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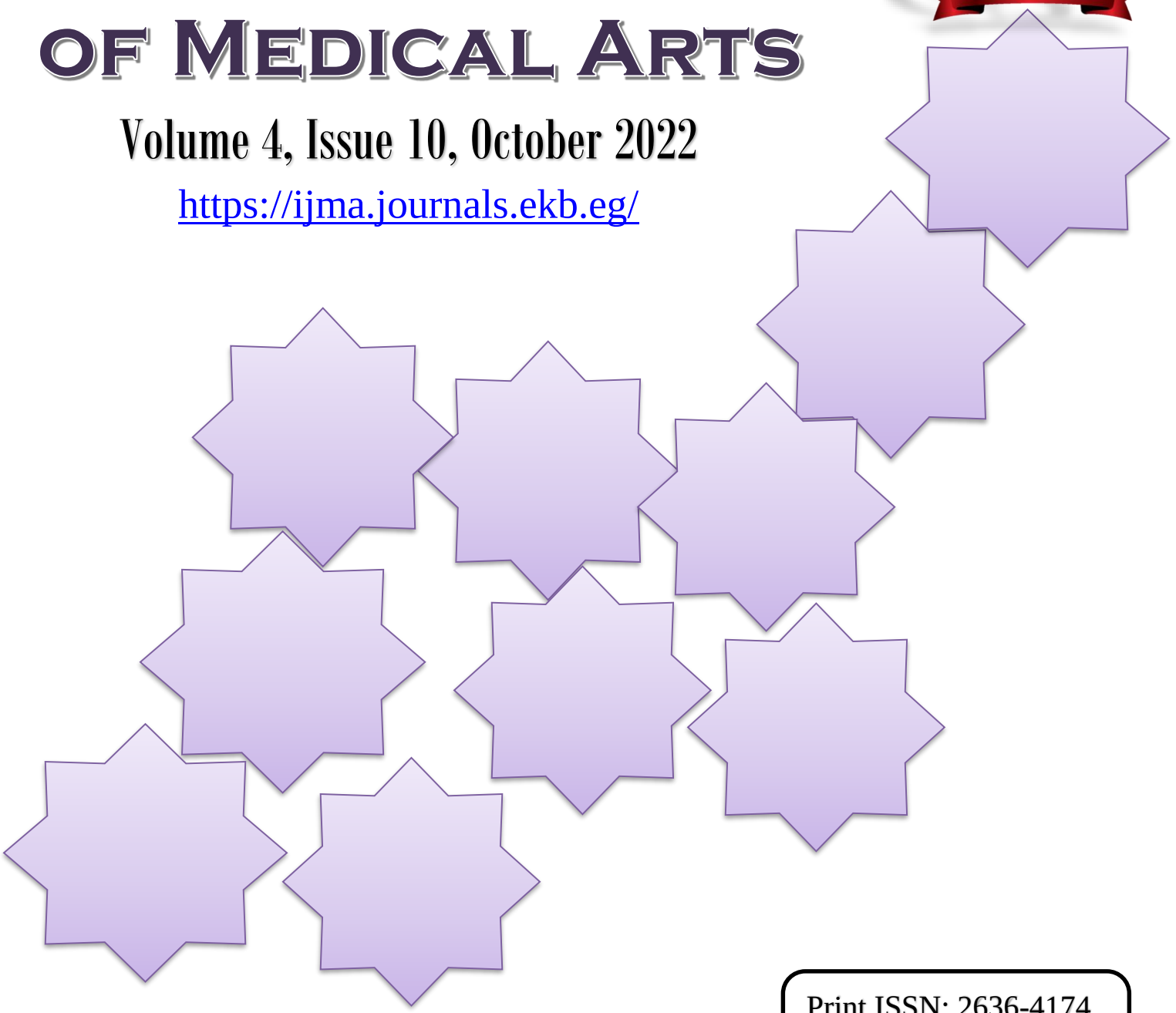

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Original Article

Psychiatric Disorders in Infertile Women with Polycystic Ovary: Prevalence and Associated Factors

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ABSTRACT

Background: Infertility is strongly linked to psychiatric disorders especially if infertility and PCOS are coincidentally present. Major depression is the commonest psychiatric disorder [15-54%], followed by anxiety [8-18%] in infertile women.

