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RELAXATION AND GUIDED IMAGERY SIGNIFICANTLY REDUCES ANDROGEN LEVELS AND DISTRESS IN POLYCYSTIC OVARY SYNDROME: PILOT STUDY

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ABSTRACT

Aim: Women with polycystic ovary syndrome (PCOS) often have elevated levels of the androgen testosterone, and are at increased risk of anxiety and depression. This study aimed to use psychological relaxation with guided imagery to decrease androgen levels and improve mood in PCOS. Methods: Repeated-measures. Thirteen women with PCOS underwent six weekly treatment sessions, and a follow-up session, of calming breathing, muscle relaxation, and guided imagery. The main outcome measures were mood and quality of life (QoL) – assessed using validated questionnaires – and hormones, which were assayed in serum using tandem mass spectrometry. Results: There was a small but statistically significant reduction in DHEAS from before to after Week 1 (p <.044) and from before to after Week 6 (p <.001). From before to after Week 6 there were also small but statistically significant reductions in androstenedione (p <.010) and cortisol (p <.003). From Week 1 to Week 6 there was a significant reduction in anxiety (p <.037). There was a significant improvement in depression from Week 1 to Week 6 (p <.034) and from Week 1 to follow-up (p <.011). There were no significant changes in free or total testosterone, nor in QoL. Conclusions: This is the first study to use a relaxation programme to reduce adrenal androgens in PCOS.

Keywords: Relaxation; androgen; depression; anxiety; polycystic ovary syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a condition affecting 8% to 17% of women aged 20 to 40 years old (Lauritsen et al., 2014). One of the diagnostic features of PCOS is elevated testosterone levels. Testosterone and other biochemicals of the androgen family (such as dehydroepiandrosterone sulfate (DHEAS) and androstenedione) contribute to the distressing physical symptoms of PCOS (infertility, acne, hirsutism, and obesity).

Women with PCOS are more at risk of anxiety and depression (Barry et al., 2011), cancer (Barry et al., 2014), and coronary heart disease and stroke (Anderson et al., 2014). The economic burden of PCOS in the United States is at least $13.9 billion annually (Azziz, 2008).

For many women with PCOS, the symptoms of excess androgen levels, such as hirsutism, are distressing. Although hirsutism is often attributed to testosterone, the correlation between testosterone and hirsutism is not strong (r = 0.24 at best; Legro et al., 2010), suggesting the contribution of other androgens to hirsutism too. Psychological factors can activate the adrenal glands, and adrenal activation stimulates not only cortisol production but androgen secretion (Leowattana, 2004). Women with PCOS may show evidence of adrenal hyperresponsivity to adrenocorticotropic hormone (ACTH), leading to increased DHEAS levels (McKenna & Cunningham, 1995; Milutinovi et al., 2011; Moran et al., 2004). Thus there may be something of a vicious circle, in which adrenal androgens contribute to the distressing symptoms of PCOS, and distress in reaction to the symptoms might lead to an increase in adrenal androgens.

Psychological relaxation techniques can non-pharmacologically reduce hypothalamic-pituitary axis (HPA) activity, alleviate anxiety and depression, and improve QoL and well-being (Deng & Cassileth, 2005). Relaxation is known to lower cortisol levels, but the evidence that relaxation can lower androgen levels is less clear, for example Cruess and colleagues (2001) found that stress-management significantly reduced free and total testosterone in breast cancer patients, whereas Carlson and colleagues (2004) found only a non-significant reduction in DHEAS levels. Few studies have used interventions to improve mood in PCOS, but a recent study of mindfulness training found a significant reduction in cortisol, stress and depression, though no improvement in QoL (Stefanaki et al., 2014).

The aim of the present study was to assess the effect of psychological relaxation and guided imagery on psychological functioning (anxiety, depression, and QoL) and hormone levels (DHEAS, androstenedione, cortisol, and testosterone) in women with PCOS.

MATERIALS AND METHODS

PARTICIPANTS

Participants were 13 women, aged between 19 and 33 years old, with a diagnosis of PCOS by the Rotterdam criteria, attending two reproductive endocrinology clinics in London teaching hospitals. Patients were also recruited from the researchers' website (www.PCOSresearch.org). Eleven participants completed the programme.

DESIGN

This study used a repeated measures design. Participants were recruited from October 2012 to May 2013, and participated in two consecutive cohorts between May and August 2013. Hormone levels and mood questionnaires were the outcome variables and were measured at baseline, at the final treatment session, and at follow-up (~3 months after their final session).

