RESEARCH

Adrenal activity and metabolic risk during randomized escitalopram or placebo treatment in PCOS

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Abstract

Background/aims: Polycystic ovary syndrome (PCOS) is associated with insulin resistance, adrenal hyperactivity and decreased mental health. We aimed to investigate the changes in adrenal activity, metabolic status and mental health in PCOS during treatment with escitalopram or placebo.

Methods: Forty-two overweight premenopausal women with PCOS and no clinical depression were randomized to 12-week SSRI (20 mg escitalopram/day, $n = 21$) or placebo ($n = 21$). Patients underwent clinical examination, fasting blood samples, adrenocorticotroph hormone (ACTH) test, 3-h oral glucose tolerance test (OGTT) and filled in questionnaires regarding mental health and health-related quality of life (HRQoL): WHO Well-Being Index (WHO-5), Major Depression Inventory (MDI), Short Form 36 (SF-36) and PCOS questionnaire.

Results: Included women were aged 31 (6) years (mean (S.D.)) and had body mass index (BMI) 35.8 (6.5) kg/m^2 and waist 102 (12) cm. Escitalopram was associated with increased waist (median (quartiles) change 1 (0; 3) cm), $P = 0.005$ vs change during placebo and increased cortisol levels (cortisol 0, cortisol 60, peak cortisol and area under the curve for cortisol during ACTH test), all $P < 0.05$ vs changes during placebo. Escitalopram had no significant effect on measures of insulin sensitivity, insulin secretion, fasting lipids, mental health or HRQoL.

Conclusion: Waist circumference and cortisol levels increased during treatment with escitalopram in women with PCOS and no clinical depression, whereas metabolic risk markers, mental health and HRQol were unchanged.

Key Words
- PCOS
- cortisol
- mental health
- quality of life
- PCOSQ
- escitalopram
- SSRI

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by insulin resistance and hyperandrogenism (1). Central obesity is closely associated with insulin resistance and low-grade inflammation (2) and obesity predicts the development of type 2 diabetes mellitus in PCOS (3). Furthermore, obesity predicted poor quality of life in women with PCOS (4), and the risk of depression was 2–5 times increased in PCOS (5, 6). PCOS is characterized by increased ovarian and adrenal androgen production (1). Adrenocorticotropic hormone (ACTH)-stimulated cortisol and 17-hydroxyprogesterone levels (17OHP) and urinary cortisol secretion were increased in

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women with PCOS vs controls (7, 8), suggesting increased hypothalamic–pituitary–adrenal (HPA) axis activity in PCOS. Increased adrenal activity was also found in patients with major depression and their first-degree relatives compared to healthy controls (9, 10). Therefore, decreased quality of life in PCOS could be associated with increased HPA activity (11).

Treatment with specific serotonin reuptake inhibitor (SSRI) is the first choice for depression and 16.3% Danish women with PCOS had prescriptions of antidepressants (6). The possible effects of SSRI on cortisol secretion, mental health and metabolic risk in PCOS are undetermined (12). Three-month treatment with escitalopram normalized cortisol secretion and improved insulin sensitivity in young healthy men with low birth weight (<2500 g) (13). Included men were insulin resistant and had high cortisol levels (13). In women, low birth weight increased the risk of elevated adrenal activity and development of PCOS (14). A meta-analysis found improved glycemic control in patients with type 2 diabetes and depression that were treated with antidepressants (15). Improved insulin sensitivity during treatment with SSRI in PCOS could affect the PCOS phenotype and could be associated with more regular menstrual cycles. We are not aware of previous studies testing this hypothesis.

The aim of the present study was to investigate the effect of 12-week escitalopram vs placebo treatment on adrenal activity, mental health, metabolic risk and PCOS phenotype in overweight women with PCOS and no clinical depression.

Materials and methods

Forty-two women with PCOS were included in a randomized, double-blind, placebo-controlled trial of 12-week medical intervention with SSRI (escitalopram 20 mg) or placebo. The study was conducted during August 2013 to March 2015 at the Department of Endocrinology, Odense University Hospital. Women were recruited from the outpatient clinic of the Department of Endocrinology and Department of Gynecology at Odense University Hospital and by advertising.

Inclusion criteria

The study included premenopausal, white women, aged 18–41 years with PCOS and BMI >25 kg/m^2 and <50 kg/m^2. All women fulfilled at least two of the Rotterdam criteria for PCOS: (1) cycle length >35 days or amenorrhea, (2) total and/or free testosterone above upper reference limit and/or hirsutism (Ferriman–Gallwey score (FG-score) ≥8) and (3) polycystic ovaries. Secondary etiologies were excluded as previously described (16). Health-related quality of life (HRQol) is inversely associated with BMI (4) and only overweight and obese women were included in the study. Included women gave informed consent to use barrier control or had an intrauterine device implanted during the study period.