Aim of the work: This study aims to estimate the prevalence and to determine the predictors of Psychiatric disorders among the infertile women.

Patients and methods: Our study is a cross-sectional-controlled study, that included 100 infertile women diagnosed with polycystic ovary syndrome [PCOS], and 100 fertile women as a control between June 2019 and June 2020. Complete medical history, general and gynecological examinations, and routine laboratory investigations were done for each woman during the enrollment. The depression intensity was assessed by the BECK depression inventory-II [BDI-II]. In addition, the Hospital Anxiety and Depression Scale [HADS-A] was used to assess anxiety.

Results: the age of women ranged between 21 and 38 years, with no significant difference between both groups. However, the body mass index [BMI] significantly increased in the study group [28.74±1.92 vs. 26.63±1.25 kg/m^2]. The infertile duration in the study group ranged between 2 and 7 years [the mean ±SD was 3.37±1.36 years]. Clinically relevant anxiety was significantly increased in the study than the control group [45% vs 25%], and the HADS-A score significantly increased in the study than the control group. Similarly, moderate and severe depression were significantly increased in the study than the control group [30.0%, 11.0% vs 15.0% and 4.0% respectively], and BDI score significantly increased in the study than the control group. Anxiety was significantly associated with infertility duration, and fasting glucose levels [higher glucose levels were associated with relevant anxiety].

Conclusion: The current work revealed a significant increase in depression and anxiety among infertile women with PCOS. Each condition seems to increase the effects of psychiatric disorders associated with the other condition.

Keywords: Infertility; Polycystic Ovary Syndrome; PCOS; Depression; Anxiety.

INTRODUCTION

Infertility is defined as the failure of conception despite regular unprotected sex for at least one year. Infertility affects about 10-15% of couples in their reproductive age. Previous studies have shown a significant relationship between infertility and psychiatric comorbidity. Major depression is the commonest psychiatric disorder [15-54%], followed by anxiety [8-18%] in infertile women [1]. The relationship between infertility and psychiatric disorders is complex. Infertile women are under greater stress and are liable to develop psychological disorders. In addition, psychiatric disorders are associated with increased infertility [2].

Polycystic ovary syndrome [PCOS] is a major health problem, as it affects about 16.6% when the diagnosis is confirmed according to the Rotterdam Criteria. The diagnosis is fixed by the presence of at least two of the following symptoms: 1] clinical and/or biochemical hyperandrogenism, 2] oligomenorrhea/ amenorrhea, and 3] ultrasonographic evidence of polycystic ovary. Clinically, PCOS presented by amenorrhea, oligomenorrhea, hirsutism, sexual dysfunction, obesity, acne, anovulation, and infertility. All these manifestations can lead to the development of different psychiatric disorders, mainly depression, anxiety, and social maladjustment [3, 4].

We suggested that, if infertility and PCOS are coincidentally present, the psychiatric disorders will be increased in prevalence and severity. However, literature is scarce about psychiatric disorders among infertile women with PCOS. Thus, we evaluated the prevalence and severity of anxiety and depression among infertile women with PCOS

PATIENTS AND METHODS

Between June 2019 and June 2020, the present study was conducted. It included 100 infertile women with diagnostic criteria of polycystic ovary syndrome [PCOS], as a purposive sample, according to revised Rotterdam Criteria for diagnosis of PCOS [4]. Another 100 fertile women [presented for other causes than PCOS] were included as a control group. All were selected from the outpatient Clinic, Department of Obstetrics and Gynecology, and Al-Azhar University Hospitals. The local Ethics Committee of Damietta Faculty of Medicine, Al-Azhar University, Damietta, Egypt, reviewed and approved the study protocol. All women signed informed consent for participation in the study, after full clarification of the study protocol and value. We recruited the cases according to the following criteria:

The exclusion criteria were Patients under a specific program for weight reduction [nutritional or gymnastic] three months before the study, administering drugs known to affect the serum levels of glucose, bone metabolism indicators, lipid profile, ovarian function, antibiotics, and anticoagulant drugs, three months before the study. In addition, pregnant women, lactating women, and those with Cushing syndrome, thyroid dysfunction, adrenal hyperplasia, hypertension, and diabetes.

