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**DEPRESSIVE AND ANXIETY SYMPTOMS IN
A SAMPLE OF WOMEN WITH UNEXPLAINED
INFERTILITY : IMPACT OF ASSISTED
REPRODUCTION TECHNIQUES (ART) ON
PSYCHIATRIC MORBIDITY**

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ABSTRACT

Objectives : To assess the psychiatric morbidity in women with unexplained infertility undergoing treatment with assisted reproductive techniques and to explore the impact of treatment on this morbidity especially on depressive and anxiety symptoms.

Design : Prospective study.

Setting : Assisted reproduction unit in a private hospital.

Patients : Women with unexplained infertility undergoing a cycle of assisted reproduction.

Intervention : Women with unexplained infertility who were scheduled for assisted reproduction cycle (IUI or FSP) were assessed both clinically and by a battery of psychometric tests including: General Health Questionnaire (GHQ-28), Beck Depression Inventory (BDI) and Hamilton Anxiety Scale (HAMA). All women were followed up after the end of one stimulated cycle by GHQ, BDI and HAMA.

Results : 86 women with unexplained infertility underwent assisted reproduction cycle. 10 women got pregnant with average pregnancy rate (11.63%)

per cycle. Before treatment, 31 women (36.05%) were found to have psychiatric morbidity when assessed by GHQ. When assessed by BDI, 27 women (31.4%) had depressive symptoms and on assessment by HAMA, 29 women (33.72%) had anxiety symptoms. After completing the treatment cycle, (44.19%) had psychiatric morbidity. 31(36.05%) had depressive symptoms and 35 women (40.7 %) had anxiety symptoms. The post treatment BDI and HAMA scores were significantly higher than the corresponding scores at baseline in women with failed treatment. Women with primary infertility and those with multiple previous treatment cycles had more psychiatric morbidity and significantly higher post treatment BDI and HAMA mean scores.

Conclusion : Depression and anxiety symptoms are common in women with unexplained infertility seeking assisted reproduction. Failure of treatment is associated with significant deterioration of depression and anxiety symptoms. Special care is highly recommended for the women with failed treatment especially those with primary infertility and multiple previous treatment cycles.

Introduction

Many studies reported that depression and anxiety are highly prevalent among infertile women (Fido, 2004, Matsubayashi et al 2004 and Lok et al, 2002).

Monga et al, 2004 reported that infertility may result in a decrease in quality of life and an increase in marital discord especially in presence of depressive and anxiety disorders (Wilson and Kopitzke, 2002).

Couples seeking medical treatment of infertility typically undergo numerous diagnostic tests and procedures. Such measures can be painful, time-consuming, expensive and often involve the sharing of intimate details of one's sexual activities.

Consequently, couples seeking infertility treatment tend to report high levels of anxiety and embarrassment when undergoing the actual procedure (McNaughton-Cassill et al, 2002).

Clearly, medical treatment of infertility can be stressful, and in most cases this stress is superimposed on the psychological and marital stress that couples are experiencing because of their inability to conceive a child on their own (Hirsch and Hirsch, 1995).

When simple infertility treatments are unsuccessful, couples may elect to try complex, invasive reproductive technologies, such as intra uterine insemination (IUI), fallopian sperm perfusion (FSP), and in vitro fertilization (IVF). Patients may be faced with emotionally and ethically loaded issues, disclosure to family and friends about conception via reproductive technology. In addition, couples frequently deal with financial stress (Csemiczky et al, 2000).

Assisted reproduction techniques (ART) have expanded the opportunities for the treatment of infertility and have led to changes in the psychological profile of couples. For many couples, ART is the last chance of having a child which generally occurs after many months and, sometimes, years of treatment failure. The aspects of ART that are stressful to the patient are multifaceted and affect all parts of her life: marital, social, physical, emotional, and religious (Franco et al 2002).

Because of the emotional consequences of infertility and the stressful nature of ART, it is clear that pa-

tients require psychological support as part of the medical treatment process, and it is the responsibility of all members of the human reproduction team to provide this support (Covington, 1997).

High frequencies of anxiety and depression were reported in assisted reproduction clinics (Chen et al, 2004 and Anderson et al, 2003). This high prevalence of illness is especially concerning given the data suggesting that women who are undergoing infertility treatment are less likely to be successful if they suffer from depression or anxiety (Smeenk et al 2001 and Verhaak et al, 2001).

In general women, react more intensely to infertility and ART than men and report greater anxiety and depression than their partners before IVF (Dhaliwal et al, 2004 and Newton et al, 1990).

