Health related quality of life among different PCOS phenotypes of infertile women

İnfertil PKOS fenotipleri arasında sağlıkla ilişkili hayat kalitesi

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Abstract

Objective: The aim of this study was to evaluate the clinical features and health quality profile differences between infertile women with polycystic ovary syndrome (PCOS) phenotypes and women with unexplained infertility.

Material and Methods: The WHOQOL-BREF were administered in a cross-sectional survey to 132 women diagnosed with PCOS (study group) and 32 women diagnosed with unexplained infertility (control group). Body mass index (BMI), duration of infertility (DOI), type of infertility (TOI) and Ferriman Gallwey scores (FG scores), were compared between the study and control groups and between different phenotype groups of PCOS: Group 1-Hyperandrogenemia (HA)-anovulation (N=34), Group 2-HA-PCO (ovulatory PCOS, (N=34), Group 3-PCO-anovulation (N=32), and Group 4-HA-PCO-anovulation (N=32) and the associations of these parameters with the health quality profile were analyzed.

Results: Physical, Spiritual and Environmental scores were significantly lower (p<0.05) in Group 1 patients (HA-AO) in comparison to the other three PCOS groups and the control group, while the same difference was observed in the social scores with a near significance (p=0.05). Linear regeression analyses revealed significant associations between type of infertility (beta coefficient: -0.423, p=0.001), FG score (beta coefficient: -0.177, p=0.016), phenotype 1 (beta coefficient: -0.236, p=0.002) and physical scores. Psychological scores were associated with the type (beta coefficient: -0.641, p=0.001) and duration (beta coefficient: -0.149, p=0.009) of infertility. Scores in the social area were only associated with type of infertility (beta coefficient: -0.443, p=0.001). Scores of environmental area were significantly associated again with the type of infertility (beta coefficient: -0.499, p=0.001) and FG scores (beta coefficient: -0.195, p=0.008). Primary infertility was a risk factor for low physical (odds ratio: 8.100, 95% CI: 3.827-17.142), social (odds ratio: 9.183, 95% CI: 4.084-20.648) and environmental (odds ratio: 9.966, 95% CI: 4.623-21.468) scores determined according to the median level.

Conclusion: FG scores, primary infertility and phenotype 1 PCOS were associated with lower health quality of life scores. Infertile women with Phenotype 1 (HA-AO) had the lowest scores.

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Key words: Health related quality of life, polycystic ovary syndrome, phenotypes, unexplained infertility, hirsutism

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Özet

Amaç: Bu çalışmanın amacı polikistik over sendromu olan infertil kadınlar ile açıklanamayan infertilitesi olan kadınlar arasında klinik özeliikler ve hayat kalite profilini karşılaştırmaktır.

Gereç ve Yöntemler: Polikistik over hastalığı tanısı alan 132 infertil hasta ve açıklanamayan infertilitesi olan 32 hastaya Dünya Sağlık Örgütü hayat kalitesi anketi kısa versiyonu uygulandı. Tüm hastalar arasında beden kitle indeksi, infertilite süresi, infertilite tipi, Ferriman Gallwey skoru gruplar arasında ve farklı PCOS fenotipleri arasında karşılaştırıldı. Fenotip grupları şu şekilde idi: Grup 1-Hiperandrojenemi (HA)-anovulasyon (N=34), Grup 2-HA-PCO (ovulatuar PCOS, (N=34), Grup 3-PCO-anovulasyon (N=32), and Grup 4-HA-PCO-anovulasyon (N=32). Bu parametrelerle hayat kalite skorunun ilişkisi irdelendi.

