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Psychiatric disorders among females with prolonged infertility with or without in vitro fertilization/intracytoplasmic sperm injection failure: a cross-sectional study

Mostafa Abdallah[1*], Ayman S. Dawood[2*], Reham Amer[3*], Mohamed Baklola[4*], Ibrahem Hamdey Rashed Elkalla[5*] and Shereen B. Elbohoty[2*]

Abstract

Objectives The present study seeks to deepen understanding of the negative impacts of infertility, with a spotlight on the experiences of Egyptian women who faced prolonged periods of infertility, and emphasizing the role that failures of in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles may play in exacerbating their psychiatric disorders and impairing their sexual functions.

Methods Embarking on a cross-sectional approach, this study was operationalized within the outpatient sectors of the Obstetrics and Gynecology Departments, synchronized with Psychiatry Departments, at Tanta University Hospitals from September 1, 2018, to December 31, 2022. The targeted population encompassed women experiencing prolonged infertility (≥ 5 years), categorically divided into two groups for meticulous analysis: Group I (with a history of IVF/ICSI failure) and Group II (without any IVF/ICSI attempts). Diagnostic tools, including the Arabic versions of the Hamilton Depression Scale (HAM-D), Hamilton Anxiety Scale (HAM-A), and the Female Sexual Function Index (FSFI), were deployed to scrutinize the mental health and sexual function outcomes of the participants.

Results A total of 236 women participated in this study (126 in Group I and 110 in Group II), with primary infertility prevalent in 73.31% of cases, averaging a duration of 9.28 ± 3.40 years. Our findings indicated a substantial presence of depression (58.47%), anxiety disorders (35.17%), and sexual dysfunctions (43.64%). Notably, significant differences ($p < 0.0001$) emerged between the groups on the HAM-D, HAM-A, and FSFI scales, with endometriosis showcasing the worst effects.

*Correspondence:
Mostafa Abdallah
mustafa.mahmoud@fmed.bu.edu.eg
Ayman S. Dawood
ayman.dawood@med.tanta.edu.eg
Reham Amer
reham.amer@med.tanta.edu.eg
Mohamed Baklola
Mohamedbaklola2000@gmail.com
Ibrahem Hamdey Rashed Elkalla
dribrahem@mans.edu.eg
Shereen B. Elbohoty
Sherin.albahouti@med.tanta.edu.eg
Full list of author information is available at the end of the article

Conclusions The findings conclusively pinpoint a pronounced link between prolonged infertility and exacerbated mental health conditions, alongside impaired sexual functions, thereby negatively affecting the quality of life of the affected women. This revelation underscores the pressing need for integrated psychiatric consultations in the therapeutic protocols of women grappling with infertility, particularly those with a history of endometriosis or failed IVF/ICSI cycles, to foster a more holistic approach to infertility management and care.

Keywords Psychiatric disorders, Infertility, IVF/ICSI failure, Female sexual function

Introduction

Infertility is defined as the failure to achieve pregnancy after 12 months of regular unprotected sex [1]. The relationship between infertility and psychiatric disorders is mutual. On one hand, prolonged infertility may lead to evolution of psychosocial problems, as patients with such condition usually experience loss of sensation, marginality and suffer stigmatization in the surrounding society. This could contribute to greater levels of depression, anxiety, tension, guilt feelings, anger, and/or severe distress that may affect sexuality and quality of life [2–4]. Furthermore, the economic burdens and the side effects of medications used for infertility management may play an additional role in the existence of such troublesome psychosocial issues [5].

From the biological point of view, infertility is considered a chronic stress that may lead to undue secretion of the stress mediators such as cortisol, and norepinephrine that trigger the fear system, producing anxiety and cause diminished response to the reward system, producing depression [6].

On the other hand, previous studies [7, 8] highlighted that mental health problems have a crucial role in the pathogenesis of infertility. The dysregulation of stress hormones and the hypothalamic–pituitary–adrenal axis that occurred in psychiatric disorders, influence adversely the hormones that affect fertility (i.e., follicular-stimulating hormone, gonadotropin-releasing hormone, prolactin, luteinizing hormone), and also the hormones that may interfere with fertility such as cortisol and endogenous opioid [6].

Women undergoing fertility treatments in the form of repeated trials of IVF/ICSI have great concern as they face struggle and stress of infertility plus the costs and unfavorable outcomes of IVF. Patients believe that their happiness is built upon successful IVF results. So, many patients put a lot of financial and emotional investment into IVF/ICSI maneuver. Physical, emotional and psychological consequences are magnified by treatment failure [9]. Psychiatric disorders were reported with high frequency following failed IVF cycles. These may be due to side effects of drugs used in stimulation, stress being present before the trials or anxiety about success of the trials. These disorders increase progressively with prolonged duration of infertility or with increased number of failed cycles [10].

