Metformin treatment of polycystic ovary syndrome improves health-related quality-of-life, emotional distress and sexuality

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BACKGROUND: In polycystic ovary syndrome (PCOS), changes in physical appearance, menstrual disturbances and infertility result in psychological distress and reduced quality-of-life. Metformin improves biochemical, clinical and reproductive parameters in PCOS women. In a prospective, observational study, we analysed the effects of metformin treatment on health-related quality-of-life (HRQL), emotional well-being and sexuality in PCOS. No placebo-treated control group was included.

METHODS: Before, during and after 6 months of treatment, changes in clinical and endocrine parameters, quality-of-life, psychological disturbances and sexuality were assessed in 64 PCOS patients using validated questionnaires (SF-36, SCL-90-R) and visual analogue scales. Patients were also compared with published normative data for the validated questionnaires.

RESULTS: During treatment, HRQL, particularly the psychosocial aspects (indicated by significant increases in SF-36 scales Vitality, Social Function, Emotional Role Function, Mental Health, Psychological Sum scale) and emotional well-being (reflected by significant lowering of SCL-90-R scales) improved. These improvements in HRQL were significantly correlated with a reduction in body weight and significantly more pronounced in patients with normalized menstrual cycles. In addition, PCOS women were significantly more satisfied with their sex life and reported higher frequencies of sexual intercourse following treatment.

CONCLUSION: Treatment can improve the psychosocial, emotional and psychosexual situation of PCOS patients. Although at least some of these effects may be related to the reduction of individual clinical symptoms (i.e. weight loss, normalization of menstrual disturbances, improvement of acne), this observational study does not allow us to clearly discern the role of symptom constellation and does not preclude non-specific and/or placebo effects. Nevertheless, emotional distress and reduced quality-of-life are clearly not an inevitable consequence of PCOS and should be considered as adjunct treatment goals in future studies.

Key words: emotional distress/insulin sensitizer/PCOS/quality-of-life/sexual satisfaction

Introduction

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders of women of reproductive age (Diamanti-Kandarakis et al., 1999; Asuncion et al., 2000). In addition to endocrine and metabolic problems, psychological aspects of PCOS are increasingly recognized. Several investigators (Eggers and Kirchengast, 2001; Sills et al., 2001; Trent et al., 2002, 2003; Coffey and Mason, 2003; Elsenbruch et al., 2003; Rasgon et al., 2003; McCook et al., 2005) have previously shown that PCOS women suffer from marked reductions in quality-of-life, impaired emotional well-being and reduced sexual satisfaction. The determinants of psychological problems in these patients remain elusive. For this reason, psychological variables are not consistently integrated as outcome parameters in treatment studies. Changes in physical appearance, particularly obesity and excessive body hair, as well as infertility have been identified as important contributors to psychosocial problems in PCOS (Mccook et al., 2005; Trent et al., 2005). The potential importance of obesity in PCOS is supported by the finding that obesity can profoundly affect quality-of-life independent of the presence of other clinical symptoms in otherwise healthy subjects (Stunkard et al., 2003). Interestingly, obesity is linked strongly to the physical dimension of quality-of-life, rather than with psychosocial status (Mannucci et al., 1999) and social adjustment (Swallen et al., 2005). Further, any kind of weight loss achieved by either dietary modification, physical activity, pharmacotherapy, surgery or combinations thereof yields significant improvement of...
physical and social functioning in obese patients (Dittmar et al., 2003; Jalil et al., 2004; Mathus-Vliegen et al., 2004; Ogden et al., 2005). Another potentially important factor, hirsutism, is per se associated with anxiety and greater psychotic symptoms (Sonino et al., 1993). Similar results have been reported for patients with acne (Mallon et al., 1999; Klassen et al., 2000). Finally, women with androgenetic alopecia experience increased self-consciousness, feelings of unattractiveness and emotional stress (Van Der Donk et al., 1994; Girman et al., 1999). However, no consistent impact of infertility on quality-of-life has been reported (Wischmann et al., 2001; Monga et al., 2004; Mccook et al., 2005; Ragni et al., 2005). Age (Fekkes et al., 2003) and ethnic background (Schmid et al., 2004) seem to influence the degree of psychological distress caused by infertility.

On the basis of these data documenting the psychological and emotional consequences of changes in outer appearance, clinical interventions in PCOS women that influence obesity, hirsutism, acne or menstrual disturbances would be expected to improve overall health-related quality-of-life (HRQL). Insulin-sensitizing drugs such as metformin and glitazones have been shown to improve all these somatic problems in PCOS patients (Velazquez et al., 1994; Diamanti-Kandarakis et al., 1998; Harborne et al., 2003; Lord et al., 2003; Hahn et al., 2004). Guyatt and co-workers recently reported an amelioration in the domains infertility, menstruation and emotions utilizing the disease-specific PCOSQ questionnaire after 44 weeks of troglitazone treatment (Guyatt et al., 2004). Except for this one report (Guyatt et al., 2004), no data exist on treatment effects of insulin-sensitizing drugs on parameters of quality-of-life, emotional well-being and sexual satisfaction in PCOS.