Bulgular: Fiziksel, Spiritual ve çevresel skorlar Grup 1 haslarda diğer PCOS gruplarına ve kontrol grubuna kıyasla anlamlı düşükken (p<0.05), aynı farklılık sosyal skorda daha düşük anlamlılıkla gözlendi (p=0.05). Lineer regresyon analiz sonucuna göre infertilite tipi (beta katsayısı: -0.423, p=0.001), FG skor (beta katsayısı: -0.177, p=0.016), grup1 (beta katsayısı: -0.236, p=0.002) ve fiziksel skorlar anlamlı ilişkili saptandı. Fiziksel skorlar infertilite tipi (beta coefficient: -0.641, p=0.001) ve süresi (beta coefficient: -0.149, p=0.009) ile anlamlı ilişkili idi. Sosyal alan skorları sadece infertilite tipi ile ilişkili saptandı (beta coefficient: -0.443, p=0.001). Çevresel alana ait skorlar yine infertilite tipi (beta coefficient: -0.499, p=0.001) ve FG skorları (beta coefficient: -0.195, p=0.008) ilişkili idi. Primer infertilite median değerlere göre saptanan düşük fiziksel (odds ratio: 8.100, 95% CI: 3.827-17.142), sosyal (odds ratio: 9.183, 95% CI:4.084 -20.648) ve çevresel (odds ratio: 9.966, 95% CI: 4.623-21.468) skorlar için risk faktörü olarak saptandı.

Sonuç: FG skoru, primer infertilite ve grup 1 PCOS düşük hayat kalite skoru ile ilişkilidir ve fenotip 1 grubundaki infertil hastalar en düşük değere sahiptir. (J Turkish-German Gynecol Assoc 2012; 13: 247-52)

Anahtar kelimeler: Sağlıkla ilişkili hayat kalitesi, polikistik over sendromu, fenotipler, açıklanamayan infertilite, hirsutizm

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Introduction

Polycystic ovary syndrome (PCOS) is a multifactiorial and polygenic pathology that manifests itself with a wide spectrum of signs and symptoms that are related to the disturbances of reproductive, endocrine, and metabolic functions. Thus, involvement of various organ systems at different degrees results in a heterogenous presentation of the disease (1). The diagnostic criteria defined for PCOS hava undergone several changes in recent years. While the clinical presentation of chronic anovulation and hyperandrogenism has been stressed as the major diagnostic criteria, the presence of normal ovulatory function in some women with PCOS has been acknowledged in recent years (2, 3). New diagnostic criteria were established in 2004, including all these three factors: presence of chronic anovulation, hyperandrogenism, and polycystic ovaries together, with a special emphasis placed on existence of polycystic ovaries on ultrasonography (4, 5). Polycystic ovary syndrome was diagnosed in the presence of two of the three diagnostic criteria. Using the possible combinations of these three criteria, four different phenotypes of PCOS are identified: hyperandrogenism (clinical or biochemichal) and chronic anovulation; hyperandrogenism and polycystic ovaries but with ovulatory cycles; and chronic anovulation and polycystic ovaries without clinical hyperandrogenism and hyperandrogenism, chronic anovulation and polycystic ovaries. At least 90% of women attending fertility clinics with failure to ovulate have PCOS (6). PCOS is associated with reduced quality of life (QoL) (7). The disorder is associated with biochemical disturbances that can lead to mood disturbances per se (8). Hirsutism, menstrual irregularity, acne and infertility have been shown to be the most distressing symptoms in adults with PCOS (9), while weight gain has been identified as the most distressing symptom in adolescents and young women with PCOS (10-12).

The aim of this study is to evaluate the clinical, endocrine, and health quality profile differences between the main PCOS phenotypes, and compare these findings with women with unexplained infertility in order to eliminate "infertility" as a major source of concern for the patients and indicate other factors that might affect the health quality profile.

Material and Methods

Among 500 women screened for presence of PCOS and found to have PCOS according to the Rotterdam Criteria, 34 consecutive patients from each phenotype were taken as the study group. Thirty-four patients with unexplained infertility were taken as the control group. Standardized screening was approved by the local Institutional Review Board, and signed written informed consent was obtained from all of the participants. According to the Rotterdam (5) criteria, PCOS was diagnosed when at least two of the following criteria were present: oligo/amenorrhea, clinical or biochemical hyperandrogenism, and PCO on ultrasonography. Other etiologies mimicking PCOS, like Cushing's syndrome, late onset adrenal hyperplasia or androgen-producing neoplasm, and thyroid dysfunction or hyperprolactinemia were considered as exclusion criteria. Patients who had taken any

