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ORIGINAL ARTICLE *Reproductive endocrinology*

Effect of an oral contraceptive on emotional distress, anxiety and depression of women with polycystic ovary syndrome: a prospective study

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STUDY QUESTION: We aimed to determine the impact of an oral contraceptive (OC) treatment on health-related quality of life (HRQOL), depressive and anxiety symptoms in polycystic ovary syndrome (PCOS).

SUMMARY ANSWER: OC therapy in PCOS improves hirsutism and menstrual disturbances, along with HRQOL. This improvement is not associated with any change in the prevalence of depressive and anxiety symptoms.

WHAT IS KNOWN AND WHAT THIS ARTICLE ADDS: Limited data are available regarding the effects of an OC on HRQOL, and depressive and anxiety symptoms in PCOS. This study reports the effects of the ethinyl estradiol/drospirenone (EE/DRSP) OC on an HRQOL questionnaire for women with PCOS (PCOSQ), depressive and anxiety symptoms after 6 months of treatment.

DESIGN: Prospective observational study. All participants completed PCOSQ, Beck Depression Inventory, Hospital Anxiety and Depression Scale and General Health Questionnaire. Serum androgens, fasting insulin, fasting and postload glucose values during an oral glucose tolerance test were measured. Changes in these variables and the scores of questionnaires were evaluated after 6 months of treatment with EE/DRSP (3 mg/30 μg).

PARTICIPANTS AND SETTING: Thirty-six patients with PCOS without a previous psychiatric diagnosis were included in the study.

MAIN RESULTS AND THE ROLE OF CHANCE: The main complaints of the patients were hirsutism and irregular menses. Accordingly, menstrual and hirsutism problems were the most serious concerns followed by emotional problems on the PCOSQ. Eight patients (22.2%) had clinical depression scores. After treatment, regular menstrual cycles were attained and hirsutism was significantly improved in all patients. Hirsutism and emotion domains of the PCOSQ improved at 6 months ($P < 0.05$ for both). Depression was improved in five of eight depressive patients and four new patients showed increased depression scores. Overall, depression, anxiety mean scores and depression rates did not show a significant change.

BIAS, CONFOUNDING AND OTHER REASONS FOR CAUTION: The study is subject to the strengths and limitations of observational study design. A limitation of our study is the small sample size and lack of data related to possible confounding factors.

GENERALIZABILITY TO OTHER POPULATIONS: Generalizable to Caucasian PCOS.

STUDY FUNDING/COMPETING INTEREST(S): This work was supported, in part, by the Turkish Academy of Sciences (Grant TUBA-GEBIP 2006).

Key words: polycystic ovary syndrome / depression / oral contraceptive / quality of life / hirsutism / oligomenorrhea

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, affecting 5–10% of this population (Azziz *et al.*, 2004). Many aspects of this syndrome, such as hirsutism, acne, obesity, menstrual abnormalities and difficulty in becoming pregnant, have a negative impact on the health-related quality of life (HRQOL) and may increase the risk of mood disorders

(Coffey *et al*., 2006; Dokras *et al*., 2011). Several studies reported that women with PCOS have an increased rate of depression and anxiety compared with healthy controls (Dokras *et al*., 2011). Hyperandrogenism and obesity along with insulin resistance (IR) and dyslipidemia appear to be associated with these mood disorders in PCOS (Rasgon *et al*., 2003; Weiner *et al*., 2004; Cinar *et al*., 2011).

Oral contraceptive pills (OCs) are first-line medical therapy in women with PCOS. In women without PCOS, some studies reported less severe depressive symptoms and better overall physical function with the use of OCs (Young *et al*., 2007), whereas change in mood, specifically depression, is one of the most common reasons given for discontinuing OC use in others (Oinonen and Mazmanian, 2002). Even though improvement of HRQOL in women with PCOS with use of metformin is reported in the literature (Hahn *et al*., 2006), no data are available regarding the potential effects of OCs on quality of life, emotional well-being, depression and anxiety in PCOS. In this prospective observational study, we aimed to determine potential impact of an OC on HRQOL, emotional well-being, depression and anxiety symptoms in patients with PCOS.