We now present data supportive of beneficial effects of metformin treatment on a variety of psychosocial variables in a prospective, observational study in a German PCOS cohort.

Materials and methods

Subject recruitment

In this prospective, observational study, PCOS patients (n = 85) were recruited from the outpatient clinics of the Division of Endocrinology, Department of Medicine and the Department of Gynecology at the University of Duisburg-Essen. On the basis of the criteria derived from the 1990 NIH conference, diagnosis of PCOS was established when oligomenorrhea (cycles lasting longer than 35 days) or amenorrhea (less than two cycles in the past 6 months) and either clinical signs of hyperandrogenism (hirsutism with a Ferriman/Gallway (FG) score of 26 or obvious acne or pronounced alopecia) or elevated total testosterone in combination with an elevated free androgen index (FAI) (normal range: testosterone <2.0 nmol/l, FAI <3.8) were found, and other pituitary, adrenal or ovarian diseases could be excluded. In addition, in all women, an adrenocorticotrophic hormone test with measurement of 17-hydroxyprogesterone was performed. When the stimulated value (after 60 min) was >10 ng/ml, a genetic analysis (21 hydroxylase deficiency) was added. All PCOS patients also fulfilled the Rotterdam criteria (ESHRE/ASRM, 2004). The presence of polycystic ovaries was defined by the ESHRE/ASRM criteria (Balen et al., 2003) as at least one ovary >10 ml or with at least 12 follicles of 2–9 mm diameter. All recruited women were required to be otherwise healthy. Previous or current psychiatric diagnoses as well as patients undergoing psychotherapy were exclusionary. PCOS subjects had not taken any medication for at least 3 months before entering the study.

Comparison data for validated questionnaires

As comparison data for the validated questionnaires (i.e. SF-36, SCL-90-R), published normative data were utilized (for further details on the questionnaire scales, see p. 2–3). For the SCL-90-R the study of Hessel et al. (2001) validated and standardized the SCL-90-R on the basis of a representative sample of the German population (2141 subjects aged 16–96 years). For the present analysis, we utilized data of the female representative subjects (n = 1222) as control group. For the SF-36 the German version of the SF-36 (Bullinger and Kirchberger, 1998) was standardized on a representative population-based sample (n = 2914). An age-matched subgroup of female subjects aged 21–30 years (n = 263) was used as comparison group for the primary SF-36 scales in the present study. For the Sum scales, no age- or gender-specific reference data exist; therefore, we utilized the normative data as published (these included men and women aged 18–65 years).

Study protocol

Patients completed the study questionnaires (see p. 2–3) prior to treatment, and 1 and 6 months following treatment initiation. All PCOS women received monotherapy with metformin. Women with a body weight (BW) ≤60 kg were treated with 500 mg metformin bid, with a BW > 60 and ≤100 kg with 850 mg bid and >100 kg 1000 mg bid. The study protocol was approved by the Ethics Committee of the University of Duisburg-Essen. All participants gave informed written consent before entering the study.

Of the 85 patients, 12 PCOS women enrolled in the study conceived on metformin and were excluded from further analysis. Two women discontinued treatment because of side effects (diarrhea) and one woman stopped for personal reasons (oral contraception). In six patients the complete set of questionnaires of all visits was not available.

Instruments and measures

Questionnaires

Quality-of-life, psychological distress and sexual satisfaction were assessed with three standardized questionnaires. HRQL was assessed with the German version of the SF-36 (Ware et al., 1998), a widely used and validated instrument containing a total of eight subscales, namely Physical Function, Physical Role Function, Bodily Pain, General Health, Vitality, Social Function, Emotional Role Function and Mental Health. In addition, the subscales are combined to yield two summary health status measures, the Physical Sum scale and the Psychological Sum scale (Ware and Sherbourne, 1992; McHorney et al., 1993). Psychological disturbances were assessed with the German version of the Symptom Check List 90 (SCL-90-R) (Schmitz et al., 2000). This widely used screening tool contains 90 items with a five-point scale (0 = not at all, 4 = extremely) and assesses psychological distress in nine areas (Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Aggression, Phobia, Paranoid Ideation, Psychoticism) as well as on three global categories, namely the Global Severity Index (GSI, fundamental psychic stress), the Positive Symptom Distress Index (PSDI, intensity of symptoms) and the Positive Symptom Total (PST, number of self-reported symptoms) (Derogatis et al., 1976; Schmitz et al., 2000). Higher scores on the scales of the SCL-90-R mean higher distress; individual scales cannot be interpreted in diagnostic categories. In addition, standardized effect sizes (SESs) (Kazis et al., 1989) were measured to give a valid, complete and clinically relevant picture of health status changes during treatment.
To address various aspects of sexual satisfaction, 100-mm visual analogue scales (VAS) were used, ranging from ‘not at all’ at the 0-mm mark to ‘very much’ at the 100-mm mark (Elsenbruch et al., 2003). VAS scales are routinely used in German studies evaluating sexuality (Arlt et al., 1999). Although the VAS scale used in this study has not been validated, it fulfills all criteria for a standardized measure since all subjects had the same instructions, questions and response options. Included were items regarding the impact of hirsutism on sexuality and on the ability to make social contacts, the importance of a satisfying sex life, satisfaction with sex life during the past month, sexual thoughts and fantasies during the past month, frequency of pain during sexual intercourse and the feeling of being sexually attractive. Women were instructed to place a mark at the point that best corresponded with their feelings. The partnership situation of the subjects and the frequency of sexual intercourse during the past month were also recorded.

