of the application of transdermal oestrogens on insulin sensitivity (12–16). To the best of the authors’ knowledge, this method of application of oestrogens has not previously been studied in PCOS, with the exception of one study (17) in which fasting insulin concentrations were lower after the oral administration of 17β-oestradiol than after the transdermal application of natural oestrogens.

In a randomized, open study in women with PCOS, we have studied the effects of a transdermal oestrogen administered together with oral cyproterone acetate, and of an oral oestrogen–cyproterone acetate combination formulation, on steroid hormone concentrations,
Patients and methods

The study group consisted of 25 oligo/amenorrhoeic women with PCOS matching the National Institutes of Health criteria (18). They were aged 25.4 ± 4.3 years and all had clinical manifestation of hyperandrogenemia in the form of hirsutism, acne, or both, in addition to an increased free testosterone index or androstenedione concentrations outside the reference range [0.40–2.65 nmol/l for testosterone, 43–95 nmol/l for sex-hormone binding globulin (SHBG), free testosterone index > 6 and 1.6–5.4 nmol/l for androstenedione]. None of the patients had taken oral contraceptives or any other steroid medication during the preceding 3 months and none had taken any other medication influencing insulin sensitivity. The local ethics committee of the Institute of Endocrinology approved the study procedure.

The patients were evaluated at the clinical department as outpatients, and after giving written informed consent they underwent a euglycaemic hyperinsulinaemic clamp in the early follicular phase of the spontaneous menstrual cycle (between days 1–7) combined with indirect calorimetry, and an arginine stimulation test. Both tests were repeated after 3 months of study treatment. Random number tables were used to allocate the women randomly to groups to receive either oral (13 women) or transdermal (12 women) oestrogens. In the peroral group, one woman decided not to undergo the second metabolic examination, and thus eventually 12 women in each group were examined. Women in the peroral group (D) received a combination formulation of oestradiol with CPA (Diane 35; Schering AG, Berlin, Germany) and those in the transdermal group (E + CPA) received oestradiol (Estraderm TTS 50; (Novartis Pharma AG, Basel, Switzerland) together with CPA (Androcure; Schering AG) 2 mg daily for 21 days in the month.

The waist and hip circumferences were measured to the nearest centimetre with a flexible and non-distensible tape, avoiding exertion of pressure on the tissues and with the individual standing barefoot. The waist circumference was measured midway between the lower limit of the rib cage and the iliac crest. The hip circumference was the maximal circumference over the femoral trochanters.

After basal blood samples had been taken, the indirect calorimetry measurement was performed using Vmax29n (Sensormedics, Yorba Linda, CA, USA) based on the dilution technique and converting gas exchange data to calories using the Weir equation. After 30 min rest on the bed, the fasting patient was placed under the hood and measurement was carried out until the standard steady state criteria were met. Subsequently, a 3 h euglycaemic hyperinsulinaemic (1 mIU/kg per min) clamp was performed as described previously (19). Insulin sensitivity was determined in the interval from 100 to 120 min. Samples for the determination of free fatty acids were taken at 150, 165 and 180 min.

The following parameters were obtained from the clamp: glucose disposal rate (M) was defined as the amount of glucose supplied by the infusion that was required to maintain the desired blood glucose concentration (mg/kg per min). The insulin sensitivity index (ISI) was defined as the ratio of the glucose disposal rate to the average insulin concentration during the period observed \( \frac{[\text{mg/kg per min}]}{(\text{mU/l}) \times 100} \). The metabolic clearance rate of glucose (MCRg, ml/kg per min) was determined as the amount of the infused glucose (in ml) divided by the average blood glucose concentration. The posthepatic clearance rate of plasma insulin (MCRI, l/kg per min) was calculated as the ratio between the rate of infusion of insulin and the steady state plasma insulin concentration.

To evaluate \( \alpha \)- and \( \beta \)-cell secretion, an arginine test was performed as described by Larsson & Ahren (20). Briefly, intravenous cannulae were placed in antecubital veins on both arms (one for the glucose infusion and the second for sampling). Baseline samples for insulin and glucagon were taken at –5 and –2 min. Subsequently, 5 g arginine (diluted in 40 ml physiologic solution) was applied as an intravenous bolus at time 0 over a period of 50 s and samples for insulin and glucagon were taken again at 2, 3, 4 and 5 min. After that, a variable-rate infusion of 15% glucose solution was commenced, to increase and maintain blood glucose concentrations between 13 and 15 mmol/l. Finally, new baseline samples were taken, the arginine bolus was repeated and new samples for insulin and glucagon were taken at 2, 3, 4 and 5 min thereafter.