Materials and Methods

Subjects

Thirty-six patients with PCOS presenting with hirsutism and/or menstrual dysfunction to the Outpatient Clinic of Endocrinology and Metabolism at Hacettepe University, Ankara, Turkey, between 1 June and 31 December 2007 were enrolled prospectively for the study. PCOS diagnosis was based on the 2003 Rotterdam criteria after excluding related disorders as suggested (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Hyperandrogenism, chronic oligoanovulation and polycystic ovaries (PCO) were defined as previously described (Yildiz *et al*., 2010). Any contraindication to OC use and a previous diagnosis of psychiatric disorder were other exclusion criteria. Patients did not take any medication for at least 3 months before entering the study. The study protocol was approved by the Institutional Review Board of the Hacettepe University School of Medicine and informed consent was obtained from all subjects.

Measurements

Clinical parameters

A standardized medical form was completed and anthropometric measurements, including BMI (kg/m^2) and waist-to-hip ratio (WHR), were determined. Hirsutism was defined by modified Ferriman–Gallwey (mFG) score $\geq$7.

Laboratory measures

Blood samples were collected between 8.00 and 10.00 a.m. on Day 2–5 of the menstrual bleeding after an overnight fast. All subjects underwent a 75 g 2 h oral glucose tolerance test. Laboratory data included total testosterone, androstenedione, dehydroepiandrostenedione-sulphate (DHEA-S), sex hormone-binding globulin (SHBG), fasting plasma glucose (FPG), fasting insulin and 2 h glucose values. Assays were performed as previously described (Yildiz *et al*., 2010). Free androgen index (FAI) and homeostatic model assessment of IR (HOMA-IR) were calculated according to their respective equations (Yildiz *et al*., 2010).

All the clinical and laboratory assessments were performed at baseline before treatment, and after 6 months of treatment with ethinyl estradiol (30 μg)/3 mg drospirenone (EE/DRSP).

Psychological measurements

All participants completed the HRQOL questionnaire for women with PCOS (PCOSQ), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS) and General Health Questionnaire 28 (GHQ) at baseline and after treatment.

PCOS health-related quality of life. PCOSQ is a multi-dimensional construct encompassing physical, emotional and social consequences of the disease. It includes five domains: emotions, body hair, weight problems, menstrual problems and infertility (Cronin *et al*., 1998). Each item is associated with a seven-point scale, in which a score of 7 denotes no problems or difficulties and one indicates maximum HRQOL impairment. The mean score of all items in a domain shows the domain score. Lower scores indicate a lower HRQOL.

Beck Depression Inventory. BDI is a 21 questions multiple choice self-report inventory that is one of the most widely used instruments for measuring the severity of depression (Beck *et al*., 1961). Scores $\geq$17 indicate severe depression needing to be treated.

Hospital Anxiety and Depression Scale. HADS is a measure of depression and generalized anxiety in hospital, outpatient and community settings (Herrmann, 1997). It evaluates the presence and severity of anxious and depressive symptoms rather than distinguishing between different types of anxiety or depression. A score of 11 or higher indicates the probable presence of the mood disorder.

General Health Questionnaire. The GHQ is a measure of the psychological function or disturbance comprising a global score and four scales for somatic symptoms, anxiety, insomnia, social dysfunction and severe depression. Psychological morbidity was identified by a standard score of $>$5 and chronic disease as $>$13 (Goldberg and Blackwell, 1970).

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences version 11.0. Paired samples Student's *t*-test and Wilcoxon's test were used for evaluating the differences before and after treatment. A χ^2 or Fisher exact test was used to evaluate categorical variables. Pearson correlations for the parameters with normal distribution and Spearman correlations for the parameters with skewed distribution were used to examine the relationship among BDI, HADS and GHQ scores and other hormonal and metabolic variables and mFG scores. Results are reported as mean $\pm$ SD. Statistical significance was defined as $P < 0.05$.

Results

A total of 36 women with PCOS aged 17–35 years were enrolled in this study and completed the required questionnaires. Presentation rates for oligomenorrhea, and unwanted body and facial hair were 27 of 36 and 33 of 36, respectively. Among 33 patients complaining of unwanted hair, 22 had mFG scores $\geq$7 and 11 had scores of 4–6. Twenty-six patients had PCO on ultrasound.

The group included both lean (BMI $<$27/kg/m^2) and overweight (BMI $\geq$27 kg/m^2) patients. The percentage of the overweight patients was 13.8% (5 of 36).