We measured the weight and height of each patient. Then, the Body mass index [BMI] was calculated by dividing weight [kg] by squared height [m^2] and BMI was included in the statistical analysis. All women answered questions about their medical and obstetric history. Then they were clinically evaluated systematically.

The clinical hyperandrogenism was measured by the Modified Ferriman Gallwey [Mfg], which was used for scoring the presence of terminal hairs over nine body areas. [i.e. upper lip, chin, chest, upper and lower back, upper and lower abdomen, thighs, and upper arms]. Each area scored from 0 to 4, and a score ≥ 8 indicates hirsutism [5].

A venous blood sample [10 ml] was drawn after 12 hours of fasting. Then, samples were centrifuged at 3000g/min for 10 minutes and serum was separated and kept at – 20ºC till the time of analysis. Laboratory investigation included fasting blood sugar, liver enzymes, and hormonal profile.

Each woman was submitted to abdominal and transvaginal ultrasound for general evaluation and measurement of ovarian volume. Ovaries with 12 or more follicles measuring 2–9 mm in diameter and/or enlarged ovarian volume [> 10 ccs] on abdominal ultrasound were considered to have a positive sonographic polycystic ovary.

The depression intensity was assessed by the BECK depression inventory-II [BDI-II] as

described elsewhere. Women received the cooperation of well-trained nurses [not included in the study] during the completion of the questionnaire when required [6]. In addition, the Hospital Anxiety and Depression Scale [HADS-A] was used to assess anxiety. It is a self-administered questionnaire consisting of 7 items. Each item scored 0 to 3, and values < 8 indicate a normal range, 8-10 mild disorder, and scores ≥ 11 reflect the clinical relevance of symptoms [7].

Statistical analysis: All collected data were anonymized and fed to the software package [the statistical package for the social sciences, version 24] [IBM®SPSS®, Inc. Chicago, USA]. The parametric data were reported as mean ± SD and the non-parametric information was presented as the median and interquartile range [IQR]. The Levene's and Kolmogorov–Smirnov tests were used to checking normal distribution. The independent sample "t"-test and Mann-Whiteny [U]-tests were used to compare parametric and non-parametric quantitative data respectively. Qualitative data were compared by Chi-square or Fisher Exact tests and a p-value < 0.05 was recognized as significant.

RESULTS

In the current work, 100 infertile women with PCOS, and 100 fertile women as the control group. the age of women ranged between 21 and 38 years, with no significant difference between the study and control groups. However, the body mass index [BMI] significantly increased in the study than the control group [28.74±1.92 vs 26.63±1.25 kg/m2]. The infertile duration in the study group ranged between 2 and 7 years [the mean ±SD was 3.37±1.36 years]. Both groups were comparable regarding acne, education, socioeconomic level, and exposure to cigarette smoking. But, the Modified Ferriman Gallwey [Mfg], was significantly increased in the study than the control group [Table 1].

The fasting serum glucose levels, aspartate transaminase [AST], free testosterone, androstenedione, luteinizing hormone [LH], prolactin, LH/FSH ratio, and total ovarian volume were significantly increased among the study than the control group. But estradiol was significantly reduced in the study than the control group [Table 2].

Clinically relevant anxiety was significantly increased in the study than the control group [45% vs 25%], and the HADS-A score significantly increased in the study than the control group. Similarly, moderate and severe depression were significantly increased in the study than the control group [30.0%, 11.0% vs 15.0% and 4.0% respectively], and BDI score significantly increased in the study than the control group [Table 3].

In the study group, anxiety was significantly associated with infertility duration, and fasting glucose levels [higher glucose levels were associated with relevant anxiety]. No other significant associations were reported [Table 4].