MEASURES

The biochemical outcomes measured were DHEAS, androstenedione, cortisol, and testosterone. Sex hormone-binding globulin (SHBG) was also measured in order to calculate the amount of bioavailable testosterone (the free androgen index, FAI). Blood samples were taken before and after the first, sixth, and the follow-up treatment session. To minimize any potential

influence of circadian rhythms, all participants were seen between 5.30pm and 8.30pm, and each participant had their treatment session scheduled at approximately the same time of day on each occasion. The mean (SD) duration between taking the pre and post session blood sample was 48 (13.2) minutes.

The psychological outcome measures were the PCOS Health-Related Quality of Life Questionnaire (PCOSQ) and the anxiety and depression subscales of the Hospital Anxiety and Depression Scale (HADS).

ASSAY METHODOLOGY

DHEAS, testosterone and androstenedione, and cortisol were assayed using liquid chromatography–mass spectrometry (LC–MS), to validated FDA guidelines. SHBG was measured using chemiluminescent microparticle immunoassay (CMIA) on the ARCHITECT i2000SR System (Abbott Diagnostics, Maidenhead, UK).

QUESTIONNAIRES

The PCOS Health-Related Quality of Life Questionnaire (PCOSQ). Thirty items assess feelings about symptoms of PCOS in the dimensions of emotions, hirsutism, obesity, infertility, menstruation, and acne. Lower scores indicate worse QoL.

The Hospital Anxiety and Depression Scale (HADS). Fourteen items measure state anxiety and depression. Scores of 8–10 indicate a mild problem; 11–14 moderate; 15–21 indicates a clinical problem.

Background data included body mass index (which may be related to androgen levels and depression) and demographic details. The Recent Life Changes Questionnaire was used as a control measure of stressful life events, measured in life change units (LCUs). Participants were offered debriefing interviews.

PROCEDURE

PCOS patients were recruited from clinics at the Royal Free London Hospital, University College London Hospital and the researchers' website. Volunteers were contacted and screened by NL, a counselling psychologist.

Psychological and hormonal measurements were done on each of the three measurement occasions (Weeks 1, 6 and follow-up). Serum samples were taken twice on each measurement day, once immediately before and once immediately after the intervention. All samples were centrifuged within two hours and stored at –80° until being analysed at the Department of Clinical Biochemistry, Manchester Hospital, Manchester, United Kingdom.

TREATMENT PROTOCOL

The psychological intervention took place in a quiet treatment room in the Gynaecology Clinic at the Royal Free London Hospital. Over six consecutive weeks, participants experienced individual relaxation therapy for 15 minutes at each session. The sessions included diaphragmatic breathing, progressive muscle relaxation, and visualization. The visualization was guided towards imagining positive images and feelings regarding whatever aspects of

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PCOS were important to each participant. After each session, NL reviewed progress and encouraged brief relaxation and visualization exercise at home.

ETHICAL APPROVAL

This study was done with the approval of the London-Stanmore Research Ethics Committee (reference 12/LO/1529). Written informed consent was given by all the patients prior to the start of the study.

STATISTICAL ANALYSIS

Comparisons across measurement occasions were made using repeated-measures *t*-tests. Correlations were measured using Pearson's *r*. Categorical data were analysed using χ^2 or Fisher's exact tests. Where a directional hypothesis was made and supported by the findings, *p* values are stated as one-tailed. The threshold for statistical significance was $p < .05$. The software package SPSS Version 22 for Windows (Armonk, NY: IBM Corp) was used for statistical analyses.

RESULTS

Eleven of the 13 participants completed the programme. Table 1 shows baseline characteristics of the participants.

*Table 1. Baseline characteristics of the participants who started the programme (*n *= 13) and those who completed the programme (*n *= 11). Two dropped out after the first session.*