Exclusion criteria

Clinical depression, evaluated by questions of depressive core symptoms, was an exclusion criterion as treatment with SSRI is the first-line treatment in persons with depression, and we did not consider allocation to placebo treatment possible. Furthermore, exclusion criteria were eating disorder, pregnancy, breastfeeding, epilepsy, diabetes (fasting plasma glucose ≥7.0 mmol/L or HbA1c >6.3%) or contraindications for escitalopram.

Metformin was paused a minimum of 4 weeks and oral contraceptives 12 weeks prior to evaluation.

Power calculation

The primary endpoint of the study was change in adrenal activity (evaluated by 60 min area under the curve (AUC) for ACTH-stimulated cortisol levels) during treatment with escitalopram/placebo. The secondary study outcomes were changes of insulin sensitivity, insulin secretion, fasting lipids, mental health and HRQoL. No previous study investigated the effect of antidepressants on cortisol levels in PCOS and a power calculation could not be performed. Studies on the same number of individuals with depression or first-degree relatives to persons with depression reported significant changes in adrenal activity during antidepressant treatment (17, 18, 19).

Approvals were obtained from the Ethics committee at the Region of Southern Denmark (registration number: S-20110089) and the Danish Medicine Agency. The study was monitored by the local Good Clinical Practice unit and was registered at www.clinicaltrials.gov: NCT01961180. Consent was obtained from each patient after full explanation of the purpose and nature of all procedures used.

Study protocol

Patients underwent clinical examination, fasting blood samples, pregnancy test, ACTH test and OGTT and

answered questionnaires by time of study inclusion and the examination program was repeated after 12-week intervention. Telephone calls were performed at weeks 2 and 6 to check for compliance and side effects. After study inclusion and initial examinations, the patients were randomized 1:1 to escitalopram or placebo. The participants received 10 mg escitalopram during the first week of the study and the dosage was then increased to 20 mg during the remaining study period. The participants down-titrated escitalopram with 10 mg the first week after study termination. Randomization was performed by our hospital pharmacy, which carried out packaging and labeling of escitalopram and placebo.

Physical examination included height, weight, waist circumference, FG score and transvaginal ultrasound ACTH test was performed at 8.00 o'clock in the follicular phase (cycle days 2–8) in women with a cycle length shorter than three months. In women with cycle length longer than three months, ACTH test was performed on a random day. An intravenous bolus of 0.25 mg Synacthen (Novartis Healthcare) was administered and cortisol and 17OHP levels were measured at 0, 30 and 60 min. The maximum cortisol and 17OHP levels during the test were defined as peak levels. Area under the curve for cortisol and 17OHP was calculated applying the trapezium rule.

A 3-h (h) OGTT was performed at 8:00 o'clock after overnight fasting on a random day of the menstrual cycle. Insulin, C-peptide and blood glucose (BG) were measured at 0, 30, 60, 90, 120 and 180 min after oral ingestion of a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

Questionnaires

Mental health assessment

Mental health assessments included the 5-item World Health Organization Well-Being Index (WHO-5), the MDI and UKU (Udvalg for Kliniske Undersøgelser). WHO-5 is a general questionnaire regarding mental health (20) and contains five positively phrased items scored from 0 to 5 with higher scores indicating greater well-being. The summed score is multiplied by 4 to translate to percentage. Scores can be rated to risk: 0–35, high risk of depression; 36–50, risk of depression and >50 no risk of depression (20). MDI is a validated depression inventory for screening and diagnosis of depression since it covers the ICD 10 criteria for depression (21). MDI contains 12 items with a total score range from 0 to 50 and higher scores indicate more severe depression (21). Patients were regarded as responders to medical treatment if MDI-total scores improved >50%. UKU is a global rating questionnaire regarding side effects to SSRIs, containing 11 questions with range from zero to three (22).

HRQoL assessment

HRQoL assessments included Short Form-36 (SF-36) and a disease-specific PCOS questionnaire (PCOSQ). SF-36 contains 36 questions grouped into eight domains: Physical function (PF), physical role limitation (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), emotional role function (RE) and mental health (MH) (23). Domains were scored from 0 to 100 with higher scores indicating better functioning and QoL. PCOSQ involved 24 items grouped into five domains: Emotions, body hair, weight, infertility problems and menstrual problems (24). Each item was answered in a seven-point rating scale with higher points indicating better functioning. Each domain value was reported as the mean value from the items involved (24).