Female's social and professional lives is strikingly affected by infertility treatments. During cycle treatment, social activities are often postponed as many women do not share their expectations or experiences with others. Also, couples did not share any data about treatment for privacy issues [11]. Moreover, cycle treatment require multiple hospital visits and result in absence from work that put lots of demands and pressure on couples relationship and family economics. Prolonged infertility duration and inability to afford the costs of treatment may lead to impaired sexual function. Healthcare providers should consider important strategies that help infertile couples to deal with their sexual and psychological problems [12].

Unfortunately, female sexual dysfunctions and psychiatric disorders like depression and anxiety are frequently pass unnoticed during management of infertility. This was attributed to health professionals who mainly focus on conception alone and neglecting other potential associated symptoms and disorders [13].

Regarding the rate of depression and anxiety in patients undergoing infertility management, there was a great variation in previously published series. Many factors were proposed to affect the prevalence and type of psychiatric disorders among infertile couples [14]. However, in Egypt the literature is scarce in this regard. The current study was conducted to access the prevalence of psychiatric disorders and sexual dysfunctions among Egyptian females with prolonged infertility. Moreover, the study aimed to evaluate the impact of failed IVF/ICSI cycles on the severity of psychiatric disorders and female sexual functions.

Materials and methods

Study design and settings

This cross-sectional study initially enrolled 324 participants from the outpatient clinics of Obstetrics and Gynecology, and Psychiatry departments at Tanta University hospitals. This study started on September 1, 2018, after the approval of the responsible ethical committee and was completed on December, 31, 2022. A formal consent

was signed from all patients to participate in the study and the protocol of the study was clarified to them.

Patients Patients were recruited in the study according to the following inclusion criteria: (a) females in their childbearing period suffering prolonged (≥5 years) infertility; (b) educated females (at least 6 years of education to be able to participate in psychometric tests). The exclusion criteria were as following: (a) previous history of psychiatric or neurologic disorders; (b) patients with major medical illness (serious renal, hepatic, endocrine disorders and cancer); (c) patients with any anatomical defects in genital tract; (d) patients who refuse to participate in the study or did not complete their questionnaires.

Allocation Patients were allocated according to history of IVF/ICSI attempts to either (Group I) who presented by prolonged infertility with prior IVF/ICSI failure or to (Group II) who had prolonged infertility without any prior IVF/ICSI trial.

Study tools

Three questionnaires either printed or in soft-copy forms were provided to enrolled patients. We used the Arabic version of Hamilton Depression Scale [15, 16] Hamilton Anxiety Scale [17, 18], and Female Sexual Function Index (FSFI) [19, 20].

Hamilton depression scale (HAM-D) consisted of 17 symptoms with variation of scale from zero to four according to severity where score of four denoted the severe degree. Some parameters are scaled from zero to two where zero denoted absence of symptoms and two denoted its presence. Final degree was calculated for each patient with the final score ranging from zero to 52. The following scale was used to determine severity of symptoms: (0–7) no depression symptoms, (8–13) mild depression, (14–18) moderate depression, (19–22) severe depression and (≥23) very severe depression [15, 16]

Hamilton anxiety scale (HAM-A) is composed of 14 symptoms with a scale from zero to four for each symptom where four is the severe degree. Total score for each patient was calculated. The range is from zero to fifty six and it was divided as follow: (0–17) no or mild depression, (18–24) mild to moderate depression, (25–30) moderate to severe depression [17, 18].

Female sexual function index (FSFI) consisted of six domains inquiring about sexual function in the last month. These domains included: desire (assessed by 2 questions), arousal, lubrication and orgasm (assessed by 4 questions for each domain), satisfaction and pain (assessed by 3 questions for each). Every domain response is gathered and multiplied in a factor and final score for each domain is calculated. The total score for each patient is the sum of all domains scores. The range of FSFI was 2–36 with a cutoff total score (≤26.55) [19, 20].

Intervention All 324 female patients were evaluated to determine eligibility for participation in the study through the following:

(A) Gynecological evaluation: to access cause, type and duration of infertility by comprehensive medical history, gynecological examination and investigations.

(B) Psychiatric evaluation: including Mini International Neuropsychiatric Interview [21, 22] with application of the above-mentioned psychometric tests for depression, anxiety and female sexual function. Participants were asked to fill in or answer all questions in the scale sections. The used forms were in Arabic language to be easily answered. Data that were collected and inserted in Excel sheet included: socio-demographic data, educational level, body mass index [BMI] = weight [kg]/squared height [m^2], infertility (type, duration and cause), whether IVF/ICSI was done or not, number of trials of IVF/ICSI, and scores of HAM-D, HAM-A and FSFI.

Statistical methods

Sample size estimation was performed using Raosoft sample size calculator. To achieve a 95% confidence level and a margin of error of 8%, the sample size was calculated at N > 107 for each study group. We intently increased our sample to compensate for possible losses.

Statistical analysis of gathered data was done by R program [23]. Shapiro–Wilk's test was used to test normality. Numerical data were expressed as mean ± standard deviation (SD) while categorical data were presented as number and percentage (%). Chi-square test (χ^2), Student's t-test and one-way ANOVA were used for comparison of variables in both groups. Pearson correlation coefficient or the Spearman rank order correlation tests were used for univariate correlation when appropriate. Kruskal–Wallis test was used to compare the effects of infertility causes on HAM-D, HAM-A and FSFI and its domains. A p-value < 0.05 was considered significant.