medication during the previous 3 months were excluded from the study. Menstrual cycle length shorter than 24 days and longer than 34 days were recorded as abnormal. Oligomenorrhea was diagnosed in patients with cycles longer than 35 days intervals, and amenorrhea was determined as the absence of menstruation for at least 6 months. Anovulation was defined as having a serum progesterone of <3 ng/mL on day 21-24 of the menstrual cycle with normal base-line hormonal values. Primary infertility was defined as failure to become pregnant after at least one year of unprotected intercourse, while secondary infertility refers to women who have been pregnant at least once but failed to conceive after at least one year of unprotected intercourse. Polycystic ovarian morphology was established using the criteria of ten or more peripheral follicular cysts 8mm in diameter or less in one plane along with increased central ovarian stroma, based on the Rotterdam-PCOS criteria (4). Women with unexplained infertility after at least one year of unprotected regular sexual intercourse were included in the study as the control group. All the patients in the control group had patent fallopian tubes detected by hysterosalpingography and/or laparoscopy, normal ovulation confirmed by a midluteal progesterone level more than 3 ng/mL and normal hormonal profile (follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol (E2) and thyroid stimulating hormone (TSH) in the early follicular phase. All the male partners had normal semen analysis according to WHO criteria (13).

Medical history regarding age, race, menstrual cycle pattern, personal and family medical history, type and duration of infertility, any previous or current use of medication, the presence of acne, and hirsutism were recorded. Body mass index (BMI), waist, and hip circumferences were recorded. Basal FSH, LH and E2 levels were measured on day-3 of the menstrual cycle. Progesterone levels were measured on the 21st day of the cycle. Hirsutism was established by using the Ferriman-Gallwey score ($\geq$7) (14). The BMI and hirsutism scores were assessed by a single investigator for all of the subjects.

Transvaginal ultrasonography was systematically performed by the same investigator using the 7.5 MHz transvaginal probe to a logic ultrasound system. Antral follicles were measured in three dimensions, and those with a mean diameter of 2-9 mm counted.

Four different phenotypes were defined as follows: Group 1-Hyperandrogenemia (HA)-anovulation, Group 2-HA-PCO (ovulatory PCOS), Group 3-PCO-anovulation, and Group 4-HA-PCO-anovulation.

Patients in all groups filled in WHOQOL-BREF (Turkish short version) at the Infertility Department of Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital between September 2010 and March 2011. Four-dimensional quality of life scales were calculated: 1-Physical, 2-Spiritual, 3-Social and 4-Environmental. Subjects were selected without intention to balance groups. Sample size was calculated with 95% CI and 80% power according to the previous study by Guestella et al. (15). WHOQOL-BREF is the abbreviated version of the original WHOQOL instrument. While the long form includes 100 items, WHOQOL-BREF has 26 items with a five point Likert type response scales-generic QoL instrument. It was developed

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by WHO as a multilingual, multidimensional profile of QoL for crosscultural use (16, 17). WHOQOL was adapted to more than 40 cultures in the world. WHOQOL-BFEF has four broad domains namely: Physical, Psychological, Social Relations and Environmental domains. The instrument assesses satisfaction with life as well as the impact of disease or illness, and it captures positive and negative aspects of QoL. WHOQOL is a profile which has a good underlying theoretical conceptualisation of Qol 22. It was validated for Turkish by Eser et al. (18).

Statistical Analysis

The statistical analyses were performed using the Statistic Package for Social Sciences (ver. 11.0; SPSS Inc., Chicago, IL). For group comparisons, analysis of variance and posthoc Tukey test was used. Binary logistic regression was used to calculate the odds ratio. Correlation analysis was used to calculate degree of associations and linear regression analysis was used to determine associations. The Chi square test was used for categorical variable comparisons. ANCOVA was used for statis-

tical adjustment. A P value smaller than 0.05 was accepted as statistically significant.

Results

Out of 170 patients recruited to the study; two patients from Group 3 and Group 4 and two patients from the control group were lost to follow-up. Overall, 164 patients with primary (N:66, 40.2%) and secondary (N:98, 59.7%) infertility were recruited to the study. One hundred and thirty-two patients had PCOS while 32 patients were in the control group. The distribution of 132 patients in PCOS phenotypes were as follows: Group 1: 34, Group 2: 34, Group 3: 32, Group 4: 32 patients. The distribution of age, duration of infertility, BMI, F/G score, WHOQOL-BREF (Turkish short version) scala is given in Table 1.

Group comparisons

The age, duration of infertility, BMI, distribution of types of infertility were similar in the study and control groups (p>0.05).