Biochemical assays

Plasma total testosterone was analyzed by liquid chromatography tandem mass spectrometry. Free Androgen Index (FAI) was calculated as (total testosterone/SHBG) × 100. SHBG was analyzed by a time-resolved flouroimmunoassay using a commercial kit (AutoDelfia, Wallac Oy, Turku, Finland). Intra-assay variation was 5.2% and inter-assay variation was 7.5%. Cortisol was analyzed by time-resolved flouroimmunoassay using commercial kit (AutoDelfia, Wallac Oy, Turku, Finland). Intra-assay variation was 2.7–3.6% and inter-assay variation was 0.8–1.9%. 17OHP was analyzed by radioimmunoassay (RIA) using a commercial kit (Coat-A-Count, Diagnostic Products Corporation, Los Angeles). Intra- and inter-assay variations were 3.5–7.1% and 5.0–11%, respectively. BG was measured with a Hemocue device (Hemocue, Ängelholm, Sweden), which converted BG concentrations to equivalent plasma glucose concentrations (25). The meter was checked with a control cuvette every day and a hemolysate every 1–2 weeks. Serum C-peptide and serum insulin were analyzed by an electrochemiluminescence immunoassay (ECLIA, Cobas e411, Roche), intra-assay CVs were between 0.8 and 4.6% and inter-assay CVs were between 1.8 and 5.0%. Plasma total cholesterol, high-density lipoprotein (HDL), cholesterol and triglyceride (TG) were analyzed by enzymatic colorimetric reactions (Modular P, Roche), and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.

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Insulin resistance

The homeostatic model assessment insulin resistance index (HOMA-ir) was calculated as (fasting plasma insulin (U/L) × fasting BG (mmol/L))/22.5 (26). Using 3-h OGTT data, peripheral insulin sensitivity was calculated as the Matsuda index (10,000/√(fasting plasma insulin (U/L) × fasting plasma glucose (mmol/L) × mean plasma insulin (U/L) × mean BG (mmol/L))) (27). AUC for insulin, C-peptide and BG during the OGTT (2 and 3 h) were calculated applying the trapezium rule.

Insulin secretion and beta cell function

Basal insulin secretion was assessed by the homeostatic model assessment b-cell function index (HOMA-%B), calculated as (fasting plasma insulin (U/L) × 20)/(fasting BG (mmol/L) – 3.5) (26). Early glucose-stimulated insulin response was calculated as the insulinogenic index (delta plasma insulin (U/L) (0–30 min)/delta BG (0–30 min) (28). We calculated an OGTT-derived disposition index based on Matsuda × insulinogenic index.

Figure 1 presents a flow chart of study participants. Forty-two women with PCOS were randomized to escitalopram or placebo and 39 completed study intervention. Twenty-two women (12 citalopram + 10 placebo) fulfilled all Rotterdam criteria (phenotype A), 15 (7 citalopram + 8 placebo) had phenotype B (hyperandrogenism and oligomenorrhea), two (1 citalopram and 1 placebo) had phenotype C (hyperandrogenism and PCO) and none had phenotype D (oligomenorrhea and PCO).

Statistics

Continuous variables were described by mean (S.D.) and results from HRQoL assessments were described using medians and quartiles. Pre-treatment differences between patients randomized to escitalopram and placebo were tested using the Mann–Whitney *U* test. Difference in prevalence between groups was compared by the chi-squared test. Changes in outcomes during escitalopram vs placebo were tested by comparing delta (Δ) values between intervention groups by Mann–Whitney *U* test.