In multiple regression analysis, we fitted a linear model (estimated using OLS) to predict HAM-D with Duration, FSFI and HAM.A (formula: HAM-D ~ Duration + FSFI + HAM-A). The model explains a statistically significant and substantial proportion of variance (R2 = 0.73, F (3, 232) = 207.30, p < 0.001, adj. R2 = 0.72). The model's intercept, corresponding to duration N = 0, FSFI = 0 and HAM.A = 0, is at − 1.25 (95% CI [− 6.09, 3.60], t (232) = − 0.51, p = 0.613). Standardized parameters were obtained by fitting the model on a standardized version of the dataset. 95% Confidence Intervals (CIs) and p-values were computed using a Wald t-distribution approximation.

Results

Initial recruitment included 324 patients; each group had 162 cases. After application of selection criteria, some patients were excluded from the study ($N=45$) as they not met the inclusion criteria ($N=28$) or they declined to participate in the study ($N=17$). The eligible patients ($N=279$) underwent the study intervention. The final number of patients who gave complete response were 236; distributed in Group 1 ($N=126$) and Group II ($N=110$) as shown in Fig. 1.

Demographic data of eligible participants are shown in Table 1. Age range was between 25 and 47 years and the mean age was (32.05 ± 4.45), BMI range was 17.3 to 33.2 kg/ m^2 with mean value 24.96 ± 3.29. Regarding education levels, most cases had middle secondary education (39.83%). The majority of patients (73.31%) were having primary infertility with a mean duration of infertility 9.28 ± 3.40 years. In our sample, depression, anxiety disorders and sexual dysfunctions were representing a substantial percent (58.47%, 35.17% and 43.64%, respectively). The mean values of HAM-D, HAM-A and FSFI scores were 11.53 ± 9.76, 15.61 ± 8.70 and 24.20 ± 7.23, respectively.

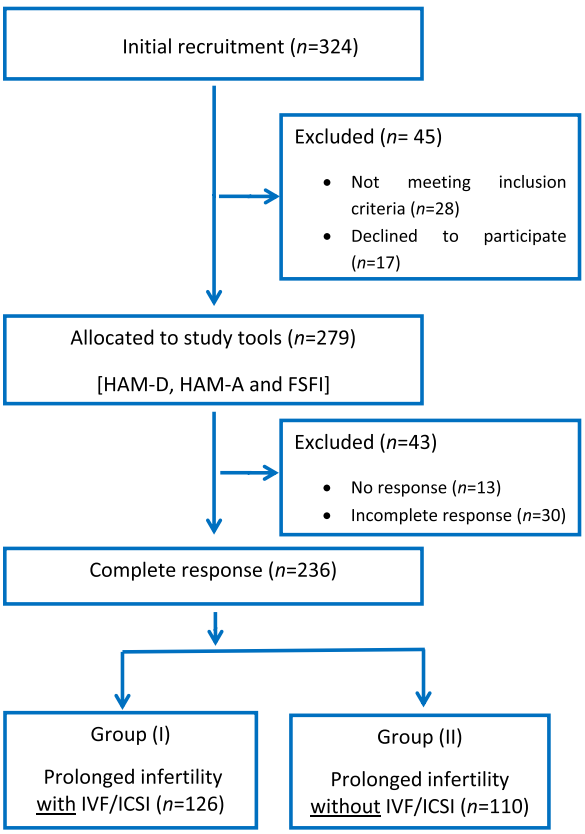

Fig. 1 Flow-chart of the enrolled patients all through the study

Regarding the effect of IVF/ICSI on psychometric scales, there was a statistically significant difference (p-value < 0.0001) between both groups regarding all studied scales (Table 2). The effect of IVF/ICSI trials on FSFI domains is shown in Table 3. There was significant difference (p-value < 0.0001) between both groups (in favor of group2) regarding all domains of FSFI except orgasm and pain.

Correlations between the studied parameters and the domains of FSFI are illustrated in Table 4 and Fig. 2. There were negative correlations between all domains of FSFI and each of age, HAM-D, HAM-A, prior IVF/ICSI trials, duration of infertility. On the other hand, there were strong positive correlations between age, duration of infertility, prior IVF/ICSI trials and scores of HAM-D, HAM-A scales. The effects of infertility cause on the mean value of HAM-D, HAM-A and FSFI scales are presented in Table 5 and the endometriosis had the major link with high HAM-D, high HAM-A scales and low FSFI. Regarding the impact of different infertility causes on the FSFI domains underlined that endometriosis followed by male factor had the worst results on FSFI (Table 6).