Clinical and laboratory parameters

In all subjects, physical examination was performed including evaluation of hirsutism by the FG-Score, the presence of acne or androgenetic alopecia and anthropometric measurements including BW in kilograms before entering the study and after 1 and 6 months on metformin. In addition, medical history was obtained by personal interview. PCOS women were instructed to document the frequency and length of menstrual bleedings. After an overnight fast of 12 h, a 75-g oral glucose tolerance test (OGTT) with determination of glucose and insulin levels at baseline and at 30, 60, 90, 120 and 180 min was performed. Insulin resistance and β-cell function were defined by the homeostasis model assessment (HOMA)-model (Matthews et al., 1985) and hyperinsulinaemia by calculating the area under the insulin response curve [area under the curve (AUC-I)]. Additionally, blood samples were obtained for the measurement of gonadotrophins, estradiol (E2) and androgens. FAI was estimated as testosterone (nmol/l)/sex hormone-binding globuline (SHBG) (nmol/l) × 100. Except for amenorrheic women, all laboratory determinations were performed in the early follicular phase of the cycle.

Automated chemiluminescence immunoassay systems were used for the determination of LH, FSH, E2, testosterone and blood glucose (G) (ADVIA Centaur, Bayer Vital, Fernwald, Germany), as well as androstendione (A), dehydroepiandrosterone sulphate (DHEA-S), insulin (I) and SHBG (Immulite 2000, DPC Biermann, Bad Nauheim, Germany). Intra-assay variation was <5% and inter-assay variation was <8% for all measured parameters.

Statistical analysis

To address changes in response to treatment in the entire cohort of PCOS patients, repeated measures analysis of variance (ANOVA) was carried out to test for significant effects of the repeated factor time (pretreatment, 1 and 6 months after treatment initiation). For non-normally distributed variables (FG-Score, HOMA-IR), Friedman tests were computed. To address the possibility that time-related changes in psychological variables differed according to the presence and/or degree of specific PCOS symptoms at baseline, patients were divided into subgroups in relation to the syndrome features, i.e. lean, overweight and obese patients (i.e. BMI < 25, ≥25 to <30, ≥30 kg/m²); patients with hirsutism (FG-Score ≥ 6) and those without hirsutism; patients with acne and patients without acne (based on the clinician’s assessment), patients with unfulfilled wish to conceive and those without unfulfilled wish to conceive (patients’ self-report) and patients with insulin resistance (i.e. HOMA-IR > 2.5) and patients without insulin resistance. In these subgroups, improvements in psychological variables over time were analysed using 2-way ANOVA with the factors group and time to test for significant interactions. These ANOVAs were computed for the key variables SF-36 Physical Sum score, SF-36 Psychological Sum score, SCL-90-R GSI and VAS sexual satisfaction score. In addition, to address possible associations between changes in clinical parameters and psychological variables, correlations were computed using Pearson’s r and Spearman’s rho for correlations with dichotomous or non-normally distributed variables, carried out on data from the entire sample of patients. Finally, to compare different patient subgroups at fixed time points (i.e. patients with normalized menstrual cycle versus those with remaining menstrual cycle irregularities following 6 months of treatment), comparisons of means were carried out using independent samples t-tests.

For validated questionnaires (SF-36, SCL-90-R), comparisons with the female German norm (controls) were carried out using independent sample t-tests at baseline (PCOS pretreatment versus controls) and following 6 months of treatment (PCOS 6 months versus controls).

Standard effect sizes (SES) were computed as described previously [d = (Mpre – Mpost)/SDpre] (Kazis et al., 1989). For dichotomous socio-demographic and clinical parameters, McNemar tests for frequency distributions were calculated. An alpha level of <0.05 was considered statistically significant for all analyses.