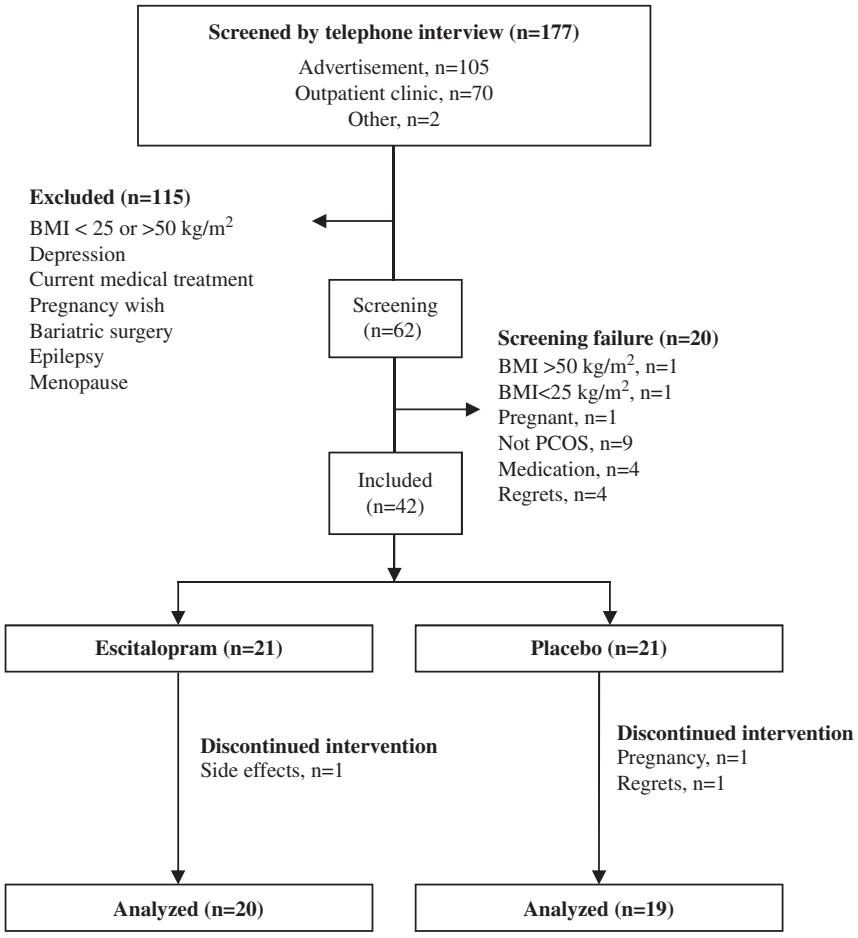

Figure 1
Consort flow chart of included and excluded subjects and study design.

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Δ-values were calculated as post-treatment minus pre-treatment value of each variable.

Multiple regression analyses were performed to investigate relationships between changes in cortisol levels (dependent variables: Δ-cortisol 0, Δ-cortisol 30, Δ-peak cortisol and Δ-AUC cortisol) and pre-treatment value of the dependent variable (cortisol 0, cortisol 30, peak cortisol or AUC cortisol), medicine group (0 placebo, 1 escitalopram) and Δ-waist (independent variables). Statistics were performed using IBM SPSS Statistics 21. Values of $P<0.05$ were considered significant.

Results

Clinical and biochemical changes during escitalopram and placebo

Waist circumference and cortisol levels (cortisol 0, cortisol 60, peak cortisol and AUC cortisol) increased significantly during escitalopram vs placebo. The median change in waist during escitalopram vs placebo was 1 (0; 3) cm vs −1 (−2; 0) cm, respectively, $P=0.005$. Δ-waist >0 cm (increasing waist during intervention) was seen in 14/20 women treated with escitalopram and in 4/19 women treated with placebo, $P=0.004$. Δ-waist >2 cm was seen in 9/20 women treated with escitalopram and in 3/19 women treated with placebo, $P=0.05$. BMI, Ferriman–Gallwey score, menstrual regularity (regular, irregular or amenorrhea) and presence of PCO (yes/no) were unchanged during the treatment period. Lipid status (cholesterol, triglycerides, LDL and HDL) and measures of insulin resistance (HOMA-ir, Matsuda index, AUC insulin and AUC C-peptide) and insulin secretion (HOMA-%B, insulinogenic index and disposition index) were unchanged during study intervention (Table 1).

Mental health and HRQoL

Changes in WHO-5, MDI and PCOSQ scores were comparable during escitalopram and placebo. The role physical (RP) domain of SF-36 increased during placebo ($P=0.04$), whereas the remaining domains of SF-36 were unchanged (Table 2).

Low WHO-5 scores <50 were in $n=5$ pre-treatment vs $n=2$ post treatment (escitalopram) and in $n=8$ pre-treatment and $n=2$ post treatment (placebo), chi test $P=0.002$. MDI scores consistent with depression were not observed in any patients at pre-treatment or after intervention.

Multiple regression analyses

Changes in cortisol during study intervention (Δ-cortisol 0, Δ-cortisol 30, Δ-cortisol 60, Δ-peak cortisol and Δ-AUC cortisol) were predicted by pre-treatment cortisol levels (cortisol 0, cortisol 30, cortisol 60, peak cortisol and AUC cortisol, respectively) in all regression models. Intervention group was an independent predictor of Δ-cortisol 60 and Δ-peak cortisol after correcting for pre-treatment cortisol levels and Δ-waist, whereas there was a trend for intervention group as predictor of Δ-AUC cortisol ($P=0.05$), Δ-cortisol 30 ($P=0.08$) and Δ-cortisol 0 ($P=0.10$). Change in waist circumference during intervention (Δ-waist) did not predict change in cortisol in any of the regression models (Table 3).