Linear regression analysis in the study showed that the duration of infertility (beta = 1.39, 95% CI [1.08, 1.71], t (232) = 8.71, $p<0.001$; Std. beta = 0.48, 95% CI [0.37, 0.59]) as well as HAM-A (beta = 0.33, 95% CI [0.21, 0.46], t (232) = 5.22, $p<0.001$; Std. beta = 0.29, 95% CI [0.18, 0.41]) and FSFI (beta = − 0.22, 95% CI [− 0.34, − 0.10], t (232) = − 3.49, $p<0.001$; Std. beta = − 0.16, 95% CI [− 0.25, − 0.07]) are significant predictors for HAM-D as shown in Table 7.

Discussion

The association between prolonged infertility and mental disorders was not clearly addressed. Prolonged infertility is linked to psychological distress and this deemed to be more pronounced when the patient had prior experiences of failed IVF cycles. The outcomes of IVF/ICSI may be affected by the patients' psychiatric disorders and vice versa. This was due to the potential negative adverse effects on neuroendocrine, hormonal or immunologic functions and hence lead to poor IVF outcomes [24, 25].

Scarce studies in our Arabic countries [25–27] in general and in the Egyptian society [6, 28–31] in particular have pertained the women's mental health in the settings of infertility with failed IVF trials. Accordingly, the present study was designed to address this issue.

In this work, approximately 60% of our patients had depression. In the same line, Zayed and El-Hadidy found that 61.2% of their primary infertility cases had depression [28]. Mikhaelet al., also documented that depression disorder represents 53.3% and 60% of the

Table 1 Demographic characteristics and the results of the studied scales of enrolled patients (*N* = 236)

Characteristics	Range	Mean ± SD	Median
Age (years)*	25.0–47.0	32.05 ± 4.45	31.00
BMI (kg/m^2)*	17.3–33.2	24.96 ± 3.29	24.60
Education**			
-Primary (6years)	35 (14.83%)		
-Preparatory (9years)	68 (28.81%)		
-Secondary (12years)	94 (39.83%)		
-Collage/postgraduate 12 <	39 (16.53%)		
Occupation**			
-Yes	87 (36.86%)		
-No	149 (63.14%)		
Infertility type **			
-Primary	173 (73.31%)		
-Secondary	63 (26.69%)		
Duration of infertility (years)*	5.0–20.0	9.28 ± 3.40	8.50
Cause of Infertility**			
-Anovulation	38 (16.10%)		
-Combined factor	36 (15.25%)		
-Endometriosis	32 (13.56%)		
-Male factor	50 (21.19%)		
-Tubal factor	35 (14.83%)		
-Unexplained infertility	45 (19.07%)		
IVF/ICSI**			
-Yes	126 (53.39%)		
-No	110 (46.61%)		
HAM-D*	0.0–46.0	11.53 ± 9.76	8.00
HAM-D severity:**			
-No depression (0–7 points)	98 (41.53%)		
-Mild depression (8–13 points)	76 (32.20%)		
-Moderate depression (14–18 points)	20 (8.47%)		
-Severe depression (19–22 points)	13 (5.51%)		
-Very severe depression (≥ 23 points)	28 (11.86%)		
HAM-A*	0–40	15.61 ± 8.70	15.50
HAM-A severity:**			
-Mild anxiety (0–17 points)	153 (64.83%)		
-Mild to moderate anxiety (18–24 points)	43 (18.22%)		
-Moderate to severe anxiety (25–30 points)	25 (10.59%)		
-Severe anxiety (31–56 points)	15 (6.36%)		
FSFI*	3.2–34.8	24.20 ± 7.23	27.35
FSFI categories:**			
-Normal (> 26.55 points)	133 (56.36%)		
-Low FSFI (≤ 26.55 points)	103 (43.64%)		

*Numerical data presented as range, mean, standard deviation and median

**Categorical data presented as number and percentage

SD standard deviation, *BMI* body mass index, *IVF* in vitro fertilization, *ICSI* intracytoplasmic sperm injection, *HAM-D* Hamilton Depression Scale, *HAM-A* Hamilton Anxiety Scale, *FSFI* Female Sexual Function Index

unexplained- versus the explained-infertility groups in their study, respectively [6]. Similar prevalence rates of depression were found in other Middle East studies; Al-Asadi and Hussein declared 68.9% depression rate among infertile women in Iraq which was significantly related to the duration of infertility [25]. Also, the study

Table 2 Effect of IVF/ICSI trials on the studies scales

Characteristics	Group (I) Prolonged infertility with IVF/ICSI trials (*N* = 126)	Group (II) Prolonged infertility without IVF/ICSI trials (*N* = 110)	t-test	*p*-value
HAM-D	15.76 ± 10.48	6.67 ± 5.88	− 8.06	< 0.0001
HAM-A	20.06 ± 8.23	10.51 ± 6.00	− 10.05	< 0.0001
FSFI	20.71 ± 7.71	28.20 ± 3.77	9.26	< 0.0001

HAM-D Hamilton Depression Scale, *HAM-A* Hamilton Anxiety Scale, *FSFI* Female Sexual Function Index