Results

Participants

Complete data sets were available for 64 PCOS women. Of untreated PCOS women at baseline (mean age 29.31 ± 6.3 years), 24 patients were single, 2 had a partner, 3 were divorced and 35 married. Ten women had children, whereas 54 PCOS patients were without children (84.4%). Of the latter, 40 patients (62.5%) mentioned that they wished to conceive a child. Forty-six women of the PCOS study population (71.9%) felt afraid of not being able to conceive. The majority of women were oligomenorrhoic (44 of 64, 67.8%), the rest were amenorrheic. Regarding clinical signs of hyperandrogenism, 34.4% of PCOS subjects presented with acne, 20.3% with mild alopecia (Ludwig Score <2) and 64.1% with hirsutism. Of the 41 hirsute women, 13 women had an FG-Score between 7 and 10, 20 women had a score between 10 and 15 and 8 patients had scores greater than 15. The median FG-Score of the PCOS cohort was 9. Elevated total testosterone levels were found in 84.4% (median: 2.4 nmol/l) and elevated androstendione levels in 66.7% (median: 4.1 nmol/l). Polycystic ovaries, defined by the ESHRE/ASRM criteria, were diagnosed in 46 women (71.8%). Of the 64 PCOS-subjects, 17 (26.5%) were lean, 16 patients (25%) were overweight with a BMI between 25 and 29.9 kg/m² and 31 women (48.5%) were obese. In the obese group, four women (6.3% of the total study population) had a BMI between 30.0 and 34.9 kg/m², 14 patients (21.9%) had a BMI between 35.0 and 39.0 kg/m² and 13 women (20.3%) had a BMI > 40 kg/m². Insulin resistance (HOMA-IR > 2.5) was diagnosed in 44 women (68.7%) (median HOMA-IR: 2.9). This sample was comparable with regard to the clinical, endocrine and metabolic characteristics to a larger sample of German PCOS patients, which we have recently described in detail (Hahn et al., 2005b).

Effects of metformin treatment on clinical and biochemical parameters

Use of metformin was associated with a significant decrease in insulin resistance measured by HOMA-IR (4.0 ± 3.6 to 2.4 ± 1.7,
decreased from 31.7 ± 5.2 to 5.8 ± 3.8 (P = 0.0355). Normal testosterone levels were achieved in 54.7% of PCOS patients. FAI decreased significantly from 8.6 ± 5.2 to 5.8 ± 3.8 (P = 0.0355). Metformin therapy also resulted in a reduction of hyperinsulinaemia, shown by a decrease in AUC-1 (317.7 ± 242.0 to 220.2 ± 121.0; P < 0.0001). The reduction in BMI was small (mean decrease: 1.1 kg/m²) but statistically significant (P = 0.003). Mean BMI decreased from 31.7 ± 9.0 kg/m² (BW: 89.5 ± 27.1 kg) at baseline to 30.6 ± 9.0 kg/m² (BW: 85.7 ± 25.8 kg) after 6 months on metformin. No significant changes were observed in HOMA-β, fasting glucose levels, LH-to-FSH ratio and DHEAS levels during treatment (data not shown).

Menstrual cyclicity improved in more than half of the PCOS women studied. After 6 months, 33 patients (51.6%) had normal menstrual cycles (28–35 days), 29 patients (45.3%) were oligomenorrhoeic and 2 patients (3.1%) remained amenorrhoeic. Therapy with metformin led to a significant improvement in acne in 12 of the 22 affected women (P < 0.05). Androgenetic alopecia and hirsutism scores did not change significantly after 6 months of treatment. These data are consistent with previous findings (Hahn et al., 2004). No significant differences were found in partner status and the proportion of women with an unfulfilled wish to conceive (following omission of women who conceived during treatment) or women feeling afraid of not being able to have children after the study period. Of the 64 PCOS women enrolled in the 6-month trial, 36 were followed for another 6 months. However, no significant further improvements in clinical or biochemical parameters were found (data not shown), except for a significant improvement in the FG-Score of 8.3 ± 5.9 at the 12-month visit compared to baseline with 9.7 ± 6.7, P = 0.04.

Effects of metformin treatment on clinical parameters according to BMI at baseline

Subgroup analysis was performed of lean (I, n = 17), overweight (II, n = 16) and obese (III, n = 31) women before and after 6 months on metformin. In all three groups, testosterone levels decreased significantly (I: 2.6 ± 1.1 to 1.8 ± 0.7, II: 2.8 ± 0.9 to 2.1 ± 0.4, III: 2.8 ± 0.9 to 2.2 ± 0.9 nmol/l). Similar effects were found for FAI (data not shown). In addition, comparable improvement of menstrual disturbances (I: 100% with oligo/amenorrhea to 47.1%, II: 100 to 43.8%, III: 100 to 51.6%) and acne (I: 29.4 ± 11.7%, II: 43.8 ± 18.8%, III: 32.3 ± 22.5%) was also found in all BMI groups. Independent of BMI, alopecia and hirsutism did not improve significantly after 6 months of therapy. BW and BMI were only reduced significantly in overweight/obese (BMI 34.3 ± 6.9 to 32.8 ± 6.6 kg/m², P < 0.0001) but not in lean (BMI 21.1 ± 1.8 to 20.7 ± 1.9 kg/m²) PCOS women.