Table I shows the clinical and hormonal characteristics of patients with PCOS at baseline and after treatment for 6 months with EE/DRSP. There was no change in BMI or WHR ($P > 0.05$), whereas mFG scores decreased significantly after treatment ($P < 0.001$). A significant decrease in total testosterone, FAI and

Table I Clinical and hormonal characteristics of patients ($n = 36$) with PCOS before and after treatment with OC for 6 months.

Parameters	Baseline	After OC treatment	P
BMI (kg/m^2)	23.3 ± 4.8	23.6 ± 4.9	NS
WHR	0.77 ± 0.07	0.78 ± 0.06	NS
mFG score	8.7 ± 4.9	5.4 ± 3.3	<0.001
Total testosterone (ng/dl)	78.6 ± 31.3	63.7 ± 28.3	<0.05
SHBG (nmol/l)	33.0 ± 28.3	172.7 ± 54.6	<0.001
FAI	12.4 ± 13.3	1.5 ± 0.9	<0.001
DHEA-S (μg/dl)	271.7 ± 107.9	214.4 ± 123.4	<0.001
Androstenedione (mg/ml)	3.6 ± 1.3	3.3 ± 1.3	NS

Results are expressed as mean ± SD.
DHEA-S, dehydroepiandrostenedione-sulphate; SHBG, sex hormone-binding globulin; FPG, fasting plasma glucose; FAI, free androgen index; mFG, modified Ferriman–Gallwey; WHR, waist-to-hip ratio.

Table II Questionnaire scores before and after OC treatment in patients with PCOS ($n = 36$).

Parameters	Baseline	After OC treatment	P
Emotion domain	4.2 ± 1.1	4.7 ± 1.2	<0.05
Body hair domain	2.9 ± 1.6[a]	4.0 ± 1.7	<0.05
Weight domain	4.8 ± 1.8	4.8 ± 1.8	NS
Infertility domain	4.7 ± 1.4	5.3 ± 1.4	0.051
Menstrual problems domain	3.9 ± 1.4	4.4 ± 1.6	0.067
BDI	10.2 ± 7.6	10.4 ± 7.1	NS
HADS	13.5 ± 7.6	13.2 ± 8.4	NS
GHQ	25.8 ± 12.6	23.2 ± 11.2	NS

Results are expressed as mean ± SD.
[a]The most serious concerns have the lowest scores. BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; GHQ, General Health Questionnaire 28.

DHEA-S levels was also observed ($P < 0.05$ for all). Furthermore, there was a significant increase in SHBG levels caused by the estrogen component of OC, inducing SHBG synthesis by the liver ($P < 0.001$).

Psychological disturbances in women with PCOS

PCOSQ results at baseline showed that hirsutism and menstrual problems were the most serious concerns followed by emotional problems in women with PCOS, whereas weight and infertility were of the least concern (Table II).

Eight patients with PCOS (22.2%) had scores ≥17 on BDI, indicating clinically significant depression. BDI scores correlated with HADS ($r = 0.696$, $P < 0.001$) and GHQ scores ($r = 0.754$, $P < 0.001$).

Changes in the scores of questionnaires after treatment

Table II shows the scores of questionnaires at baseline and after treatment. No significant change was found in the weight domain of the PCOSQ. As expected, with the improvement in mFG scores, a significant improvement in the domains of emotion and body hair was observed ($P < 0.05$). On the other hand, a non-significant trend in improvement in the scores of menstrual problems and infertility domains was observed with the regulation of menstrual cycles (P values of 0.067 and 0.051, respectively). The change in body hair domain scores of PCOSQ was negatively correlated with the change in serum DHEA-S levels ($r = -0.619$; $P < 0.001$). The change in the emotion domain of the PCOSQ was negatively correlated with the change in mFG scores ($r = -0.479$; $P < 0.01$). No other significant correlation was observed between the changes in androgens and the changes in the scores of HRQOL.

Subgroup analyses were performed among patients with hirsutism scores ≥7 ($n = 22$), and among patients with oligomenorrhea ($n = 27$). Similar to the whole group, a significant improvement in the domains of emotion and body hair was also observed among hirsute patients (3.8 ± 1.0 versus 4.6 ± 1.4 $P < 0.05$; 2.4 ± 1.2 versus 3.6 ± 1.7 $P < 0.05$, respectively). The change in the body hair domain score was negatively correlated with the change in DHEA-S levels ($r = -0.649$; $P < 0.05$). The change in the emotion domain of the PCOSQ was negatively correlated with the change in DHEA-S and testosterone levels and hirsutism scores ($r = -0.589$, -0.482 and -0.641, respectively; $P < 0.05$ for all). Patients with oligomenorrhea showed a significant improvement in the emotion domain (4.2 ± 0.9 versus 4.7 ± 1.2; $P < 0.05$) and a trend for improvement in the menstrual problems domain (3.9 ± 1.4 versus 4.3 ± 1.7; $P > 0.05$) at after 6 months of treatment with OC.