Table 3 Effects of IVF/ICSI on the FSFI

	Group (I) Prolonged infertility with IVF/ICSI trials (*N* = 126)	Group (II) Prolonged infertility without IVF/ICSI trials (*N* = 110)	t-test	*p*-value
Desire	3.08 ± 1.68	4.81 ± 1.23	8.91	< 0.0001
Arousal	3.36 ± 1.38	4.79 ± 1.03	8.91	< 0.0001
Lubrication	3.42 ± 1.34	4.60 ± 1.09	7.35	< 0.0001
Orgasm	3.16 ± 1.61	3.83 ± 1.10	3.67	0.01
Satisfaction	3.53 ± 1.71	4.91 ± 1.16	7.14	< 0.0001
Pain	4.16 ± 1.99	5.25 ± 1.09	5.11	0.002

Table 4 Correlation between all domains of FSFI and the studied parameters

Variables	Age	BMI	HAM-D	HAM-A	Duration of infertility	Infertility type	Prior IVF/ICSI trials
Desire	− 0.49	0.08	− 0.60	− 0.58	− 0.56	− 0.02	− 0.49
Arousal	− 0.44	0.09	− 0.55	− 0.56	− 0.56	− 0.01	− 0.50
Lubrication	− 0.40	0.001	− 0.52	− 0.50	− 0.46	− 0.001	− 0.43
Orgasm	− 0.31	0.01	− 0.43	− 0.35	− 0.36	− 0.004	− 0.17
Satisfaction	− 0.38	− 0.04	− 0.51	− 0.44	− 0.39	− 0.01	− 0.42
Pain	− 0.39	0.07	− 0.39	− 0.37	− 0.33	0.07	− 0.29

of Fido reported comparable high rates of anxiety, depression, and suicidal ideation among Kuwaiti infertile females [31].

With regard to anxiety disorders, 35.17% of our patients had anxiety, which agreed with the results of Alosaimi et al., who established that anxiety disorder represented 21.2% of their sample [26]. Concurrently, Abo-Elabbas et al., reported that anxiety disorder was existing in 45% of their study and it was significantly associated with infertility duration [29]. Higher anxiety rates were recognized in the study of Victor et al., as anxiety represents 73.3% in the unexplained infertility group and 60% in the explained infertility group [6]. Also, Zayed and El-Hadidy reported anxiety disorder in 82.8% among their primary infertile women [28]. The higher rates of anxiety in the latter two studies may be explained by the difference in selection criteria and the characteristics of the included infertile women (type, cause and duration of infertility) in these studies.

In contrast, some researchers [32] demonstrated that there is no statistically significant difference of depression and anxiety levels in both fertile and infertile groups. Guz et al., explained their results by the high prevalence rates of depression in Turkey, mainly owing to rapid changes in socioeconomic status and lifestyle [32].

Several studies in developed countries reported lower prevalence rates (10–20%) of depression and/or anxiety in infertile women. These discrepancies in the findings across different countries may reveal the identity of the married Arabic females who is aiming motherhood, which when not occurred involuntary leads to high frequency of psychological distress and mental disorders. In our society, which is likely to be the same in most developing countries, the increased psychiatric co-morbidity among infertile women might be owing to the lack of social support and financial security and because of the distinctive belief of maternity in the value and role of women [33–37].

Regarding the effect of IVF/ICSI failures on the results of psychometric scales in our work, there was a statistically significant increase in depression and anxiety scores in Group I with failed IVF trials than the other group

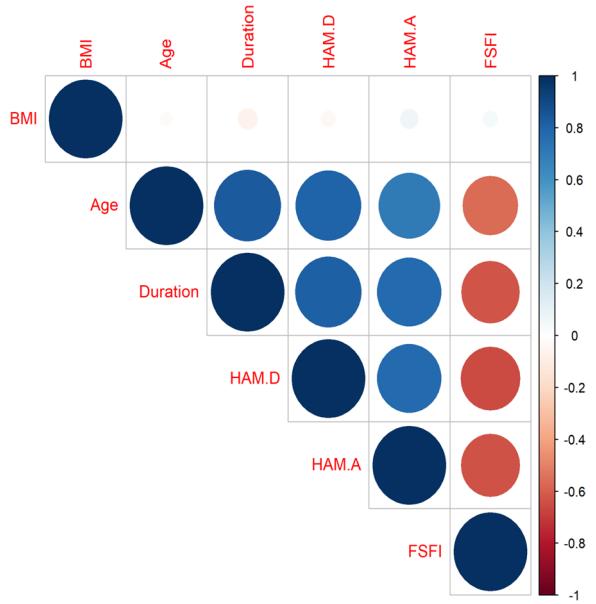

Fig. 2 Correlation plot of different parameters in the study group. r close to 1 means positive correlation and close to -1.0 indicates negative correlation, while around 0 means no significant correlation can be seen. *HAM-D* Hamilton Depression Scale, *HAM-A* Hamilton Anxiety Scale, *FSFI* Female Sexual Function Index