Table 1. The distribution of age, duration of infertility, BMI, F/G score, WHOQOL- BREF (Turkish short version) scala in PCOS phenotypes and in women with unexplained infertility (Control group)

			PCOS Phenotypes				p values
		Group 1 HA-AO N=34	Group 2 HA-PCO N=34	Group 3 PCO-AO N=32	Group 4 HA-PCO-AO N=32	Control N=32	
Age		24.9±2.6	25.7±2.4	25.3±2.9	24.9±2.7	25.2±2.7	0.78
Duration of infertility		3.2±1.26	3.26±1.6	3.19±1.5	3.19±1.5	3.25±1.5	1.00
Type of Infertility	Primary	9	16	12	15	14	0.38
	Secondary	25	18	20	17	18	
Ferriman-Gallwey Scores		15.8±2.8	13.9±2.2	5.6±1.9	14.9±1.9	5.2±1.9	0.00
BMI		29.7±4.2	27.9±4.5	27.5±4.1	28.6±4.2	27.7±4.0	0.20
Physical Scores		14.2±2.4	16.2±2.2	16.1±1.9	16.1±1.9	16.6±1.7	0.00
	BMI Adjusted	14.3±0.3	16.3±0.3	16.0±0.3	16.1±0.3	16.5±0.3	0.00
	F/G Adjusted	15.4±0.48	17.0±0.39	14.5±0.5	17.1±0.4	14.9±0.5	0.00
	BMI+F/G Adjusted	15.6±0.4	17.0±0.3	14.4±0.5	17.1±0.4	14.8±0.5	0.00
Spiritual Scores		13.8±2.3	15.1±2.2	14.8±2.2	14.9±2.3	15.2±2.5	0.10
	BMI Adjusted	13.9±0.4	15.1±0.4	14.7±0.4	14.9±0.4	15.2±0.4	0.191
	F/G Adjusted	14.9±0.5	15.7±0.4	13.5±0.6	15.7±0.5	13.9±0.6	0.06
	BMI+F/G Adjusted	14.9±0.5	15.7±0.4	13.5±0.5	15.7±0.5	13.9±0.6	0.07
Social Scores		14.5±3.2	15.8±3.1	15.7±2.9	16.2±2.5	16.5±2.5	0.05
	BMI Adjusted	14.5±0.5	15.2±0.5	15.7±0.5	16.1±0.5	16.5±0.5	0.08
	F/G Adjusted	15.6.0±0.6	16.2±0.8	14.3±0.8	17.3±0.5	15.4±0.5	0.06
	BMI+F/G Adjusted	15.6±0.6	16.5.0±0.5	14.3±0.7	17.1±0.6	15.0±0.7	0.07
Environmental Scores		13.1±2.4	14.3±2.3	14.6±1.9	14.5±1.9	15.3±2.3	0.01
	BMI Adjusted	13.2±0.3	14.2±0.3	14.6±0.5	14.5±0.4	15.1±0.6	0.03
	F/G Adjusted	14.2±0.5	14.9±0.4	14.6±0.3	14.5±0.3	15.0±0.3	0.02
	BMI+F/G Adjusted	14.2±0.5	14.9±0.5	13.3±0.5	15.3±0.5	13.6±0.6	0.09

BMI: Body mass index, F/G: Ferriman Gallwey, HA: Hyperandrogenemia, PCO: Polycystic ovary, AO: Anovulation

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Ferriman-Gallwey scores were statistically significantly higher in Group 1, Group 2 and Group 4 patients in comparison to Group 3 patients (PCOS-AO) and the control group. Physical, Spiritual and Environmental scores were significantly lower (p<0.05) in Group 1 patients (HA-AO) in comparison to the other three groups and control group. Adjusted and unadjusted means among groups were shown in Tables 1 and 2.

Comparison of Categorical variables

Group 1 phenotype was compared to other phenotypes according to the rates of low scores: There were 23 (67%) low physical scores in Group 1 and 52 (40%) in others. The low physical scores were 41% in Group 2 (N:14), 43% in Group 3 (N:14), 45% in Group 4 (N:13) and 34% in the Control Group (N:11) (p=0.004). There were nineteen (59%) low social scores in Group 1 and 48 (35%) in others (p=0.045). Low environmental scores were observed in 22 (69%) subjects in Group 1 and 58 (43%) in others (p=0.037). Although spiritual scores were lower in Group 1 in comparison to the other groups, the difference was not statistically significant.