Discussion

In the present study, cortisol levels and waist circumference significantly increased during escitalopram vs placebo treatment in overweight premenopausal women with PCOS and no clinical depression, whereas mental health, measures of insulin resistance and insulin secretion, and fasting lipids were unchanged. To our knowledge, this is the first randomized trial regarding HPA axis activity, mental health and metabolic risk during treatment with a SSRI in women with PCOS. Increased cortisol and 17OHP responses during ACTH test is well documented in PCOS (7), and we included measurements of 17OHP to determine adrenal activity and adrenal androgen production. Our findings of increased cortisol levels during escitalopram treatment contrasted findings from trials in patients with depression and their first-degree relatives (17, 18, 19, 29). However, findings were not uniform as some studies reported unchanged or increased cortisol secretion during SSRI treatment in patients with depression (30, 31). We could not confirm results from a recent placebo-controlled study where 3 months treatment with 20 mg escitalopram normalized cortisol levels in healthy men with low birth weight (13). However, the study by Buhl *et al.* (13) included lean men (mean BMI 22 kg/m^2) and adrenal activity was established by 24-h cortisol patterns (10 cortisol measurements/24 h) instead of a stimulation test. High BMI is closely associated with low HRQol in PCOS (4), and we therefore included only overweight and obese women with PCOS in the present study. Furthermore, central and overall obesity is associated with increased cortisol secretion (32) and the pathogenesis of PCOS may be different in obese compared to lean phenotypes (1).

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Table 1 Clinical and biochemical characteristics, ACTH test and OGTT by pre-treatment and during escitalopram vs placebo.

	All ($n=39$)	Escitalopram ($n=20$)		Placebo ($n=19$)	
		Pre-treatment	12 weeks	Pre-treatment	12 weeks
Clinical data					
Age (years)	31 (6)	31 (6)		33 (7)	
BMI (kg/m^2)	35.8 (6.5)	35.7 (6.7)	35.9 (6.6)	35.9 (6.5)	35.7 (6.1)
Waist (cm)	102 (12)	101 (12)	102 (13)*	103 (13)	102 (12)
FG-score	11 (4)	13 (5)	13 (5)	9 (3)	10 (3)
PCO no/yes (n)	15/24	7/13	7/13	8/11	9/10
Cycles R/IR/A (n)	1/22/15	1/11/8	4/10/6	0/11/7	3/9/6
Fasting blood samples					
Total testosterone (nmol/L)	1.56 (0.61)	1.67 (0.60)	1.72 (0.57)	1.44 (0.61)	1.3 (0.49)
Free androgen index	6.2 (3.5)	7.0 (3.8)	7.5 (4.8)	5.4 (3.1)	4.8 (2.2)
Insulin (pmol/L)	139 (66)	164 (107)	120 (51)	144 (74)	143 (65)
C-peptide (pmol/L)	1228 (759)	1087 (233)	1045 (266)	1376 (1056)	1135 (320)
HOMA-ir	4.8 (2.4)	4.4 (2.1)	4.2 (2.4)	5.3 (2.6)	5.1 (2.6)
Cholesterol (mmol/L)	5.0 (0.8)	5.0 (0.9)	5.1 (0.6)	4.9 (0.7)	4.8 (0.7)
Triglycerides (mmol/L)	1.6 (0.8)	1.7 (0.8)	1.5 (0.6)	1.6 (0.7)	1.5 (0.8)
LDL (mmol/L)	3.1 (0.7)	3.1 (0.7)	3.2 (0.6)	3.1 (0.6)	3.0 (0.6)
HDL (mmol/L)	1.1 (0.2)	1.2 (0.2)	1.2 (0.2)	1.1 (0.2)	1.1 (0.2)
ACTH test (8.00 o'clock)					
Cortisol 0 min (nmol/L)	371 (162)	364 (194)	399 (170)*	378 (125)	345 (159)
Cortisol 30 min (nmol/L)	688 (118)	692 (132)	709 (121)	684 (105)	644 (111)
Cortisol 60 min (nmol/L)	768 (116)	767 (128)	763 (109)*	769 (106)	703 (117)
Peak cortisol (nmol/L)	772 (116)	774 (131)	774 (110)*	767 (684; 800)	704 (117)
AUC cortisol (10^2 nmol × min/L)	377 (69)	377 (81)	387 (68)*	769 (106)	351 (67)
17OHP 0 min (nmol/L)	2.0 (1.2)	1.8 (0.8)	2.1 (1.0)	2.3 (1.4)	1.9 (1.2)
17OHP 30 min (nmol/L)	4.4 (2.1)	4.1 (1.8)	4.1 (1.3)	4.7 (2.5)	5.1 (2.2)
17OHP 60 min (nmol/L)	4.5 (2.0)	4.3 (1.8)	4.1 (1.4)	4.7 (2.2)	4.9 (1.6)
Peak 17OHP (nmol/L)	4.7 (2.1)	4.5 (1.9)	4.3 (1.3)	4.9 (2.4)	5.5 (2.2)
AUC 17OHP (nmol × min/L)	230 (101)	214 (84)	216 (69)	247 (117)	256 (95)
OGTT					
Glucose 0 min (mmol/L)	5.4 (0.6)	5.4 (0.6)	5.4 (0.8)	5.4 (0.6)	5.4 (0.6)
Glucose 2 h (mmol/L)	7.0 (1.7)	7.8 (2.0)	6.6 (1.7)	7.5 (2.1)	7.4 (2.2)
NGT/IGT/T2D	30/8/1	18/2/0	16/4/0	12/6/1	11/6/1
HOMA-%B	229 (126)	203 (94)	207 (113)	255 (151)	225 (117)
Matsuda index	47 (31)	50 (32)	64 (37)	43 (32)	52 (37)
Insulinogenic index (10^{-2})	6.3 (4.7)	5.4 (1.3)	5.5 (1.4)	7.1 (0.7)	5.5 (1.6)
Disposition index	2.4 (1.0)	2.5 (1.0)	3.2 (1.5)	2.3 (1.1)	2.5 (1.3)
2-h AUC glucose (mmol/L min)	932 (197)	878 (165)	862 (220)	989 (216)	935 (213)
3-h AUC glucose (mmol/L min)	1294 (258)	1218 (200)	1194 (274)	1373 (292)	1328 (317)
2-h AUC insulin (10^3 pmol/L min)	123 (65)	113 (53)	101 (47)	134 (75)	118 (61)
3-h AUC insulin (10^3 pmol/L min)	164 (88)	145 (70)	126 (57)	183 (102)	168 (93)
2-h AUC C-peptide (10^3 pmol/L min)	450 (123)	432 (113)	407 (107)	469 (132)	426 (105)
3-h AUC C-peptide (10^3 pmol/L min)	662 (187)	629 (173)	574 (150)	697 (200)	651 (167)