Blood glucose was determined in whole blood by an electrochemical method (Super GL, Dr Müller Geräte Bau, GmBH, Freital, Germany). Insulin was estimated and C peptide was measured using IRMA kits (Immuno-techn, Marseilles, France). The cross-reactivity of the antisemur with both insulin and glucagon was less than 0.05%. Proinsulin was determined by ELISA (IBL, Hamburg, Germany), with no cross-reactivity with insulin and C peptide. Glucagon was determined by RIA (IBL).

Total cholesterol and triglycerides were determined enzymatically (reagents from Boehringer Mannheim, using a Cobas Mira S autoanlyser, Hoffmann-La Roche, Basel, Switzerland; high-density lipoprotein (HDL)-cholesterol was determined using the same method after precipitation. Free fatty acids (FFA) were determined by the enzymatic colourimetric method, using a kit from WAKO Chemicals (Neuss, Germany).

Testosterone, androstenedione, dehydroepiandrosterone (DHEA), DHEA sulphate (DHEAS), oestradiol, luteinising hormone (LH), follicle-stimulating hormone.
(FSH) and SHBG were determined as stated previously (21). Insulin-like growth factor (IGF)-I was determined using an IRMA kit (Immunotech) with a sensitivity of 3 ng/ml and intra- and interassay coefficients of variation (CV) of 7.4 and 8% respectively. IGF binding protein (IGFBP)-3 was determined using an IRMA kit (Immunotech) with a sensitivity of 50 ng/ml and intra- and interassay CVs of 6.0 and 9.5% respectively.

**Calculations and statistics**

The acute insulin response (AIR) to arginine was calculated as the mean of +2 to +5 min samples minus the pre-stimulus insulin concentration for the fasting values (AIRf) and glucose-potentiated values (AIRg). The slope between AIR at fasting blood glucose and at blood glucose 14 mmol/l (slopeAIR = ΔAIR/Δglucose) was calculated as a measure of the glucose potentiation of β-cell secretion. The corresponding acute glucagon responses (AGRf, AGRg) and the slopeAGR were calculated in the same manner. Disposition indices (Di) were calculated according to Kahn et al. (22) using the values of ISI and AIRf (Di,f), AIRg (Di,g) or slopeAIR (Di,s).

The anti-lipolytic index was calculated according to Jacob et al. (23), as:

\[ \text{FFA0} - (\text{FFA150} + \text{FFA180})/3/\text{IRI120} – \text{IRI0} \]

where IRI is insulin.

Statistical evaluation was performed using multiway repeated-measures ANOVA with treatment and status as between- and within-factors respectively, and with treatment × status interaction followed by least significant differences (LSD) multiple comparisons between individual subgroups. Most of the variables were treated by power transformation to achieve a Gaussian distribution of data and homoscedasticity. The variables with absolute values of Studentised residuals greater than 2.5 (outliers) were not included in the model. The treatment effect (treatment with D compared with treatment with E+CPA) was evaluated using the ANOVA model involving the status both before and after medication, and separately in the subgroups of patients treated with D and with E+CPA using LSD multiple comparisons after the ANOVA test. The LSD multiple comparisons were also used for assessment of the differences between the subgroups after medication.

**Results**

**Clinical parameters**

Body weight, body mass index, waist circumference, waist:hip ratio, and systolic and diastolic blood pressures did not change significantly in either the D- or the E-CPA-treated group (Table 1).

In group E+CPA, an improvement in menstrual cyclicity was seen in six of the 12 women. In three women, breakthrough bleeding was observed, and in another three, an irregular menstrual cycle was not improved.

**Table 1** Clinical, biochemical and hormonal values in women with PCOS before and after treatment with either peroral or transdermal oestrogens together with cyproterone acetate.