Treatment effects on quality-of-life

Prior to treatment, PCOS patients demonstrated significantly decreased quality-of-life, measured with the SF-36 when compared with the female German norm population (controls) (Elsenbruch et al., 2003), consistent with our previous findings. These decrements in quality-of-life were particularly pronounced in the psychological areas of quality-of-life, as evidence by significantly lower scores on the scales Vitality, Social Role Function, Emotional Role Function and Mental Health (Figure 1A). Accordingly, the Psychological Sum score was significantly lower in patients compared with controls (Figure 2). Lower scores were also found in some, but not all scales representing physical aspects of quality-of-life (Figure 1B), hence the Physical Sum score was not significantly different from controls (Figure 2).

To address the effects of treatment on quality-of-life, ANOVAs were computed to test for the presence of significant time effects. In response to treatment, significant time effects, indicating improvements, were found for the SF-36 scales Physical Role Function (F = 6.1, P = 0.005), General Health Perception (F = 3.8, P = 0.03), Vitality (F = 6.9, P = 0.003), Social Role Function (F = 4.6, P = 0.015) and the Psychological Sum score (F = 3.9, P = 0.029) (Figures 1 and 2). Treatment effects were clearly larger for the psychological than physical aspects of quality-of-life, which is also illustrated by the finding that the SES for the Physical Sum Scale was small (d = 0.04) compared with a large SES for the Psychological Sum Scale (d = 0.39).

Despite the significant improvements in quality-of-life following 6 months of treatment, quality-of-life remained significantly decreased in PCOS patients compared with the German norm, as evidenced by significantly lower scores for the majority of SF-36 scales (Figures 1 and 2).

Psychological disturbances

Prior to treatment, PCOS patients demonstrated significantly higher SCL-90-R scale scores, indicating greater psychological disturbances, in some of the questionnaire’s dimensions (i.e. Interpersonal Sensitivity, Depression, Aggression) when compared with the German norm (Figure 3). No differences were found for the remaining scales, as well as for two of the three global scores, i.e. the GSI (GSI: 0.53 ± 0.39 in PCOS versus 0.45 ± 0.42 for controls) and the PST (PST: 31.5 ± 17.1 in PCOS versus 26.6 ± 19.6 in controls). Only the PSDI differed significantly between groups (1.54 ± 0.85 in PCOS versus 1.36 ± 0.45 in controls, P < 0.05).

Significant treatment-related improvements in emotional well-being were evident for the scales Somatization (F = 5.9, P = 0.007), Obsessive–Compulsive (F = 9.0, P = 0.001), Interpersonal Sensitivity (F = 8.2, P = 0.002), Depression (F = 6.9, P = 0.003), Anxiety (F = 5.6, P = 0.01), Aggression (F = 5.2, P = 0.01), Phobia (F = 5.4, P = 0.01) and Psychoticism (F = 6.4, P = 0.005) (Figure 3). Consistent with the improvements on the primary scales, time effects were also found for the SCL-90-R’s global scales (GSI: F = 5.3, P = 0.014, PSDI: F = 3.2, P = 0.06, PST: F = 12.1, P = 0.0001). In agreement with the SF-36 data, the SCL-90-R’s global score (GSI) showed a large SES (d = 0.44), indicating that treatment of PCOS patients was effective in improving emotional well-being. Similar results were found for the PSDI (d = 0.4). Treated PCOS patients even demonstrated significantly lower scores, indicating reduced emotional distress, compared with the German norm, on two of the SCL-90-R scales (Anxiety, Phobia) (Figure 3).
**Sexual self-worth and sexual satisfaction**

Treatment significantly increased the frequency of sexual intercourse, especially the number of patients who reported more than 10 sexual contacts per month (Table I). In addition, following treatment, PCOS women were significantly more satisfied with their sex life ($F = 5.9$, $P = 0.006$), felt less pain during sexual intercourse ($F = 3.8$, $P = 0.032$) and reported a lowered impact of excessive body hair on sexuality ($F = 4.1$, $P = 0.023$) (Table I). On the other hand, no changes were observed in the importance of a satisfying sex life, the amount of sexual thoughts and fantasies, the perception of own sexual attractiveness and the feeling that there exist difficulties forming social contacts due to changes in outer appearance.