Demographic variable		Participants (including dropouts) (*n* =13)	Participants (excluding dropouts) (*n* =11)
Age	Mean (SD)	27.23 (4.68)	27.09 (4.59)
BMI	Mean (SD)	26.00 (6.91)	26.55 (7.49)
Menstrual cycle	Oligomenorrheic	62% (n = 8)	64% (n = 7)
	Amenorrheic	23% (n = 3)	18% (n = 2)
	Normal	15% (n = 2)	18% (n = 2)
Socioeconomic class[a]	Managerial	42% (n = 5)	40% (n = 4)
	Intermediate	16% (n = 2)	20% (n = 2)
	Manual	42% (n = 5)	40% (n = 4)
Ethnicity			
	Caucasian	77% (n = 10)	82% (n = 9)
	Asian	15% (n = 2)	9% (n = 1)
	Mixed race	8% (n = 1)	9% (n = 1)

a Socioeconomic class not reported by one participant

Some of the participants who completed the programme were taking medication throughout the programme and had been on this medication for some time. Four (36%) were taking combined oral contraceptives (n = 1 cyproterone acetate and ethinylestradiol; n = 1 ethinyl estradiol + drospirenone; n = 2 ethinylestradiol and levo norgestrel), two (18%) were taking metformin, one (9%) was taking thyroxin, one (9%) was taking venlafaxine, and three (28%) were not taking any relevant medication. In most cases the women were on these medications for a period of years before starting the programme. Thus any effects of medication were very likely stable, and the impact of these drugs on hormones and psychological outcomes would have been consistent on all measurement occasions.

HORMONE LEVELS

Table 2 shows that there was a significant reduction in DHEAS comparing pre and post Week 1 (t = 1.921, d.f. = 9, $p < 0.044$) and pre Week 6 to post Week 6 (t = 4.301, d.f. = 10, $p < 0.001$). There was also a significant reduction in androstenedione (t = 2.766, d.f. = 10, $p < 0.010$), and cortisol (t = 3.521, d.f. = 10, $p < 0.003$) pre Week 6 to post Week 6. There was no change in free or total testosterone.

PSYCHOLOGICAL FUNCTIONING

Table 2 shows that from Week 1 to Week 6 there was a significant reduction in anxiety (t = 2.01, d.f. = 10, $p < 0.037$) and depression (t = 2.10, d.f. = 10, $p < 0.034$). There was also a significant reduction in depression from Week 1 to Week 6 (t = 2.05, d.f. = 7, $p < 0.034$) and from Week 1 to 3 months follow-up (t = 2.34, d.f. = 8, $p < 0.024$). There was a non-significant improvement in QoL from Week 1 to Week 6. There was no significant relationship between outcomes and the type of medication being taken, nor between outcomes and the stressful life event scores of participants.

Two women dropped out after the first session; one participant did not appear to show any response to the treatment and the other said she didn't think that the programme was suitable for her. To adjust for the effect of dropout, an intention-to-treat (ITT) analysis was done using the baseline-observation-carried-forward (BOCF) method. All 13 participants who started the programme were included, carrying forward their baseline scores as their follow-up scores. There were no significant changes in outcomes in the BOCF analysis compared to the findings in Table 2.

DEBRIEFING INTERVIEWS

Two participants who completed the six sessions agreed to be interviewed. They both said that they felt good after the sessions ('refreshed', 'happier and calmer'), and that the experience was very positive and helpful.

DISCUSSION

The results of this study lend support to our hypothesis that a psychological intervention can produce significant improvements in hormone and mood outcomes. The three adrenal hormones measured, DHEAS, androstenedione and cortisol, were all significantly reduced from pre Week 6 to post Week 6.

Table 2. Means (SDs) and paired t*-tests comparing scores at the different measurement occasions*

Outcome	*n*	Week 1 Pre	Week 1 Post	*n*	Week 6 Pre	Week 6 Post	*n*	Follow up Pre	Follow up Post
DHEAS µmol/L	10[a]	3.62 (1.64)	3.43 (1.41)*[b]	11	3.53 (1.42)	3.27 (1.36)***[c]	9	4.11 (2.14)	4.20 (2.45)
Cortisol nmol/L	10	215.57 (111.16)	175.42 (90.77)	11	200.03 (138.62)	160.20 (132.03)**[c]	9	224.63 (115.95)	218.12 (122.51)
A4 nmol/L	9	4.08 (1.69)	3.91 (1.67)	11	3.85 (2.20)	3.50 (1.95)**[c]	9	3.67 (1.12)	3.63 (1.20)
T nmol/L	9	0.98 (0.37)	0.99 (0.39)	11	1.04 (0.69)	0.96 (0.79)	9	0.96 (0.41)	0.89 (0.33)
SHBG nmol/L	7[f]	97.12 (70.65)	94.07 (67.23)	11	90.60 (62.05)	91.69 (65.50)	9	99.41 (67.70)	98.87 (67.85)
FAI nmol/L	7[f]	1.76 (1.56)	1.95 (1.74)	11	2.24 (2.87)	2.06 (3.21)	9	1.20 (0.58)	1.11 (0.45)
Anxiety	11	11.09 (4.30)	–	11	8.64 (3.75)*[d]	–	8	8.50 (6.02)	–
Depression	11	6.36 (3.75)	–	11	4.27 (3.41)*[d]	–	8	4.50 (3.25)*[e]	–
PCOS QoL	11	3.86 (1.13)	–	11	4.37 (1.15)	–	8	4.31 (1.35)	–