<table>
<thead>
<tr>
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<th>Peroral</th>
<th>Transdermal</th>
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<tr>
<td></td>
<td>Before</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>24.7±0.4</td>
<td>24.5±3.5</td>
</tr>
<tr>
<td><strong>WHR</strong></td>
<td>0.79±0.06</td>
<td>0.78±0.07</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>113.2±9.5</td>
<td>116.8±9.2</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>71.3±5.9</td>
<td>74.3±5.5</td>
</tr>
<tr>
<td><strong>Total cholesterol (mmol/l)</strong></td>
<td>4.48±0.59</td>
<td>5.16±0.91*</td>
</tr>
<tr>
<td><strong>HDL-cholesterol (mmol/l)</strong></td>
<td>1.28±0.27</td>
<td>1.51±0.24*</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/l)</strong></td>
<td>0.81±0.30</td>
<td>1.08±0.35</td>
</tr>
<tr>
<td><strong>Free fatty acids (mmol/l)</strong></td>
<td>0.66±0.26</td>
<td>0.57±0.15</td>
</tr>
<tr>
<td><strong>Blood glucose (mmol/l)</strong></td>
<td>4.83±0.47</td>
<td>4.59±0.53</td>
</tr>
<tr>
<td><strong>Testosterone (nmol/l)</strong></td>
<td>2.51±1.02</td>
<td>2.60±0.98</td>
</tr>
<tr>
<td><strong>DHEA (nmol/l)</strong></td>
<td>25.9±12.3</td>
<td>16.0±8.7*</td>
</tr>
<tr>
<td><strong>DHEAS (µmol/l)</strong></td>
<td>5.76±2.42</td>
<td>4.65±1.97</td>
</tr>
<tr>
<td><strong>17-OH progesterone (nmol/l)</strong></td>
<td>2.01±0.77</td>
<td>1.24±0.67**</td>
</tr>
<tr>
<td><strong>SHBG (nmol/l)</strong></td>
<td>41.3±18.0</td>
<td>173.4±53.4****</td>
</tr>
<tr>
<td><strong>LH (IU/l)</strong></td>
<td>6.48±3.62</td>
<td>3.23±3.90**</td>
</tr>
<tr>
<td><strong>FSH (IU/l)</strong></td>
<td>4.1±1.44</td>
<td>2.72±2.23</td>
</tr>
<tr>
<td><strong>IGF-I (ng/ml)</strong></td>
<td>331.4±114.5</td>
<td>244.6±126.7*</td>
</tr>
<tr>
<td><strong>IGFBP-3 (ng/ml)</strong></td>
<td>3320±514</td>
<td>33394±393</td>
</tr>
<tr>
<td><strong>Insulin (mIU/l)</strong></td>
<td>7.4±4.4</td>
<td>9.5±3.9*</td>
</tr>
<tr>
<td><strong>Glucagon (pmol/l)</strong></td>
<td>40.5±12.1</td>
<td>39.7±8.5</td>
</tr>
<tr>
<td><strong>Proinsulin (pmol/l)</strong></td>
<td>5.1±4.2</td>
<td>6.2±7.5</td>
</tr>
<tr>
<td><strong>C peptide (nmol/l)</strong></td>
<td>0.49±0.09</td>
<td>0.50±0.10</td>
</tr>
</tbody>
</table>

Values are mean±SD. BMI, body mass index; WRR, waist : hip ratio; SBP, DBP, systolic and diastolic blood pressures. *P < 0.05, **P < 0.01, ****P < 0.0001, compared with before treatment.
Biochemical and endocrine parameters

In group D, total cholesterol and HDL-cholesterol increased significantly (both \( P < 0.05 \)). In group E+CPA, cholesterol did not change significantly. Fasting FFA did not change after any of the treatments. No significant change was observed in triglycerides in group E+CPA and a trend towards an increase was seen in group D. Fasting glucose concentration did not change significantly in either group.

As regards steroid hormone concentrations, 17-OH progesterone (\( P < 0.01 \)), DHEA (\( P < 0.05 \)) and LH (\( P < 0.01 \)) decreased significantly and SHBG increased (\( P < 0.0001 \)) in group D. In group E+CPA, a significant decrease in LH (\( P < 0.05 \)) was observed. FSH, DHEAS, testosterone, androstenedione and oestradiol concentrations did not change significantly in either group.

IGF-I decreased significantly in group D (\( P < 0.05 \)), but did not change in group E+CPA. IGFBP-3 did not change after either treatment.

Fasting insulin increased significantly in group D (\( P < 0.05 \)). Fasting glucagon, proinsulin and C peptide did not change in any treatment group (Table 1).

Metabolic parameters

Glucose disposal rate (\( P < 0.004 \)), ISI (\( P < 0.02 \)) and MCRg (\( P < 0.002 \)) decreased significantly in group D; in contrast, in group E+CPA, no change in these parameters was observed. MCRi during clamp did not change significantly in either group. The anti-lipolytic index increased significantly in group E+CPA (\( P < 0.0001 \)) (Fig. 1).