**Correlation between clinical and psychological variables during metformin treatment**

HRQL

In order to address possible associations between metformin-induced clinical and/or biochemical improvements and psychological changes, correlation was computed, and subgroups of patients with defined clinical improvements were compared. Initially, women who showed a normalization of menstrual disturbances following metformin treatment were compared with those with remaining a-/oligomenorrhoeic. The results revealed significant lower SF-36 scores, and thus lower quality-of-life, in a-/oligomenorrhoeic women, representing both physical and psychological aspects of HRQL (Physical Role...
Function, $P < 0.0001$; General Health Perception, $P < 0.01$; Physical Sum Scale, $P < 0.05$; Social Function, $P < 0.05$). In addition, effects of changes in BW were addressed with correlational analyses: change of BMI was significantly correlated with changes in the SF-36 scale General Health Perception ($r = 0.31$, $P = 0.042$). Reduction in BW (weight loss in kilograms) was correlated with changes in the dimensions Vitality ($r = 0.39$, $P = 0.008$), Mental Health ($r = 0.34$, $P = 0.026$) and the Psychological Sum Scale ($r = 0.32$, $P = 0.032$). For excessive body hair, no significant correlations were found between measures of HRQL and hirsutism score; although baseline hirsutism scores were significantly correlated with several SF-36 scales (Pain: $r = -0.29$, $P < 0.01$; General Health Perception: $r = -0.26$, $P < 0.01$; Physical Sum scale: $r = -0.48$, $P < 0.001$). Patients with acne presented with lower HRQL in the SF-36 subscale Pain ($P < 0.05$). No correlation was found between acne and other HRQL scales. Furthermore, alopecia, androgen levels and parameters of insulin resistance had no impact on either basal or changes in quality-of-life in PCOS women.

### Psychological disturbances

Before metformin treatment, hyperandrogenism, measured by elevated total testosterone, was correlated with the SCL scales Somatization ($r = 0.42$, $P = 0.008$) and Obsessive-Compulsive ($r = 0.38$, $P = 0.017$). Normalization of androgen levels correlated with the Obsessive-Compulsive scale ($r = -0.40$, $P = 0.013$). Interestingly, neither obesity, menstrual irregularities, hirsutism score, acne, alopecia nor any other of the evaluated biochemical parameters were significantly correlated with psychological disturbances, measured with the SCL scales. The only exception was the SCL’s Somatization scale, which was significantly correlated with BMI ($r = 0.22$, $P < 0.05$) and hirsutism score ($r = 0.24$, $P < 0.05$) at baseline.

### Sexuality

At baseline, some dimensions of the VAS were correlated significantly with BMI, namely sexual attractiveness, pain during intercourse, difficulty making social contacts due to outer appearance and importance of a satisfying sex life. The occurrence
of hirsutism correlated with the VAS sexual satisfaction scales sexual attractiveness, impact of body hair on sex life and difficulty making social contacts due to appearance (data not shown). Menstrual cyclicity, acne, alopecia or biochemical parameters, especially androgens, were not related to parameters of sexuality measured by VAS.

**Psychological changes in PCOS-symptom subgroups**

To address the possibility that changes in psychological variables differed according to presence and/or degree of specific PCOS symptoms, patients were divided into subgroups in relation to the main syndrome features, i.e. obesity, hirsutism, acne, unfulfilled wish to conceive and insulin resistance as measured at baseline prior to treatment. In these subgroups, changes in psychological variables over time were analysed using 2-way ANOVA to test for interactions between the factors group and time, carried out for the key psychological variables. Several baseline differences in psychological variables were observed in the symptom subgroups, consistent with our recent report specifically addressing the association between psychosocial functioning and PCOS clinical features in a larger sample of untreated patients (Hahn et al., 2005a). Briefly, in the present sample of untreated patients, psychological aspects of quality-of-life (SF-36 Psychosomatic Sum score), psychological well-being (SCL-90-R GSI) and sexual satisfaction (VAS scale) were reduced in obese patients when compared with lean patients (and accordingly in patients with insulin resistance), and were also diminished according to degree of hirsutism and the presence of acne (data not shown). In addition, physical quality-of-life was reduced in obese patients compared with overweight and lean PCOS patients as well as in patients with insulin resistance. Patients with an unfulfilled wish to conceive had improved psychological quality-of-life and sexual satisfaction compared with those with no current wish to conceive, which we have previously attributed to a better partnership situation of these patients (Hahn et al., 2005a). Despite these baseline differences between clinical symptom subgroups, significant ANOVA time effects were found for the majority of key psychological variables, indicating significant improvements over time irrespective of subgroup (ANOVA time effects for analysis of acne subgroups: for SF-36 Physical Sum score \( P = 0.014 \), for GSI \( P = 0.011 \), for VAS sexual satisfaction \( P = 0.008 \); ANOVA time effects for analysis of BMI subgroups: for SF-36 Psychological Sum score \( P = 0.024 \), for GSI \( P = 0.023 \), for VAS sexual satisfaction \( P = 0.023 \); ANOVA time effects for analysis of hirsutism subgroups: for SF-36 Psychological Sum score \( P = 0.053 \), for GSI \( P = 0.008 \), for VAS sexual satisfaction \( P = 0.014 \); for subgroups created based on current wish to conceive: for SF-36 Psychological Sum score \( P = 0.06 \), for GSI \( P = 0.017 \), for VAS sexual satisfaction \( P = 0.015 \); ANOVA time effects for analysis of insulin resistance subgroups: for SF-36 Psychological Sum score \( P = 0.035 \), for GSI \( P = 0.015 \), for VAS sexual satisfaction \( P = 0.013 \). Interactions of group and time were observed only for the ANOVA analysis of BMI subgroups for the variable SF-36 Physical Sum score \( P < 0.05 \) with improved scores only in the obese subgroup.