Table 5 Effect of infertility causes on the mean value of the studies scales

	HAM-D	HAM-A	FSFI
Anovulation (*N* = 38)	7 (9)	13 (10)	28.1 (6)
Endometriosis (*N* = 32)	**22 (15)**	**26.5 (11)**	**9.4 (8.45)**
Male factor (*N* = 50)	9 (7)	15 (10)	25.4 (8.8)
Tubal factor (*N* = 35)	6 (9)	12 (8)	28 (3)
Combined factors (*N* = 36)	7.5 (7)	12 (7)	28 (1.95)
Unexplained (*N* = 45)	9 (8)	16 (9.5)	27.4 (3.95)
p-value[a]	< 0.00001*	< 0.00001*	< 0.00001*

Data are presented as median (IQR)

[a] Kruskal–Wallis test for comparison between the effects of cause of infertility on variables

*Statistical significant

without IVF cycles. Similarly, Holley et al., assessed the prevalence of psychiatric disorders following IVF failure [38] and reported that 38.6% of their patients had major depressive disorders following failed IVF cycles compared to 25.9% who did not had prior IVF treatment. They recommended through assessment of the patients following failed IVF cycles to provide psychological treatment if required [38]. Similar results and recommendations were reported later by Malina et al. [39].

On the contrary, Karaca et al., found that the quality-of-life scores were better among infertile patients with prior IVF failure, compared to those undergoing their first IVF trial. They also reported that repeated IVF/ICSI failure did not elevate anxiety levels [40]. They elucidated their results as IVF trial is a discontented practice which is proposed to be much more intense at the start but by the time couples usually accustomed to the situation and the impact of IVF failure becomes less severe. The couples undergoing first time IVF trial, in their opinion, had higher depression levels that elicited by the increased desire of having a child after prolonged infertility [40].

The relationship between infertility and female sexual dysfunction is a bidirectional relation [41]. Infertility can be a consequence of some sexual problems [42]. Many people had the belief that pregnancy is the score of the sexual intercourse, and they loss their sexual desire gradually when conception does not take place [43]. Various studies [14, 44–46] had dissimilar findings regarding the effect of infertility on the couple's sexual relationship. Besharat et al., and Ozturk et al. highlighted that infertile women have more sexual dysfunctions than fertile ones [14, 44]. Conversely, Gulec et al., and Zareet al. established those sexual behaviors was not significantly different in fertile and infertile couples [45, 46]. These dissimilar results may be explained by the fact that women sexual functions are robustly affected by other confounders such as sexuality education and husband response.

In the current study, approximately half of our patients (43.64%) had sexual dysfunction. Previous studies reported various rates and types of sexual troubles

Table 6 Effect of infertility causes on the mean value of all FSFI domains

Variable	Desire	Arousal	Lubrication	Orgasm	Satisfaction	Pain
Anovulation (*N* = 38)	4.8 (2.4)	4.8 (2.4)	4.8 (1.2)	4 (2.4)	5.4 (2)	6 (1.8)
Endometriosis (*N* = 32)	**1.2 (0)**	**2.4 (1.8)**	**2.4 (2.1)**	**1.2 (2.5)**	**0.8 (1.4)**	**1.2 (3.8)**
Male factor (*N* = 50)	3.9 (2.4)	3.9 (2.4)	3.6 (1.5)	4 (1.6)	4 (1.2)	4.8 (2)
Tubal factor (*N* = 35)	4.8 (2.4)	4.8 (1.2)	4.8 (2.1)	4 (1.2)	4.8 (2)	4.8 (1.2)
Combined factors (*N* = 36)	4.8 (2.1)	4.8 (2.4)	4.2 (1.2)	3.6 (1.8)	4.8 (1.4)	6 (1.2)
Unexplained (*N* = 45)	4.2 (1.2)	4.2 (1.2)	4.2 (1.2)	4 (0.6)	4.8 (2.2)	4.8 (1.2)
p-value[a]	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*

[a] Kruskal–Wallis test for comparison between the effects of cause of infertility on domains of FSFI

*Statistical significant

Table 7 Linear regression analysis for predictors affecting HAM-D scale

Predictor variable	Coefficient (B)	Standard error (SE)	t-value	*p*-value
Duration	1.39346	0.16000	8.709	001
FSFI	− 0.21957	0.06292	− 3.490	001
HAM.A	0.33064	0.06331	5.222	001

among infertility patients [47, 48]. Khademi et al., underlined that 93% of infertile women had abnormal scores on the Sexual Function Questionnaire [47]. Tayebi in his study sample demonstrated several sexual issues (orgasm disorder in 83.76%, decreased sexual desire in 80.7%, dyspareunia 67.7%, and vaginismus 76.7%) and they found that more than 50% of patients had reduced frequency of coitus after infertility diagnosis [48].