Note: * = p<.05; ** = p <.01; *** = p<.001. Significant values are one-tailed. Follow up was at roughly 13 weeks after session 6. '–' = outcomes were not measured at this timepoint because psychological outcomes were measured pre these sessions, not post. DHEAS = dehydroepiandrosterone sulfate. A4 = androstenedione. T = testosterone. SHBG = sex hormone binding globulin. FAI = free androgen index ((total testosterone × 100) / SHBG). QoL = Quality of Life.
a *n* is 10 rather than 11 because one participant accidentally missed giving their blood sample post Week 1;
b Pre Week 1 vs Post Week 1;
c Pre Week 6 vs Post Week 6;
d Pre Week 1 vs Pre week 6;
e Pre Week 1 vs Pre 3 months;
f *n* is 7 because in some cases there was insufficient serum to assay for SHBG

In contrast to the present study, Cruess and colleagues (2001) found that both free and total testosterone levels were significantly decreased in women with early-stage breast cancer diagnosis randomized to a ten-week cognitive-behavioural stress management (CBSM) group. Our findings regarding psychological functioning reflect those of Stefanaki and colleagues (2014), who found improvements in stress (measured in the present study as anxiety) and depression. As for those researchers, the present study found no significant improvement in PCOS QoL. The QoL findings in both studies suggest that the psychological intervention, although having an impact on mood and adrenal hormones, did not have a significant impact on participants' perception of their PCOS symptoms. An alternative explanation is that the PCOSQ (Barnard et al., 1997) is not sufficiently sensitive to the psychological impact of PCOS, and a more sensitive alternative needs to be developed.

The present study found a statistically significant improvement in anxiety from baseline to Week 6, demonstrating an improvement from mild anxiety to almost normal levels. Depression scores also significantly reduced – albeit within the normal range – from baseline to Week 6, and from baseline to follow-up.

The results of the present study are unlikely to have been influenced by circadian rhythms because the blood samples, taken pre and post the relaxation session, were taken within an hour of each other, and at roughly the same time of the evening on each measurement occasion for each participant. Furthermore, DHEAS and androstenedione are relatively stable throughout the day, and cortisol levels are relatively stable in the early evening, which is when the serum samples were taken (Young et al., 2001; also Ostrowska et al., 1998).

Despite the small sample size and lack of control group, this pilot study has several strengths. The assay method used to measure hormones was liquid chromatography tandem mass spectrometry, the gold standard methodology for measuring testosterone at the low levels seen in women, which gives us confidence that the hormone levels found were assessed accurately. Although the main potential confounding variables (individual differences, medication use) were eliminated by the repeated measures design and stability of medication use, there is of course the possibility that – despite the intervention occurring at the same time of day for each participant on each measurement occasion – the results were due to chance variations in hormone levels, or some other unknown factor. The group was relatively homogenous in having similar age and BMI. The lack of correlation between life-change unit (LCU) scores and the outcomes across all measurement occasions suggests that stressful life events were not related to outcomes. The fact that the participants were taking medication commonly used by women with PCOS makes the findings generalizable to the average woman with PCOS.

This is the first paper to report a psychological intervention for women with PCOS which causes a significant reduction in adrenal androgen levels. The reductions were generally modest, and in the absense of other information we must speculate that, given that androgen sensitivity is likely to be subject to individual differences (Wang & Zane, 2008), the physiological impact will vary from person to person. The intervention we used was minimal in order that the programme could be relatively inexpensive to deliver and easy for other research groups to replicate. The effects found in this pilot study might be increased by extending the duration of the intervention (e.g. to 30 minutes), and having more frequent sessions (e.g. two per week). As a next step, a future study should use a larger sample size and a randomized controlled trial design, and assess changes to physiological outcomes such as menstrual functioning and BMI.

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