Data presented as mean (s.d.) or numbers (n). Baseline SSRI vs placebo: no significant differences.

*$P<0.05$ Δ-SSRI vs Δ-placebo, Mann–Whitney U test for two samples (continuous data) or Chi squared test (categorical data)

A, amenorrhea; ACTH test, adrenocorticotropic hormone stimulation test; AUC, area under curve; cycles R, regular; FG-score, Ferriman–Gallwey score; IR, irregular; OGTT, oral glucose tolerance test.

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Table 2 Mental health during treatment with escitalopram vs placebo.

	All ($n=39$)	Escitalopram ($n=20$)		Placebo ($n=19$)	
		Pre-treatment	12 weeks	Pre-treatment	12 weeks
WHO-5 well-being index	64 (43; 73)	64 (48; 72)	68 (61; 76)	56 (40; 76)	68 (52; 76)
Major depression inventory	14 (6; 23)	13 (7; 22)	12 (5; 17)	14 (5; 25)	5 (4; 11)
SF36					
PF: physical function	90 (85; 95)	90 (85; 95)	90 (85; 95)	90 (85; 95)	93 (85; 96)
RP: role limitations physical	100 (75; 100)	100 (75; 100)	100 (75; 100)*	75 (75; 100)	100 (94; 100)
BP: bodily pain	90 (68; 100)	90 (68; 100)	90 (58; 100)	90 (75; 100)	85 (65; 100)
GH: general health	60 (50; 85)	60 (55; 70)	65 (55; 80)	65 (45; 85)	70 (55; 86)
VT: vitality	55 (30; 70)	55 (30; 65)	60 (35; 80)	50 (34; 75)	71 (54; 75)
SF: social function	100 (69; 100)	100 (63; 100)	100 (88; 100)	100 (69; 100)	100 (88; 100)
RE: role limitations emotional	100 (50; 100)	100 (67; 100)	67 (67; 100)	83 (33; 100)	100 (67; 100)
MH: mental health	76 (62; 84)	76 (60; 88)	80 (72; 88)	72 (62; 84)	84 (68; 12)
PCOS-Q					
PCOSQ emotion	4.3 (6.6; 5.1)	4.1 (3.4; 4.7)	5.0 (3.7; 5.8)	4.3 (3.6; 5.2)	4.6 (4.0; 5.8)
PCOSQ body hair	2.8 (1.6; 4.6)	2.6 (1.6; 4.9)	2.8 (1.5; 5.0)	3.1 (2.1; 4.6)	3.0 (2.4; 4.6)
PCOSQ weight	2.0 (1.2; 3.4)	2.2 (1.2; 3.2)	2.2 (1.4; 2.7)	1.8 (1.2; 3.4)	3.0 (2.0; 3.6)
PCOSQ infertility problems	5.0 (3.5; 6.3)	4.3 (3.1; 5.9)	6.8 (4.1; 6.5)	5.4 (3.6; 6.3)	6.0 (3.8; 6.8)
PCOSQ menstrual problems	4.3 (3.2; 5.5)	4.3 (3.3; 5.1)	5.0 (4.3; 5.5)	4.1 (3.1; 6.0)	4.8 (4.3; 6.0)

Data presented as median (quartiles).
*$P<0.05$ Δ-SSRI vs Δ-placebo, Mann–Whitney *U* test for two samples.