The arginine-stimulated secretion of insulin in the presence of fasting concentrations of glucose (AIRf) and the hyperglycaemia-potentiated secretion of insulin (AIRg) did not change significantly after any treatment. The arginine-stimulated hyperglycaemia-potentiated secretion of glucagon decreased significantly in group D (AGRg: \( P < 0.01 \)), with no change in group E+CPA (Fig. 2).

The disposition index derived from AIRf (Dif) did not change significantly in any group. Those derived from AIRg (Dig) (\( P < 0.0001 \)) and the slope (Dis) (\( P < 0.0001 \)) decreased significantly in group D and did not change in group E+CPA (Fig. 3).

Results from indirect calorimetry demonstrated that resting energy expenditure did not change significantly in either group. Lipid oxidation decreased significantly (\( P < 0.05 \)) in group D (Table 2).

Discussion

This study demonstrates a significant decline in insulin sensitivity and \( \beta \)-cell function after a 3-month course of treatment with a combination peroral formulation of oestradiol with CPA (Diane 35), in comparison...
with no significant changes in these parameters after transdermal application of oestrogen (plus oral CPA). The study was conducted in women of fertile years with intact uterus. Both groups received the same gestagen in the same dose, and the results obtained therefore probably reflect the effects of the oestrogens per se.

Hitherto, there has been only scant information regarding insulin sensitivity in women with PCOS after treatment with combined oral contraceptives. The results reported are discrepant. In studies that used clamps as the reference method for the evaluation of insulin resistance, decreased insulin sensitivity was found after the use of combined oral contraceptives in PCOS in some (10, 11, 21) but not in all studies (24 – 27).

It is likely that heterogeneity in the populations of patients studied could explain the discrepancies. Diane 35 was recently compared with metformin in both obese and lean women with PCOS (26, 28). Deterioration in glucose tolerance (increase in the area under the glucose curve during an oral glucose tolerance test) after the antiandrogen formulation was found in obese, but not in lean, women with PCOS. The nature of the progestin used could also have an influence: combined oral contraceptives containing norgestimate were not associated with a deterioration in insulin sensitivity (24), whereas the use of combined oral contraceptives containing norethidrone resulted in a significant decrease in insulin sensitivity both in controls and in the women with PCOS (11).

A close association between endogenous oestrogen concentrations and insulin resistance has recently been found in postmenopausal women (29). It would therefore probably be appropriate to take into account the dose of oestrogens when examining the role of different contraceptives in insulin resistance. To our knowledge, there is no study directly comparing low-dose (30–37.5 μg) with ultra-low (20–30 μg) or extremely low-dose (less than 20 μg) preparations of ethinyloestradiol, either in healthy fertile women or in women affected with PCOS.

In the present study, the arginine-stimulated secretion of glucagon was significantly decreased after

Figure 2 Insulin and glucagon secretion after arginine in women with PCOS before and after treatment with either a combination peroral formulation of oestradiol with cyproterone acetate (D) or transdermal oestrogen plus cyproterone acetate (E+CPA). AIRf, acute insulin response to arginine (fasting glucose concentration); AIRg, acute insulin response to arginine (blood glucose 14 mmol/l); AGRf, acute glucagon response to arginine (fasting glucose concentration); AGRg, acute glucagon response to arginine (blood glucose 14 mmol/l).
treatment with the combination peroral formulation of oestradiol with cyproterone acetate (Diane 35). Inappropriately high glucagon secretion is suspected of having a role in the development of impaired glucose tolerance (30). Our finding of a decreased glucagon secretion is supported by others (31). It is possible that the decrease in glucagon could be a mechanism of adaptation to the decreased insulin sensitivity. In fact, fasting blood glucose declined slightly after the combined oral formulation, probably as a reflection of the decreased hepatic production of glucose in conditions of reduced glucagon concentrations.

It is important to examine insulin resistance and secretion not only separately, but also simultaneously. β-Cell dysfunction was found to be an important event in the development of NIDDM (32–34). Insulin sensitivity and secretion are inversely and proportionally related, so that the product of these two parameters (Di) is always a constant (35). The Di is more heritable than either insulin resistance or insulin secretion alone (36). When insulin resistance and secretion were examined repeatedly in individuals who progressed to hyperglycaemia, insulin secretion declined progressively by more than 70%, whereas insulin sensitivity declined by only about 15% (37). We used the arginine stimulation test to determine various aspects of β-cell function. The acute insulin response to arginine in the presence of fasting blood glucose concentrations

<table>
<thead>
<tr>
<th>Treatment: NS</th>
<th>Treatment: p&lt;0.0001</th>
<th>Treatment: p&lt;0.0001</th>
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<tbody>
<tr>
<td>Treatment: NS</td>
<td>Treat.x Status: NS</td>
<td>Treat.x Status: NS</td>
</tr>
<tr>
<td>D: NS</td>
<td>p&lt;0.04</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>E+CPA: NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>After: p&lt;0.03</td>
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Table 2 Energy expenditure and substrate oxidation in women with PCOS before and after treatment with either peroral or transdermal oestrogens together with cyproterone acetate.