Regarding the effect of IVF/ICSI on all FSFI domains, there was significant decrease in domains of FSFI (desire, arousal, lubrication and satisfaction) in group I who had prolonged infertility with prior IVF/ICSI trials. In the same line, previous studies [49–52] noticed that women undergoing IVF/ICSI often report sexual problems in the form of decreased desire, poor arousal and lubrication, and orgasm difficulties. Berger et al. 2016 recommended incorporation of appropriate medical treatment and involvement of psychiatric therapy for infertile couples to treat psychogenic erectile dysfunction in men and low sexual desire in women [53].

In the present article, there were strong positive correlations between age, duration of infertility, prior ICSI trials and both HAM-D and HAM-A. The findings of Berg et al. agreed with our results as they revealed that psychological stress and anxiety in childless women raised with the time of infertility [54]. Also, Ramezanzadeh and his colleagues showed that anxiety and depression were most common after 4–6 years of infertility and become more severe after 7–9 years [55]. Domar and Seibel highlighted that depression increases after 2–3 years of infertility and come back to normal range following 6 years [56]. On the contrary, other studies established that patients with infertility for an intermediate to long time had less symptoms of anxiety/depression than others in the first stage of their trouble [57, 58].

Findings of prior studies about patient 'age and its association with anxiety and/or depression were divergent. Facchinetti et al., estimated no significant relationship between age and depression or anxiety [59]. Domar and his colleagues, reported a positive correlation between them [60], while Guz et al., documented that depression, anxiety and self-esteem improved in the women as age and duration of infertility increased [32]. This discrepancy between studies may be related to other confounders that may affect patients' psychological state and emotional reactions such as patient education, socioeconomic standard, occupation and family/husband role. These factors may affect the common believes and the coping strategies of the infertile women and facilitate other pleasant aspects of their life other than motherhood.

On the other side, we found strong negative correlations between age, duration of infertility, prior ICSI trials, HAM-D, HAM-A and the FSFI. Corresponding findings were obtained by Krakas et al. and Iris et al. who found that sexual functions of females suffering primary infertility were noticeably reduced after prolonged duration of infertility (5 years or more) [61, 62]. As well, Turan et al. and Dong et al., stated that prolonged infertility duration was a precipitating factor for sexual dysfunction [63, 64]. Likewise, Hasanzadeh et al., recommended concomitant therapy for patients with prolonged infertility to improve their well-being and sexual functions [65]. Ozturk et al., found that the FSFI scores were markedly reduced if infertility was complicated by depressive disorders [14]. Parallel to these results, Kucur et al., found that total FSFI and its domains were inversely correlated with depression scores [49].

Regarding the cause of infertility, endometriosis followed by male and unexplained infertility were found to be the top factors affecting sexual functions and its domains in the present work. Comparable results were obtained by Tripoli et al. [66], Giuliani et al., [67] and Ashrafi et al., who delineated strong negative impact of endometriosis on female sexual dysfunction and its domains [68]. In the same way, Nasiri Amiri et al., investigated the relationship between polycystic ovary syndrome (PCOS) and female sexual dysfunction. They reported no evidence to link between PCOS and sexual dysfunction, but they found that infertility contributed markedly to poor sexual function in PCOS cases [50].

Based on our results, endometriosis had the highest impact on depression, anxiety and sexual functions scores. The correlation between psychiatric disturbances (especially anxiety and depression) and endometriosis was confirmed innumerous studies [69–72].The chronic pelvic pain, dyspareunia, and infertility that caused by endometriosis are affecting several aspects of patient life (physical, reproductive, economical), thus it has a significant effect on mental, sexual heath and quality of life. Matching to our opinion, Pluchino and his colleagues established that endometriosis inversely affects various domains of sexual functions [73]. Mousa et al., [27] and van Barneveld [74] confirmed that endometriosis patients had significantly more symptoms of anxiety and depression compared to healthy controls [27, 74]. However, other studies revealed that depression is more

common in cases with unexplained infertility, while anxiety is more common in patients with endometriosis [55, 75].

Linear regression analysis for predictors affecting HAM-D in the current study demonstrated that the infertility duration, HAM-A and FSFI were predictors of HAM-D. Comparable to our finding, Lakatos et al., accessed linear regression analyses in infertile women to evaluate predictors of depression and anxiety and they established that anxiety and depressive symptoms were correlated to patient age, maternal bond, social and sexual issues [76]. Omani-Samaniet al., revealed that participants with ≥ 5 years infertility were 1.51-fold and 1.30-fold more likely than others to suffer anxiety and depression, respectively [4]. Elsous et al., reported that duration of marriage (>6 years), at least one abortion, primary infertility, and male factor of infertility were predictors for depression among infertile women [77]. However, in the study of Vo et al., women who reported infertility caused by male factor and caused by both couple had 3.09-times higher odds and 3.63-times higher odds to suffer depression, respectively, compared to those who had causes related to the wife [78].

In our results, for a one-unit increase in the duration variable, and HAM-A score the predicted change in HAM-D score would increase 1.4 and 0.3, respectively, holding all other predictor variables constant. For a one-unit increase in the FSFI variable, the predicted change in HAM.D score would decrease by 0.2 holding all other predictor variables constant. In the same line, the study of Omani-Samani et al., demonstrated that each one-year increase in infertility duration increases the odds of having depression by 4% (OR = 1.04), Cases with at least one failed prior treatments were 1.41-fold more likely to be depressed (OR = 1.41) [4].