Correlations

Type of infertility (r=-0.464, p<0.001), FG scores (r=-0.318, p<0.001), BMI (r=-0.245, p=0.002) and phenotype of PCOS (r=0.300, p<0.001) were significantly correlated with physical scores. Type of infertility was significantly correlated with psychological scores (r=-0.677, p<0.001). Type of infertility (r=-0.462, p<0.001) and phenotype (r=0.215, p=0.006) were correlated with social scores. Type of infertility (r=-0.531,

p<0.001), phenotype (r=0.246, p=0.001) and FG scores (r=-0.274, p<0.001) were correlated with environmental scores.

Regression analyses

Linear regression analyses revealed significant association between type of infertility (beta coefficient: -0.423, p=0.001), FG score (beta coefficient: -0.177, p=0.016), phenotype 1 (beta coefficient: -0.236, p=0.002) and physical scores. Psychological scores were associated with the type (beta coefficient: -0.641, p=0.001) and duration (beta coefficient: -0.149, p=0.009) of infertility. Scores in the social area were only associated with the type of infertility (beta coefficient: -0.443, p=0.001). Scores of environmental area were significantly associated again with type of infertility (beta coefficient: -0.499, p=0.001) and FG scores (beta coefficient: -0.195, p=0.008)

Odds ratios

Primary infertility was a risk factor for low physical (odds ratio: 8.100, 95% CI: 3.827-17.142), social (odds ratio: 9.183, 95% CI: 4.084-20.648) and environmental (odds ratio: 9.966, 95% CI: 4.623-21.468) scores determined according to the median level.

Discussion

Polycystic ovary syndrome has diverse clinical manifestations that affect the reproductive life (infertility, anovulation, hypernadrogenism) and metabolic features (insulin resistance, impaired glucose tolerance, increased cardivascular disease risk, type 2 diabetes mellitus). The adverse impact of this heterogenous condition on psychological features (increased anxiety, depression and worsened quality of life) has become a new area of research in the last decade (19). The common manifestations of PCOS; infertility, obesity, acne, hirsutism, menstrual irregularities have a negative impact on mood and psychological status. Depression, anxiety, negative body image and psychosexual dysfunction are the most common exacerbations of the negative impact of PCOS on the quality of life (20). Infertility is related with impaired health-related quality of life. A review of 14 studies that investigated the effect of infertility on QoL and health-related quality of life (HRQOL) among infertile women and men revealed that infertile women had more impaired QOL and HRQOL and lower scores in several QOL and HRQOL domains; mainly mental health, social functioning and emotional behaviour in comparison to men (21). A Turkish study on infertile couples revealed that, while physical and psychological health and social relations domain score was similar in infertile men and women; the quality of life in the environmental domain was greater in infertile women when compared to that of infertile men (22). Variables affecting quality of life of infertile individuals were found to affect women and men in similar ways. The authors stressed the importance of awareness of the factors that affect quality of life of the patients among nurses and health care professionals. In our study, the main aim was to analyze the health quality scores of infertile women with and without PCOS and the differences between 4 PCOS phenotypes. We have selected a group of infertile subjects with similar socioeconomical, educational status and

Table 2. The distribution of physical, spiritural, social, enviromental scores in infertility types

		Type of İnfertility		
		Primary N=66	Secondary N=98	p values
Physical		15±2.2	17.1±1.5	0.00
	BMI Adjusted	15.0±0.2	17.0±0.1	0.00
	F/G Adjusted	15.0±0.1	17.0±0.1	0.00
	BMI+F/G Adjusted	15.0±0.1	17.0±0.1	0.00
Spiritual		13.4±0.2	16.7±1.1	0.00
	BMI Adjusted	13.5±0.1	16.7±0.2	0.00
	F/G Adjusted	13.5±0.1	16.7±0.2	0.00
	BMI+F/G Adjusted	13.5±0.1	16.7±0.2	0.00
Social		14.6±2.9	17.4±2.1	0.00
	BMI Adjusted	14.6±0.3	17.4±0.2	0.00
	F/G Adjusted	14.6±0.3	17.3±0.2	0.00
	BMI+F/G Adjusted	14.9±0.3	17.3±0.2	0.00
Environmental		13.3±2.0	15.8±1.7	0.00
	BMI Adjusted	13.4±0.1	15.7±0.2	0.00
	F/G Adjusted	13.6±0.1	15.7±0.2	0.00
	BMI+F/G Adjusted	13.6±0.1	15.7±0.2	0.00

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tried to establish homogenous groups according to the known parameters affecting the tests.