<table>
<thead>
<tr>
<th></th>
<th>Peroral Before</th>
<th>After</th>
<th>Transdermal Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting energy expenditure (kcal/24 h)</td>
<td>1234±219</td>
<td>1234±165</td>
<td>1227±214</td>
<td>1261±224</td>
</tr>
<tr>
<td>Lipid oxidation (%)</td>
<td>55.7±12.0*</td>
<td>43.4±18.0*</td>
<td>58.0±15.8</td>
<td>47.4±21.5</td>
</tr>
<tr>
<td>Saccharide oxidation (%)</td>
<td>25.9±13</td>
<td>33±17.9</td>
<td>24.7±15.7</td>
<td>29.3±24.0</td>
</tr>
<tr>
<td>Protein oxidation (%)</td>
<td>18.7±8.2</td>
<td>23.4±9.4</td>
<td>17.3±6.7</td>
<td>22.9±9.5</td>
</tr>
</tbody>
</table>

Values are means±s.d. *P < 0.05 compared with before treatment.
determines the direct and acute β-cell response to a secretory challenge and is thus related to the exocytic machinery. Slope is a measure of the glucose-induced potentiation of the arginine-induced secretion of insulin (38). We have demonstrated a decrease in the Di (as a product of slopeAIR or of glucose-potentiated arginine-stimulated insulin secretion and the ISI) and no change in the Di derived from arginine-stimulated secretion of insulin in the presence of fasting concentrations of blood glucose after peroral treatment with oestrogen. Thus insufficient compensation of the insulin resistance is probably related, not to inefficient exocytosis, but to the mechanism of glucose recognition.

We observed a significant decline in IGF-I after peroral oestrogens. This is in accordance with the experience of others (39), who found a decrease in IGF-I in postmenopausal women after oral, but not transdermal, oestrogens. A decrease in IGF-I was also observed after combined oral contraceptive use in women of fertile age (40, 41).

The decline in lipid oxidation after peroral oestrogens and the improvement in the anti-lipolytic index after transdermal oestrogens are in accordance with studies conducted in both growth hormone deficient and postmenopausal women and comparing oral and transdermal administration of oestrogen. Oral oestrogens have been shown to act as growth hormone antagonists, leading to the suppression of postprandial lipid oxidation and a decline in IGF-I (42, 43).

HDL-cholesterol and total cholesterol increased significantly after peroral oestrogens, and triglycerides also tended to increase. In contrast, lipid concentrations did not change significantly after transdermal treatment. These data are in agreement with previous observations (44–48). Dyslipidaemia (decrease in HDL-cholesterol and increase in triglycerides) is common in women with PCOS (49, 50). The question still remains whether these women are at increased risk for cardiovascular disease (51). Conversely, it has previously been reported that combined oral contraceptives may increase the risk of myocardial infarction (52). To date, there are no studies specifically addressing the use of combined oral contraceptives in women with PCOS and the impact of their use on cardiovascular morbidity and mortality.

Peroral oestrogens significantly increased SHBG concentrations and thus the free androgen index declined markedly. The increase in SHBG is a result of the hepatic effects of oestrogens (the stimulation of hepatic proteosynthesis). These observations are in accordance with the findings of previous studies (47). Testosterone concentrations tended to decline after transdermal application of oestrogen. LH declined significantly after either oral or transdermal treatment. Thus more marked androgen suppression was achieved with peroral oestrogen treatment. Further investigations are required as to whether these effects have any long-term consequences regarding hirsutism and acne. The present study was designed primarily to evaluate the metabolic effects of either oral or transdermal administration of oestrogens and androgenic symptoms were thus not evaluated systematically.

In conclusion, peroral oestrogens are associated with significant deterioration in insulin sensitivity and secretion in women with PCOS. These undesirable metabolic effects were not present when oestrogens were applied transdermally.

Acknowledgements

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