Limitations

The strength of the present study lies in its comparative nature. However, it should be viewed in the context of some shortcomings. First, there was no follow up of our participants after filling out the study tools as the study is a cross-sectional one. Second, the heterogeneity of our cases regarding causes of infertility and type/duration of hormonal therapy they were receiving. It is known that such therapies may cause mood swings and may have potential influence on psychiatric outcomes. However, it was difficult to obtain adequate sample size for the current research in light of the exclusion of cases receiving hormonal therapy, as most infertile patients have a long history of these therapies. In addition, it was not applicable, due to ethical reasons, to ask them to stop their medications which are considered a promise and hope for many infertile couples. Furthermore, even if the infertile woman presents to our clinics after discontinuing hormonal therapy, it is difficult to ascertain the extent to which previous hormonal treatment affected her mood state, as the impact of these therapies on the body may continue for several months after stopping, and each body may have his own unique response. So, future multicenter longitudinal studies could be more informative to confirm our preliminary results and to include a wide scale of similar cases in order to follow the short and long-term effect of hormonal therapy on mental health and reassess the psychometric scales after receiving suitable psychiatric treatments.

Another shortcoming of this work is that it did not address the role of husband and family support nor the impact of cultural and environmental aspects on the infertile woman and their psychometric evaluation. Nevertheless, it is worth mentioning that most of our participants had rural residency with comparable environmental backgrounds and cultural beliefs since our Tanta university hospitals serve a wide catchment area in the middle of Nile delta, the most majority of which lives in rural areas. So, our study did not specifically categorize participants based on their urban or rural settings. We suggest that future research should explicitly incorporates cultural dimensions and family dynamics to provide a more nuanced understanding of the psychological impacts of infertility. Moreover, analysis of the role of husband/ family support of infertile couples in reducing the infertility-related stress could be an interesting subject for future research.

We acknowledge that incorporating a quality-of-life questionnaire to track the physical and mental components of an infertile woman's life would enrich our understanding of the broader impacts of infertility. Although this element was not explicitly addressed in this research, our results confirmed that prolonged infertility, especially in the IVF group, was associated with worsening mental health issues alongside poor sexual functions, all of which would be expected to have a negative impact on patients' quality of life.

Future prospective longitudinal and comparative studies with larger sample size is strongly recommended to overcome the aforementioned limitations and to capture more comprehensive data on the subject.

Conclusions

Prolonged infertility was found to be associated with considerable rates of depression, anxiety and poor female sexual functions. Females who underwent prior trials of failed IVF/ICS had remarkably higher levels of depression, anxiety and sexual dysfunction than those who did not. There was an inverse correlation between

all domains of female sexual functions and each of the age, duration of infertility, prior IVF/ICSI trials as well as scores of depression/anxiety scales. There were strong positive correlations between scores of anxiety/depression and each of the age, duration of infertility and prior IVF/ICSI trials. Endometriosis, as a common cause of infertility, had the major link with high depression and anxiety scales and low sexual function results. Infertility duration, levels of anxiety and sexual dysfunction were strong predictors affecting HAM-D. We recommend involving psychiatric and reproductive medicine consultants in the multidisciplinary team responsible for management of prolonged infertility.

Abbreviations

BMI	Body mass index
FSFI	Female Sexual Function Index
HAM-A	Hamilton Anxiety Scale
HAM-D	Hamilton Depression Scale
IVF/ICSI	In vitro fertilization/intracytoplasmic sperm injection

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Author contributions
The design of the study was done by MA, AD, RA, MB, IE and SE. Collection of data was done by AD, RA, and SE. Analysis and interpretation of data was done by MA, AD, RA, IE and SE. Manuscript writing was done by MA, AD, RA, IE and SE. Revising the manuscript critically for important intellectual content and editing it was done by MB, IE and SE. Approval of the manuscript to be published was done by MA, AD, RA, MB, IE and SE.

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Availability of data and materials
The datasets used during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The research was carried out following ethical guidelines, and we received approval from the Tanta University Faculty of Medicine Institutional Review Board (IRB) with an ID of 32519/08/18 beforehand. Each patient willingly signed a formal agreement to take part in the study, and we explained the study's plan to them. We assured them that their data would be kept private, and they were informed of their freedom to opt out or decline to participate without facing any negative repercussions. Informed consent to participate has been obtained from the participants.

Consent for publication
Not applicable.

Competing interests
There were no conflicts of interest disclosed by the authors.

Author details
[1]Obstetrics and Gynecology Department, Benha University, Benha, Egypt. [2]Obstetrics and Gynecology Department, Tanta University, Tanta, Egypt. [3]Psychiatry Department, Faculty of Medicine, Tanta University, Tanta, Egypt. [4]Faculty of Medicine, Mansoura University, Mansoura, Egypt. [5]Psychiatry Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt.

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