Acne was significantly increased in relevance than mild or no depression [70.7% vs 32.2%]. In addition, relevant depression had significantly higher total and free testosterone levels than mild depression. However, significantly lower FSH was associated with relevant depression [Table 5].

Table [1]: Patient characteristics among study and control groups

Variable		Study [n=100]	Control [n=100]	Test	P value
Age [years]	Mean±SD Min.- Max.	26.82±3.03 21-38	27.38±2.39 21- 38	1.45	0.15
BMI [kg/m^2]	Mean±SD Min.- Max.	28.74±1.92 23.88 – 35.25	26.63±1.25 23.59-29.64	**9.21**	**<0.001***
Infertility duration	Mean±SD Min.- Max.	3.37±1.36 2-7			
Acne	[n,%]	48 [48.0%]	40 [40.0%]	1.29	0.25
Education [n,%]	Secondary or lower Higher or postgraduate	27 [27.0%] 73 [73.0%]	36 [36.0%] 64 [64.0%]	1.87	0.17
Socioeconomic level	Low Moderate High	11 [11.0%] 61 [61.0%] 28 [28.0%]	6 [6.0%] 66 [66.0%] 28 [28.0%]	1.66	0.43
Exposure to cigarette smoking		26 [26.0%]	21 [21.0%]	0.69	0.40
Modified Ferriman Gallwey [Mfg] score	Mean±SD Min. – Max.	8.86±1.04 7-12	2.51±1.25 1-5	**38.8**	**<0.001***

Table [2]: Laboratory investigations among study and control groups

Variable	Study [n=100]	Control [n=100]	Test	P value
Fasting glucose [mg/dl]	115.05±19.55	105.65±7.58	**4.48**	**<0.001***
ALT [U/dl]	20.28±4.65	20.11±4.15	0.27	0.78
AST [U/dl]	14.99±2.77	13.84±1.94	**3.40**	**0.001***
Total testosterone [mg/dl]	49.28±10.31	48.54±9.04	0.54	0.77
Free testosterone [pg/ml]	2.62±1.45	2.03±0.73	**3.60**	**<0.001***
Estradiol [pg/ml]	34.27±10.0	42.54±7.59	**6.58**	**<0.001***
Androstenedione [ng/ml]	3.88±1.05	2.17±0.50	**14.81**	**<0.001***
Follicle-Stimulating Hormone [FSH]	5.68±1.25	5.73±1.07	0.28	0.77
Luteinizing Hormone [LH]	12.37±2.45	11.34±1.44	**3.64**	**<0.001***
Prolactin	14.52±5.96	12.98±2.18	**2.42**	**0.016***
Thyroid stimulating hormone	2.36±0.88	3.39±0.68	0.25	0.80
LH/FSH ratio	2.37±1.05	2.08±0.65	**2.28**	**0.024***
Total ovarian volume [CC]	21.71±3.80	7.32±2.03	**33.39**	**<0.001***

Table [3]: Anxiety and depression among the study and control groups

Variable		Study [n=100]	Control [n=100]	Test	P value
HADS-A score	Mean±SD	10.01±2.99	7.04±3.23	**6.72**	**<0.001***
	Min.- Max.	4-15	2-14		
BDI score	Mean±SD	17.67±9.43	13.99±5.72	**3.33**	**0.001***
	Min.- Max.	3-37	5-34		
Anxiety	None or irrelevant	55 [55.0%]	75 [75.0%]	**8.79**	**0.003***
	Clinically Relevant	45 [45.0%]	25 [25.0%]		
Depression categories	None to mild	59[59.0%]	81 [81.0%]	**11.52**	**0.001***
	Moderate to severe	41 [41.0%]	19 [19.0%]		