**Discussion**

Recently, evidence of psychosocial distress and decrements in quality-of-life both in treated and untreated samples of patients with PCOS has accumulated. Thus far, little attention has been paid to treatment status in studies on psychological issues in PCOS. Except for one recent report on the effects of glitazone treatment (Guyatt et al., 2004), little is known with regard to the sensitivity of psychological variables to treatment. Our own previous findings describing emotional distress and decrements in quality-of-life in German PCOS patients included only untreated patients (Elsenbruch et al., 2003; Hahn et al., 2005a). We now present the first report on the effects of treatment

| Table I. Frequency of sexual intercourse, sexual self-worth and sexual satisfaction in polycystic ovary syndrome (PCOS) women before (PCOS 0) and after 6 months treatment (PCOS 6) |
|--------------------------------------------------|-----------------|-----------------|--------|
| Frequency of sexual intercourse during the past 4 weeks<sup>a</sup> | % (n) | % (n) | \( P \) |
| 0 times | 20.3 (13) | 12.5 (8) | |
| 1–5 times | 45.4 (29) | 35.9 (23) | |
| 5–10 times | 23.4 (15) | 29.7 (19) | |
| >10 times | 10.9 (7) | 21.9 (14) | |
| During the past 4 weeks<sup>b</sup> | \( M \) (SD) | \( M \) (SD) | |
| How satisfied were you with your sex life? | 47.8 (28.8) | 57.8 (27.2) | 0.006 |
| How many sexual thoughts and fantasies did you have? | 49.9 (25.7) | 49.9 (26.3) | NS |
| In general<sup>b</sup> | \( M \) (SD) | \( M \) (SD) | |
| How important is a satisfying sex life for you? | 75.1 (22.5) | 63.8 (23.3) | NS |
| Do you find yourself sexually attractive? | 36.5 (27.1) | 41.7 (26.8) | NS |
| How much does excessive body hair impact your sexuality? | 41.9 (34.7) | 36.9 (32.5) | 0.023 |
| How often do you experience pain during intercourse? | 20.4 (25.0) | 14.4 (19.8) | 0.032 |
| Does your appearance make it difficult to form social contacts? | 29.9 (30.8) | 21.8 (27.3) | NS |

<sup>a</sup>Significant change in frequency distribution over time: \( P = 0.01 \) Wilcoxon ranked sign test.

<sup>b</sup>Assessed with 100 mm visual analogue scales (minimum: ‘not at all’ = 0 mm, maximum: ‘very much/very often’ = 100 mm); data shown as mean (\( M \)) and SD in mm. \( P \) values show significant time effects of repeated measures analysis of variance (for \( F \) values, see text); NS, not significant.
on psychosocial and psychosexual variables in PCOS and show marked improvements in quality-of-life, emotional distress and sexual satisfaction following treatment. These data would suggest that the psychosocial aspects of PCOS are in fact influenced by treatment status, which should be taken into account in future studies. However, the results of our study must be interpreted with caution, as it was not a placebo-controlled randomized trial. All our patients were treated with the insulin sensitizer metformin, which has become a standard treatment option in PCOS. Using a placebo for a control group would have thus implied denial of an effective and safe therapy. We further did not compare against oral contraceptives, as the majority of patients wished to conceive. Hence, based on our data, it is not possible to evaluate the effects of metformin itself or to separate placebo from treatment effects. Clearly, our results must be interpreted with caution, and in addition to placebo effects and non-specific effects of the entire medical setting, either a direct effect of medication on psychological status is conceivable, or indirect effects via modifications of hormonal and metabolic abnormalities, as previously described (Velazquez et al., 1994; Diamanti-Kandarakis et al., 1998).

However, we also observed some interesting associations between clinical treatment effects and psychological improvements, which suggest that some of the effects may be related to the clinical effects of metformin. For example, changes in BW were significantly correlated with improvements in psychological aspects of HRQL. This finding is consistent with previous data from our group (Hahn et al., 2005a) as well as from others (Hashimoto et al., 2003; Mccook et al., 2005; Trent et al., 2005), showing that obesity is a primary mediator of decrements in HRQL in PCOS. Together with the present data, these results would suggest that weight reduction is a primary goal in PCOS, not only in the context of lowering the long-term health risks associated with obesity but also to improve psychosocial well-being and quality-of-life in afflicted patients. Further studies should address whether obese PCOS patients may also benefit from lifestyle programmes aimed at weight reduction in addition to pharmacological treatment.