The purpose of the current study is : to evaluate the prevalence of psychiatric symptoms in a sample of women scheduled for assisted reproduction treatment cycle using a screening tool for psychiatric morbidity, and to explore the impact of treatment on depressive and anxiety symptoms.

Subjects and Methods :

The study was conducted during the period from August 2002 until August 2003 in a private hospital in

Saudia Arabia. The protocol of the study was approved by the hospital ethical board. 106 women with unexplained infertility scheduled for assisted reproduction techniques : intrauterine insemination (IUI) and fallopian tube sperm perfusion (FSP) were counselled to participate in the study. 94 women accepted. An informed consent was obtained from them. Of them 86 completed the study (drop out rate = 8.51%).

The age of female participants ranged from 21-36 years with a mean of 27.7 years. They had at least 2 years of infertility. No history of psychiatric illness prior to the diagnosis of infertility, and no family history for psychiatric illness were detected in all the women included in the study.

Infertility work up :

All women underwent thorough infertility evaluation including history, clinical examination, semen analysis, mid luteal phase progesterone, early follicular phase assay of prolactin, FSH, LH, and TSH, transvaginal sonography, as well as a tubal patency test. Unexplained infertility was diagnosed if the results of infertility evaluation proved to be normal.

Women underwent controlled ovarian stimulation using urinary Gonadotropins. Ovarian response was monitored by transvaginal sonography (TVS). Intra uterine in-

semination was done 32-36 hours after the hCG administration according to the protocol used by (Mostafa et al, 2004).

Clinical pregnancy was considered upon the visualization of an intrauterine pregnancy sac using TVS.

Psychiatric work up :

All women were subjected to full psychiatric history taking and clinical examination using the semi structured psychiatric interview used in Ain Shams University Psychiatric Department. Diagnoses were based on ICD-10 research criteria.

Psychometric assessment :

Base line assessment :

This evaluation was conducted in the early follicular phase before starting the assisted reproduction cycle.

Screening of the participants for the presence of psychiatric morbidity was done using the General Health Questionnaire (GHQ-28). Subjects who scored 4 or more represented the group with psychiatric morbidity (group I) and those who scored less than 4 represented the group free of psychiatric morbidity (group II).

Beck Depression Inventory (BDI) and Hamilton Anxiety Scale

(MAMA) were applied for assessment of depressive and anxiety symptoms respectively in all women.

Final assessment :

After the cycle of treatment was completed, (GHQ-28) was reapplied to all women to explore the impact of treatment on their psychiatric wellbeing, then; (BDI) and (MAMA) were reapplied to assess the impact of treatment on depressive and anxiety symptoms.

Psychometric tools :

General Health Questionnaire 28 (GHQ-28) : It is a self-administered screening test, designed to identify short-term changes in mental health (depression, anxiety, social dysfunction and somatic symptoms). It is a pure state measure. It is a measure of morbidity and is neither syndrome nor medical disorder specific. The GHQ is ideal for use in community and non-psychiatric settings and has four different versions. The GHQ-28 is the most well-known and popular version of the GHQ with a cut off score of 4 offering the best predictive value. The reliability and validity of the questionnaire has been extensively studied and it is widely accepted as an efficient screening instrument for non-psychotic psychological disturbances (Goldberg and Williams, 1988).

Beck Depression Inventory

(BDI) : It was developed by Beck (1961). It is one of the most widely used measures for assessing depression severity in diagnosed patients and for detecting possible depression in normal populations. It is composed of 21 self-report items, each of which corresponds to a specific category of depressive symptom and/or attitude. Each category describes a specific behavioural manifestation of depression and consists of a graded series of 4 self-evaluative statements describing increasing levels of severity from neutral to maximal. Numerical values from 0-3 are assigned each statement to indicate the degree of severity. A total score ranging from 0 to 63 is obtained by summing scores across items. Its reliability and validity are well documented (Beck et al, 1988).

Hamilton Anxiety Scale (HAMA) : It is a rating scale developed in the late 1950s to assess anxiety symptoms. The scale is designed to be administered by a clinician. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a 5 point scale, ranging from 0 (not present) to 4 (severe) with the total score ranging from 0 to 56. The HAMA has been used extensively to monitor treatment response in studies of generalized anxiety disorder and may also be useful for this purpose in clinical settings. A score of 14 has been suggested as the threshold for clinically significant anxiety, but scores of 5 or less are typical in in-

dividuals in the community. Reliability and Validity are fairly good.