HADS: Hospital Anxiety and Depression Scale; BDI: BECK depression inventory

Table [4]: Association between anxiety and other variables in the study group

Variable		No or mild [n=55]	Relevant [n=45]	Test	P value
Age [years]		27.09±3.27	26.49±2.70	0.99	0.32
BMI [kg/m^2]		28.83±1.94	28.63±1.91	0.51	0.60
Infertility duration		3.04±1.20	3.63±1.43	**2.60**	**0.030***
Acne		22 [40.0%]	26 [57.8%]	3.13	0.08
Education [n, %]	Secondary or lower	14[25.5%]	13[28.9%]	0.14	0.70
	Higher or postgraduate	41[74.5%]	32[71.1%]		
Socioeconomic level	Low	7[12.7%]	4[8.9%]	0.37	0.82
	Moderate	33 [60.0%]	28[62.2%]		
	High	15[27.3%]	13[28.9%]		
Exposure to cigarette smoking		17[30.9%]	8[20.0%]	1.53	0.23
Modified Ferriman Gallwey [mFG] score		9.0±1.05	8.69±1.02	1.49	0.14
Fasting glucose [mg/dl]		110.80±16.63	120.24±21.69	**2.46**	**0.015***
ALT [U/dl]		20.42±4.33	20.11±5.07	0.33	0.75
AST [U/dl]		14.78±2.69	15.24±2.87	0.83	0.41
Total testosterone [mg/dl]		48.93±10.93	49.71±9.62	0.38	0.71
Free testosterone [pg/ml]		2.58±1.33	2.66±1.59	0.27	0.79
Estradiol [pg/ml]		34.91±9.43	33.49±10.71	0.71	0.48
Androstenedione [ng/ml]		3.81±1.01	3.98±1.10	0.78	0.43
Follicle-Stimulating Hormone [FSH]		5.69±1.28	5.66±1.22	0.13	0.89
Luteinizing Hormone [LH]		12.67±2.96	12.01±1.58	1.33	0.18
Prolactin		14.86±5.78	14.10±6.21	0.62	0.53
Thyroid stimulating hormone		2.37±.79	2.36±0.99	0.08	0.93
LH/FSH ratio		2.41±1.08	2.31±1.02	0.45	0.64
Total ovarian volume [CC]		21.38±3.62	22.11±4.01	0.95	0.34
BDI score		16.96±8.69	18.53±10.31	0.82	0.41

BDI: BECK depression inventory

Table [5]: Association between depression and other variables in the study group

Variable		No to mild [n=59]	Relevant [n=41]	Test	P value
Age [years]		26.49±2.62	27.29±3.51	1.30	0.19
BMI [kg/m^2]		28.73±2.02	28.75±1.79	0.04	0.96
Infertility duration		3.37±1.35	3.36±1.39	0.03	0.98
Acne		19 [32.2%]	29[70.7%]	**14.38**	**<0.001***
Education [n, %]	Secondary or lower Higher or postgraduate	19 [32.2%] 40 [67.8%]	8 [19.5%] 33 [80.5%]	1.97	0.16
Socioeconomic level	Low Moderate High	7 [11.9%] 32 [54.2%] 20 [33.9%]	4 [9.8%] 29 [70.7%] 8 [19.5%]	2.96	0.23
Exposure to cigarette smoking		14 [23.7%]	12 [29.3%]	0.38	0.53
mFG score		8.85±1.03	8.88±1.08	0.14	0.88
Fasting glucose [mg/dl]		115.12±19.12	114.95±20.39	0.04	0.96
ALT [U/dl]		20.02±4.75	20.66±4.55	0.67	0.50
AST [U/dl]		15.20±2.66	14.68±2.92	0.92	0.35
Total testosterone [mg/dl]		46.90±9.10	52.71±11.10	**2.86**	**0.005***
Free testosterone [pg/ml]		1.83±0.48	3.75±1.63	**8.54**	**<0.001***
Estradiol [pg/ml]		34.25±9.33	34.29±11.01	0.02	0.98
Androstenedione [ng/ml]		3.79±1.04	4.02±1.06	1.07	0.29
Follicle-Stimulating Hormone [FSH]		5.90±1.10	5.36±1.38	**2.19**	**0.031***
Luteinizing Hormone [LH]		12.42±2.88	12.31±1.66	0.22	0.82
Prolactin		13.78±5.53	15.59±6.46	1.50	0.13
Thyroid stimulating hormone		2.29±0.87	2.48±0.90	1.05	0.29
LH/FSH ratio		2.23±0.91	2.56±1.21	1.57	0.11
Total ovarian volume [CC]		21.81±3.67	21.56±4.02	0.32	0.74
BDI score		9.85±3.04	10.24±2.96	0.64	0.51