We found significantly increased waist circumference during escitalopram treatment, but changes in waist were not associated with changes in cortisol levels in multiple regression analyses. Instead, pre-treatment cortisol level was the most important predictor of change in cortisol during study intervention. The change in waist during study intervention was highly significant, but it is possible that the change in waist was too small to affect cortisol secretion, and we observed no significant changes in BMI. In accordance with our results, Knorr and coworkers reported no significant correlations between changes in cortisol levels and changes in waist or weight in first-degree relatives to patients with depression treated with escitalopram (33). Furthermore, Buhl and coworkers reported significantly decreased cortisol levels during escitalopram and unchanged body composition established by magnetic resonance imaging (13). Depression is closely associated with the metabolic syndrome, where weight gain may prevail (34), but loss of appetite may also occur (35), and the effect of SSRI treatment on body composition is debated (35, 36). Previous studies reported increased (37, 38), unchanged (13, 36, 39) or decreased (40) waist circumference during treatment with SSRI in different study populations,

Table 3 Multiple regression analyses.

Dependent variables	Independent variables			
	Pre-treatment cortisol#	Medicine group	Δ-Waist	R^2
Δ-Cortisol 0	−0.5 (0.00)**	75 (0.10)	−5.4 (0.48)	0.34 (0.002)*
Δ-Cortisol 30	−0.6 (0.001)*	68 (0.08)	−2.9 (0.65)	0.33 (0.003)*
Δ-Cortisol 60	−0.3 (0.009)*	61 (0.04)*	−0.03 (0.99)	0.28 (0.009)*
Δ-Peak cortisol	−0.3 (0.005)*	71 (0.03)*	−1.5 (0.78)	0.30 (0.005)*
Δ-AUC cortisol	−0.5 (0.002)*	4007 (0.05)	−1.4 (0.78)	0.29 (0.006)*
	Pre-treatment cortisol#	Medicine group	Δ-BMI	R^2
Δ-Cortisol 0	−0.5 (0.001)**	57 (0.18)	11.2 (0.55)	0.34 (0.002)*
Δ-Cortisol 30	−0.5 (0.001)*	55 (0.08)	10.4 (0.52)	0.33 (0.002)*
Δ-Cortisol 60	−0.3 (0.01)*	61 (0.03)*	−0.83 (0.95)	0.28 (0.009)*
Δ-Peak cortisol	−0.4 (0.005)*	68 (0.03)*	−1.2 (0.92)	0.30 (0.005)*
Δ-AUC cortisol	−0.4 (0.004)*	3394 (0.08)	−511 (0.78)	0.24 (0.006)*

Predictors of changes in cortisol levels during intervention. Data presented as β-coefficient (*P*-value), *$P<0.05$, **$P<0.001$. Models regarding predictors of changes in cortisol 0, cortisol 30, cortisol 60, peak cortisol and AUC cortisol during intervention. Entered independent variables in each regression model: #pre-treatment value of each individual dependent variable (cortisol 0, cortisol 30, cortisol 60, peak cortisol, or AUC cortisol), medicine group (0 placebo, 1 SSRI), and change in body composition (Δ-waist or Δ-BMI).

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whereas we are not aware of data in PCOS. Previous publications pooled data from males and females (36, 37, 38, 39, 40), which could have affected study results. Furthermore, in some papers, the type of SSRI may have affected the study outcome with escitalopram having a smaller (36) or a higher (38) effect on fat mass compared with other SSRIs. Even a small reduction in weight would have significant implications for PCOS phenotype and risk of diabetes and long-term data are needed to determine the effect of escitalopram on waist and body composition in PCOS. Changes in adrenal activity during escitalopram vs placebo were tested by comparing Δ-values between intervention groups. Interestingly, we found that women in the placebo group experienced lowering of cortisol levels during intervention, which could have affected significant findings of the present study. Our results could support that participating in a clinical trial may have a positive effect of adrenal activity and HRQol. Results of clinical trials without a placebo group should be interpreted with caution.