Statistical Analysis : Data were presented in terms of mean, range, standard deviation, and percentage. Comparison between groups was done using the Mann Whitney test, Fisher exact test and, Chi square

test. The relationship between various variables was assessed using Spearman's rank correlation. values of less than 0.05 were considered significant. The SPSS (Chicago, IL, USA) and Graph pad Prism, 4 (USA) computer soft war were used for statistical analysis.

Results:

Sample characteristics:

The demographic and clinical characteristics are summarized in table (1).

Table 1:

Age: mean \pm SD (range)	27.7 \pm 3.3 (21 – 36)
Parity:	
Primary infertility:	56 (65.12%)
Secondary infertility:	30 (34.88%)
Duration of marriage (years):	4.2 \pm 2.3 (2 – 12)
Level of education:	
Primary school:	21 (24.42 %)
Secondary school:	26 (30.23 %)
University or equivalent:	39 (45.35%)
Infertility duration:	
2 – 3 years:	36 (41.86 %)
3 – 4 years:	28 (32.56%)
More than 4 years:	22 (25.58%)
Number of previous treatment cycles:	
First cycle:	31 (36.05%)
One previous cycle:	37 (43.02%)
More than One previous cycle	18 (20.93%)

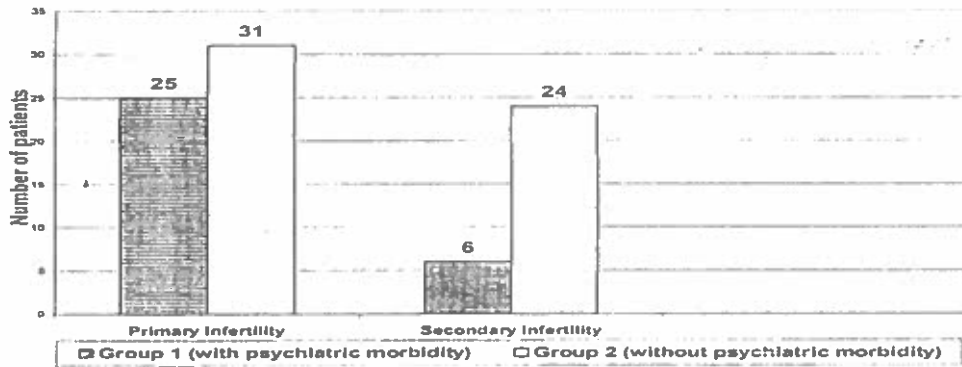
86 women with unexplained infertility underwent a cycle of assisted reproduction treatment, at the end of which, 10 women (11.63%) had clinical pregnancy confirmed by ultrasound scan. 76 women (88.37%) had unsuccessful treatment cycle.

Baseline psychiatric evaluation :

On screening for psychiatric morbidity using the GHQ-28 : out of the 86 women who completed the study 31 (36.05%) scored \geq 4 and

55 (63.95%) scored $<$ 4. On comparing women with psychiatric morbidity and those without (group I and II), there was no significant difference in the demographic characteristics including age, education, duration of marriage and infertility duration (Mann Whitney test, $P > 0.05$). On comparing the parity between group I and II, a significant difference was found between both groups with more prevalence of psychiatric morbidity in women with primary infertility (Fisher's exact test, $P = 0.0334$). (Figure 1).

Figure (1):



On comparing the number of previous treatment cycles between group I and II, a significant difference was found between both

groups with more prevalence of psychiatric morbidity in women who had more than one previous treatment cycles (Table 2) :

Table 2:

Number of treatment cycles	Group I	Group II	Total	Chi-square	P
First cycle:	6 (6.98 %)	25 (29.07%)	31 (36.05%)		
One previous cycle:	14 (16.28 %)	23 (26.74%)	37 (43.02%)		
More than One previous cycle	11 (12.79 %)	7 (8.14%)	18 (20.93%)		
Total	31(36.05%)	55(63.95%)	86(100%)	8.703	0.0129 *

* = statistically significant

27 women (31.4%) had depressive symptoms as assessed by BDI : 19 (22.09 %) mild, 6 (6.98%) moderate and 2 (2.33%) severe.

en (16.28%) moderate and 4 women (4.65%) severe.

29 women (33.72 %) had anxiety symptoms as assessed by MAMA : 11 women (12.79%) mild, 14 wom-

Post treatment psychiatric evaluation :

GHQ was reapplied to all women, 38 (44.19%) scored ≥ 4 on GHQ

and 48 (55.81%) scored < 4.