BDI: BECK depression inventory

DISCUSSION

Results of the current work revealed that the prevalence of anxiety was 45.0%, while that of depression was 41.0% among women with infertility and PCOS. The prevalence in the control group was 25.0%, and 19% anxiety and depression, respectively. Anxiety was significantly associated with a longer duration of infertility and higher serum glucose levels. Depression on the other side was significantly associated with increased acne, higher total, and free testosterone levels, and lower follicle-stimulating hormone. **Lakatos *et al*.** [8] showed a significant increase in depression and anxiety disorders in infertile than fertile women. About half of infertile women had depressive symptoms.

In previous studies, depressive and anxious symptoms were significantly increased in infertile women with PCOS than in control groups. This was attributed to high androgens and high ovarian hormones with ovulation induction treatments [9, 10].

The results of the current work are in line with the previous literature because the most common psychiatric illnesses in infertile women are depression and anxiety, and both negatively affect the patient's quality of life [11, 12].

As in the current work, in most studies conducted on infertile women, there was no significant association between the age of the patients and the level of depression or anxiety [13, 14]. However, **Gulseren *et al.*** [15] found improvement in symptoms of depression and anxiety as age increased. Two factors could explain the absent association between patient age and psychiatric disorders in infertile women with PCOS. With advancing age, infertile women were exposed to more social pressure and stigma which may increase the symptoms of anxiety and depression. On the other side, with advanced age, women become more mature and their ability to cope with stressors is increased [1].

Almeshari *et al.* [16] reported that more than one-third of the women with PCOS [40%] had anxiety symptoms [18% had moderate while 6% had severe anxiety]. This is explained by the nature of anxiety being a secondary effect of PCOS. This could be attributed to clinical manifestations of PCOS like acne, obesity, and hirsutism with low self-esteem. In addition, this may be attributed to the fear of their ability to conceive in the future [17]. Other researchers suggested that clinical symptoms of PCOS are possibly increasing stress among women due to low self-esteem, negative body image, and

concerns about the ability to have a future partner or their fertility [18-20].

Almeshari *et al*. [16] reported depression in 49%. Another study reported a prevalence of 40% [21]**.** Several causes are responsible for increased depression. The first is infertility, menstrual irregularities, or hormonal factors. Another study, however, reported a prevalence of 31.7% [22]. These could be attributed to different ethnic variations and different inclusion criteria.

Mild to moderate depression and anxiety were more prevalent than moderate to severe symptoms. These results are consistent with **Almeshari *et al*.** [16] who reported mild to moderate depression in 30% compared to 19% of moderate to severe manifestations. However, one meta-analysis reported a high prevalence of moderate to severe depression in PCOS women [10].

Infertility due to PCOS could stimulate stress and psychiatric issues like social maladjustment, loss of control, and social stigma. Moreover, infertility is usually associated with lower self-esteem, and divorce with significant stress [23]. However, the effect of infertility on women depends on different factors, mainly the ability of women to cope with social stressors and traditions. An interesting Austrian study was conducted to address the social and religious factors in women with PCOS and infertility. Austrian females reported that infertility is not as much of an obstacle as it is for Muslim immigrant women [24].

In short, the results of the current work revealed a significant increase in depression and anxiety among infertile women with PCOS. Each condition seems to increase the effects of psychiatric disorders associated with the other condition. However, the cause-effect relation-ship could not be established. In addition, the small number of patients limits the generalization of the results of the current study. However, the current study is one of few studies that examined psychiatric disorders among infertile women with PCOS. This opens the door for future studies.

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