BDI, HADS and GHQ scores did not show a significant improvement with OC treatment. Among eight depressive patients at baseline, five showed an improvement in BDI score at 6 months and three showed no significant change. Moreover, four patients who were not depressed at baseline showed an increase in BDI score and were depressed after 6 months OC treatment. The conversion rate of depression over the study period was 11.1% (4 of 36) and this change in depression rate after treatment was not significant.

Depression scores and metabolic parameters

We divided the patients into three groups to evaluate potential differences of metabolic parameters in patients with and without depression; Group 1—the patients who developed depression and who showed no improvement in depression ($n = 7$), Group 2—the patients who showed improvement in depression ($n = 5$) and Group 3—the patients without depression ($n = 24$). Fasting insulin and HOMA-IR levels showed no significant change in any group at 6 months. There was a significant increase both in the FPG (72.6 ± 13.1 versus 87.3 ± 20.9; $P < 0.05$) and 2 h plasma glucose values (74.4 ± 19.5 versus 115.1 ± 26.3; $P < 0.05$) in Group 1, whereas glucose values showed no significant change in Groups 2 and 3 (data not shown).

Discussion

We report here that at the 6-month follow-up study, using a standardized PCOSQ survey, OC use improves emotional well-being of patients with PCOS, along with an improvement of hirsutism and menstrual disturbance. This study also shows that despite an improvement in HRQOL in patients with PCOS, no significant change occurs in BDI, HADS or GHQ mean scores or prevalence rates of depression, indicating that OCs might have no influence on the natural clinical course of psychiatric disorders in PCOS.

Little is known about the effect of medical treatment on quality of life in PCOS patients. Metformin treatment for 6 months in PCOS resulted in an improvement in quality of life as measured by questionnaires non-specific for PCOS (Hahn *et al*., 2006). This improvement was correlated with reduction in body weight and normalization of menstrual cycles but metformin did not improve hirsutism. Also, metformin does not seem to result in weight loss in all patients with PCOS (Nieuwenhuis-Ruifrok *et al*., 2009). Ancillary PCOS-specific HRQOL data are available from a few clinical trials (Guyatt *et al*., 2004; Thomson *et al*., 2010). In one clinical trial, troglitazone treatment for about 9 months in obese women with PCOS significantly decreased hirsutism and improved menstrual cycles. The changes in hirsutism scores were correlated with reductions in hair growth and improvements in the weight, infertility and menstrual problems domains of the PCOSQ, whereas the regulation of menstrual cycles was correlated with improvements in infertility and menstrual problems domains (Guyatt *et al*., 2004). In another trial, lifestyle management with diet and exercise resulted in weight loss in obese women with PCOS along with improvements in emotion, body weight and menstrual problems domains of the PCOSQ (Thomson *et al*., 2010). The change in weight was associated with the changes in emotion and body weight scores (Thomson *et al*., 2010). In line with previous studies, we observed a significant increase in the scores for emotion and body hair domains and a non-significant trend for increase in the scores of menstrual problems and infertility domains of the PCOSQ, along with regulation of menstrual cycles and improvement in hirsutism. Taken together, these data suggest that improvement (by any means) in clinical complaints of patients, such as hirsutism, menstrual irregularity and obesity, leads to an improvement in relevant domains of the PCOSQ.

Several studies have shown that women with PCOS are more likely to experience depressive symptoms than healthy women (Rasgon *et al*., 2003; Mansson *et al*., 2008; Deeks *et al*., 2010; Cinar *et al*., 2011). The rate of depression in PCOS ranges from 14 to 67% (Cinar *et al*., 2011; Dokras *et al*., 2011) and the prevalence of anxiety is reported to be as high as 34–57% (Benson *et al*., 2009; Deeks *et al*., 2010). In our recent study, we found an 8.1-fold increased risk of depression in patients with PCOS compared with healthy women (28.6 versus 4.7%) (Cinar *et al*., 2011). In the present study, 22.2% of patients had scores $\geq$17 on BDI, indicating clinically significant depressive symptoms.