In a a recent study by Greil et al. (23), it was stated that, while both primary and secondary infertility is related to fertility specific stress, women with primary infertility are particularly distressed and caregivers should address their emotional needs. Consistent with this result, we have shown that primary infertile individuals differ from secondary infertile women according to their life quality scores. In the presented study, especially the primary infertile women in both PCOS groups and the control group of women with unexplained infertility were found to be under significant distress compared to women with secondary infertility.

In our study, the health quality scores were similar among the 3 PCOS groups and unexplained infertile patients except for the PCOS phenotype 1 that presents itself with clinical hyperandrogenemia and menstrual abnormalities. Phenotype 1 patients, who had significantly higher BMI and FG scores in comparison to the other pheotypes, also showed significant score differences in the WHOQOL-BFEF that can be attributed to these differences. BMI and FG adjusted mean scores were found to be similar among all groups except for physical scores. A recent study form Turkey comparing the psychological health of 226 PCOS patients with 85 BMI-adjusted healthy controls found 8.1 fold increased depression scores in PCOS patients and, similar to our study, menstrual problems and hirsutism were reported to be the most severe concerns on the HRQOL followed by emotional problems (24).

Life quality scores have been studied in several groups of subjects including PCOS patients. However, the presented study is a pioneering study that evaluates the WHOQOL-BFEF scores in infertile subjects with and without the diagnosis of PCOS, and the variations of WHOQOL-BFEF score among different phenotypes of PCOS. A previous study investigated the depression, anxiety scores and quality of life of PCOS subjects before and after laser treatment of hirsutism and compared them to the control group. The study concluded that laser treatment appeared to reduce the severity of facial hair, resulting in improvement of depression and anxiety scores and psychological quality of life in women with PCOS (25). Our results support the idea that FG scores and health related quality of life are interrelated especially in the physical domain.

Kumarapeli et al. compared the scores of women with PCOS with the control group, and they concluded that PCOS occurring in South Asians adversely affected their psychological well-being and health related quality of life. The psychological distress in South Asians was found to be related to hirsutism rather than to obesity, contrary to the white European women with PCOS (26). In our study we also did not find a direct relation between BMI and scores and the presence of hirsutism was a prominent factor affecting quality of life.

Sundararaman et al. applied the "Goldberg's General Health Questionnaire" (GHQ 28) to PCOS subjects in order to assess the psychological status. The authors stated that women presenting with PCOS had increased psychological distress, which was related to the severity of physical manifestations of the condition, such as hirsutism, obesity and increased waist circumference (27).

Obese subjects were found to have lower physical and psychological scores when compared with the healthy population reference group in some studies. Pan et al. suggested that obesity can cause impaired HRQOL, that can be improved through body weight loss intervention (28). Obesity and health related quality of life were assessed in non-pregnant Turkish women aged betwen 15-49. The authors repoted that, after adjusting for age, level of education and co-morbid illnesses, subjects with a BMI higher than normal value had significantly lower HRQOL scores, compared to normal-weight individuals on each of the domains, except for the environmental domain. The study results suggested that the body weight alone could negatively affect HRQOL. In conclusion, body weight should also be controlled in studies examining HRQOL (29). Therefore in the current study, the means were compared after adjustment for FG, BMI and FG-BMI.

While managing PCOS, the psychological issues accompanying this multifaceted disease should not be underestimated and a special multi-disciplinary approach is crucial.

The weakness of the present study is the limited number of subjects in each phenotype of PCOS and the lack of evidence to explain why phenotype 1 had lower physical scores after adjustment for BMI and FG score, because phenotype 4 with all the criteria for PCOS diagnosis did not differ from other phenotypes. Future studies with larger number of variables are needed to assess health quality of life in phenotype 1.

Conclusion

FG scores, primary infertility and phenotype 1 PCOS were associated with lower health quality of life scores in the physical domain.

Conflict of interest

No conflict of interest was declared by the authors.

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