Changes in HRQoL were comparable between escitalopram and placebo in the present study, but the SF-36 domain, RP improved significantly during placebo vs escitalopram treatment. We found comparable changes in mental health (WHO-5 and MDI scores) between escitalopram and placebo, but the presence of low WHO-5 scores decreased significantly during placebo, which supported a positive effect of trial participation. Side effects to SSRI treatment could affect mental health and patients' emotions (41), but UKU was unchanged during study intervention, supporting that side effects did not affect our study outcomes. Women in the present study did not fulfill clinical criteria for depression, and it may be argued that out study population was 'too healthy' at baseline in comparison to studies performed on patients with clinical depression. The results of the present study were, however, in accordance with Knorr *et al.* (42), where changes in depression scores were similar between escitalopram and placebo in healthy relatives to patients with depression. Buhl did not report HRQol during treatment with escitalopram in healthy males with low birth weight (13), but the authors found no structural changes in the limbic brain morphology during study intervention. A recent meta-analysis on mental health during SSRI therapy found no placebo-controlled trials in patients with depression (43). The meta-analysis concluded that treatment with SSRI improved depression scores in patients with depression, but the clinical effect of improved depression scores was questionable and the risk of side effects and serious adverse events during SSRI was increased (43). These results were, however, questioned due to unclear definition of side effects and omission of clinical trials from the meta-analysis (44). Escitalopram treatment is not registered for treatment of patients without clinical depression, and our data support that escitalopram is not effective in treating impaired HRQol in PCOS. More studies are needed regarding the effect of escitalopram in women with PCOS and clinical depression.

Measures of insulin resistance were unchanged during escitalopram in the present study. Escitalopram is an inhibitor of 5-hydroxytryptamine and stimulates serotonergic activity. Increased serotoninergic activity was associated with increased insulin sensitivity (45). In accordance, glycemic control was improved in patients with type 2 diabetes during treatment with SSRI (15) and insulin sensitivity increased in non-diabetic study populations (13, 37, 40). The median BMI of our study population was 33 kg/m^2 and the participants had high fasting insulin levels, supporting an insulin resistant PCOS phenotype. Our study could be underpowered to detect small changes in insulin sensitivity during escitalopram, but we found no improvement of PCOS characteristics including cycle regularity, which further supported that escitalopram did not improve insulin sensitivity to any clinically relevant extent. Furthermore, we found no changes in lipid levels during escitalopram. Previously, there have been reports on changes in TG in non-PCOS populations during SSRI (35, 36, 40, 46). However, findings were not uniform as some authors reported increased (35, 46), decreased (40) or unchanged (36) TG levels during escitalopram treatment. None of these studies reported data on women alone and various patient populations and types of antidepressants were included in the studies (35, 36, 40, 46). SSRI treatment could stimulate α_1 receptors in fat tissue and enhance lipolysis (47). In accordance, a microdialysis study showed acute release of glycerol and free fatty acids from the subcutaneous fat tissue during treatment with escitalopram (47). Furthermore, changes in lipid status could be secondary to changes in weight, insulin sensitivity or HPA axis activity. Our finding of unchanged metabolic status during treatment with escitalopram is reassuring given common use of antidepressive treatment in PCOS (4, 6).

Strengths and limitations may apply to the present study. The study was randomized, placebo-controlled, double-blinded, and participants were thoroughly evaluated in one single medical center. It was not possible

to do a power calculation and the present study should therefore be considered a pilot study. Adrenal activity was evaluated by ACTH test performed in the morning, but the study results could have been strengthened by adding 24-h s-cortisol profiles or measurement of urinary cortisol excretion. We used a combination of disease-specific and generic questionnaires to describe HRQoL. Measures of insulin sensitivity were calculated at fasting and by measures derived from 3-h OGTT. The euglycemic–hyperinsulinemic clamp is the golden standard to measure insulin sensitivity, but the present study did not support any clinical relevant changes in glucose tolerance, insulin sensitivity or insulin secretion after escitalopram treatment. Our study design could have been improved by adding measurements of free fatty acids and inflammatory markers such as adiponectin or interleukins.

We included overweight and obese women with PCOS and our study results may not apply in lean women with PCOS. Furthermore, different study results may be found in women with PCOS and major depression.

In conclusion, treatment with escitalopram increased cortisol levels and waist circumference in women with PCOS and no clinical depression, whereas mental health and measures of insulin resistance were unchanged. More studies are needed to determine long-term metabolic and clinical outcomes after SSRI treatment in other PCOS phenotypes and in women with PCOS and depression.

Declaration of interest

Lundbeck sponsored escitalopram and placebo, but was not involved in economy, planning of project or evaluation of results and writing of the article. The other authors have nothing to declare.

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