There are few studies of the effect of treatment on depression in women with PCOS. Thomson *et al*. (2010) reported that weight loss by dietary restriction alone or combined with exercise caused improvement in depression scores in overweight and obese women with PCOS. In a mail survey study of 60 women with PCOS, Kerchner *et al*. (2009) reported a similar proportion of metformin or OC use in women with PCOS with and without depression. In an internet-based cross-sectional survey study, Barnard *et al*. (2007) reported similar rates of depression in patients with PCOS with or without antiandrogen treatment despite a better quality of life in women taking antiandrogen medication. In Barnard *et al*. (2007), metformin and any contraceptive drugs were classified as antiandrogen. Another cross-sectional study of 32 patients with PCOS reported depression in half of these women and suggested that patients receiving OCs were less depressed than patients not using OCs (Rasgon *et al*., 2003). Our study provides prospective data indicating no significant improvement in depression and anxiety scores after 6 months of OC use in patients with PCOS despite improvement in hirsutism and menstrual irregularity associated with improvement in HRQOL. Four additional patients with PCOS developed clinically significant depressive symptoms during the study. The detection rate of new cases was 11.1%. Among eight depressive patients at baseline, five showed an improvement in BDI scores, whereas no significant change was observed in the other three patients. Overall, these data suggest that even though weight loss might result in improvement of depressive symptoms in obese patients with PCOS, treatment of hirsutism and menstrual irregularity by an OC does not alter the elevated risk of depression and anxiety in PCOS.

Mood-related side effects, such as irritability, mood swings and depressive symptoms, are among the major reasons for discontinuing OCs in women (Oinonen and Mazmanian, 2002). On the other hand, a majority of the women report unchanged or improved mood while on OCs (Joffe *et al*., 2003). In the prospective studies, increased anxiety and increased depressive mood were reported in 7 and 10% of women on OCs, respectively (Ernst *et al*., 2002), whereas discontinuation rates owing to adverse mood symptoms were as high as 14–21% (Larsson *et al*., 1997). A history of depression, a high level of psychological distress prior to OC use and socioeconomic factors increase the risk of becoming depressed when taking OCs (Oinonen and Mazmanian, 2002). Considering these data, we might speculate in our study that potential adverse effects of OCs on mood might have played a role in the lack of benefit in depressive symptoms and anxiety despite an improvement in HRQOL in women with PCOS.

An interesting finding of our study is the increase of fasting and postload glucose levels with OC use in patients with PCOS with depression. We did not observe such a disturbance with OC use in patients with PCOS without depression. We have recently reported a relationship between depression scores and postload glucose in a large group of women with PCOS (Cinar *et al*., 2011). However, there are no longitudinal data assessing the relation between glucose homeostasis and depression in PCOS. It remains to be determined whether long-term OC use shows variable effects on glucose tolerance in patients with PCOS with and without depressive symptoms.

One should note as a limitation of our study its relatively small sample size and lack of data related to possible confounding factors, such as diet and physical activity, since these parameters are important in the restoration of ovarian function and improvement in body composition and hyperandrogenism (Vigorito *et al*., 2007; Palomba *et al*., 2008, 2010; Giallauria *et al*., 2009; Moran *et al*., 2011). Nevertheless, our prospective observational study design enabled us to evaluate the potential impact of an OC in PCOS on quality of life, depression and anxiety in a real-life setting. Another limitation is that we report

depression rates based on scores in screening tests that are outside the normal range and confirmation of depression by clinical assessment was not included in our study design. Lastly, we report effects of a single OC and other OCs might have different effects.

In conclusion, treatment with an OC for 6 months in PCOS improves hirsutism and menstrual irregularities along with an improvement in quality of life. However, these benefits are not associated with amelioration of depression and anxiety in PCOS, suggesting that OCs might have no influence on the natural course of psychiatric disorders in PCOS.

Authors' roles

N.C.: contributed to acquisition, analysis and interpretation of the data and drafting the article. A.H.: contributed to acquisition of the data, and critical revision of the paper. B.D.: contributed to conception and design, analysis and interpretation of the data and critical revision of the paper. B.O.Y.: contributed to conception and design, acquisition, analysis and interpretation of the data and critical revision of the paper. The final version of the paper was approved by all authors.

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Conflict of interest

The authors have nothing to disclose.

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