In addition, we observed that normalization of menstrual cycle disturbances following treatment was associated with improved HRQL. A negative impact of menstrual problems on quality-of-life has previously been discussed by others (Mccook et al., 2005) and is consistent with the notion that PCOS patients suffer from a ‘loss of feminine identity’ (Kitzinger and Willmott, 2002). Hence, amelioration of this key symptom of PCOS (which may obviously also be achieved by other treatments) can clearly contribute to an improvement of the psychological situation of afflicted women. In addition, in our PCOS cohort, higher frequencies of sexual intercourse and greater satisfaction with sex life were observed following treatment. Whether these were related to a normalization of elevated androgen levels, reflect greater sexual motivation due to improved emotional well-being, or an increased hope and effort to become pregnant remains unclear. Nevertheless, in the context of infertility problems in PCOS, an increase in sexual intercourse frequency along with improved sexual satisfaction is an interesting finding. Clearly, the association between clinical and biochemical abnormalities, mood dysfunction and sexual (dys)functions in PCOS should be explored in future studies.

To further address the possibility that changes in psychological variables differed according to the presence and/or degree of specific PCOS symptoms, additional analyses were completed with subgroups of patients created in relation to the main syndrome features, including subgroups with obesity, hirsutism, acne, unfulfilled wish to conceive or insulin resistance. Together, these data showed differences in psychological functioning according to the presence and/or degree of specific PCOS symptoms both prior to and following treatment. However, the lack of consistent evidence of interactions between subgroup and treatment response in psychological parameters suggests that psychological improvement during treatment was present in all PCOS symptoms subgroups, although the extent of this effect differed somewhat according to symptom constellation. Clearly, our approach to address the important issue of PCOS symptom subgroups was limited by the fact that we created subgroups on the basis of the presence or absence of individual clinical symptoms at baseline, when in reality patients present with various combinations of PCOS symptoms, and each individual clinical symptom may show different treatment-induced improvements. Clearly, it is conceivable that it is in fact the combination of clinical symptoms which is critical for treatment-related improvements in psychosocial functioning. Unfortunately, it is exceedingly difficult (and impossible given our sample size) to discern the role of (1) pretreatment symptom constellation and (2) treatment-induced changes in symptom constellation, in psychological improvements. Nevertheless, overall it is evident that subgroups of PCOS patients with more pronounced decrements in quality-of-life and increased emotional distress exist (Elsenbruch et al., 2006), and it is likely that psychosocial functioning is at least in part determined by the presence and extent of specific symptoms and/or symptom combinations. Although patients with more pronounced psychosocial distress may benefit more from medical treatment also at the psychological level, further studies are needed to discern the role of the PCOS syndrome features in both clinical and psychological treatment responses. Taken together, in this observational study, we document that during treatment with metformin, significant improvement of HRQL, emotional well-being and sexual satisfaction are observed in PCOS women. However, even in treated patients, HRQL remains reduced, which may be related to the persistence of individual clinical symptoms such as hirsutism and the unfulfilled wish to conceive. On the contrary, in treated PCOS patients, all SCL-90-R scales improved to normal or even better levels compared with the control population. Hence, emotional distress and psychological disturbances are not an inevitable consequence of the diagnosis. While PCOS is associated with decreased sexual self-worth and self-esteem and feelings of stigmatization due to changes in outer appearance, the present data suggest for the first time that treatment may reduce these problems, possibly by inducing weight loss and ameliorating menstrual irregularities as well as acne. However, the present study is not a placebo-controlled, double-blind treatment trial, which precludes any definite conclusions with regard to the question whether and to what extent the observed
improvements are related to metformin treatment itself. Clearly, several factors other than metformin are likely to have contributed to the observed effects, including the treatment situation per se and non-specific effects of attention. Traditional PCOS therapies based on oral contraceptives or clomiphene are judged unsatisfactory by most women (Sills et al., 2001), who visit on average 4.5 physicians before the PCOS diagnosis is reached (Cecchini, 2001). Confirmation of the diagnosis, provision of detailed information on PCOS, together with the availability of metformin as a new therapeutic modality with well-established clinical benefits in a specialized, interdisciplinary clinical setting would be expected to have positive psychological effects. Clearly, the present data call for further study. Clinically, it would be important to improve physicians’ knowledge and awareness regarding ways to identify and address psychological problems in PCOS women; scientifically, to integrate psychological and psychosexual variables as well as quality-of-life issues as adjunct treatment goals.

References


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