31 (36.05%) had depressive symptoms as assessed by BDI 15 women (17.44%) mild 12 women (13.95%) moderate and 4 women (4.65%) severe (Figure 2).

35 women (40.7%) had anxiety symptoms as assessed by HAMA: 12 women (13.95%) mild, 18 women (20.93%) moderate and 5 women (5.81%) severe (Figure 3).

Figure (2) :

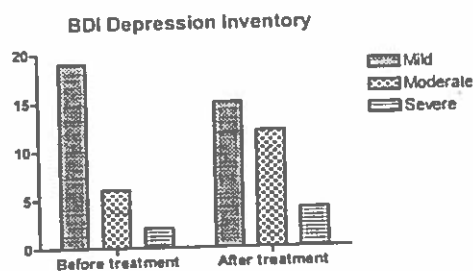
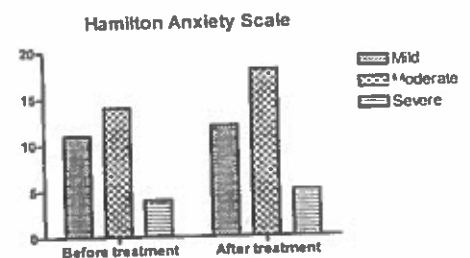


Figure (3) :



The post treatment BDI scores for the whole sample and for the group with failed treatment (Failed ART) were significantly higher than the corresponding scores at baseline

but for the group with successful treatment (Successful ART) the scores decreased significantly after pregnancy as shown in table 4 :

Table 4: Depressive symptoms before and after treatment [BDI mean scores \pm SD]:

	Before treatment	After treatment failure	Mann Whitney U	P value
Whole sample	9.13 \pm 5.61	11.03 \pm 7.54	3042	0.0445 *
Failed ART	8.62 \pm 5.47	11.26 \pm 7.69	2107	0.004 *
Successful ART	11.7 \pm 5.33	7.3 \pm 3.89	23.50	0.0433 *

* = statistically significant

The post treatment HAMA scores of the whole sample and of the group with failed treatment (Failed ART) were significantly higher than the corresponding scores at baseline but for the group

with successful treatment (Successful ART) the scores decreased after pregnancy but the differences were not statistically significant as shown in table 5 :

Table 5: Anxiety symptoms before and after treatment [HAMA mean scores \pm SD]:

	Before treatment	After treatment	Mann Whitney (U)	P value
Whole sample	14.13 \pm 8.11	16.63 \pm 8.74	2985	0.0291 *
Failed ART	14.07 \pm 8.18	17.18 \pm 8.78	2172	0.0083 *
Successful ART	14.6 \pm 7.89	12.4 \pm 7.47	33.00	0.2176 ns

* = statistically significant and ns = not significant

Women with primary infertility had significantly higher post treatment BDI and HAMA mean scores than those with secondary infertility (Mann Whitney, $P < 0.01$ and $P < 0.001$ respectively).

Women with multiple treatment cycles had significantly higher post treatment BDI and HAMA mean scores than those attending first treatment cycle (Mann Whitney, $P < 0.05$ for both).

No statistically significant correlations were found between the post treatment BDI and HAMA mean scores and demographic factors or duration of infertility ($P > 0.05$).

DISCUSSION

Many studies indicate that levels of depression and anxiety are high in infertile women (Fido, 2004 and Matsubayashi et al 2004). On the other hand, some reports show that there is no statistically significant difference between the depression and anxiety levels of both healthy and infertile groups (Guz et al, 2003, Berg and Wilson, 1990).

Dhaliwal et al, 2004 reported that psychological components play a significant role in infertility of unknown etiology. Women with unexplained infertility might be very anxious and express the most distress because the cause of their infertility has not been determined (Domar et al, 1992). Souter et al 2002 reported higher scores for psychiatric morbidity in women with an identifiable cause for infertility than those with unexplained infertility. On the other hand, Lok et al 2002 found no difference in BDI scores between women with unexplained infertility and women with different identifiable causes for infertility.

In the current study : Psychiatric morbidity was assessed in women with unexplained infertility undergoing an ART cycle. Before treatment, 31 (36.05%) scored ≥ 4 on the GHQ-28 in comparison to 33% in the study of Lok et al 2002 who studied only the women with failed assisted reproduction treatment and used GHQ-30 with 5 as cut-off score. Souter et al, 2002 used GHQ-12 and found (47.1%) had positive score $\geq 6/12$ and (32.5%) had a

score of $\geq 8/12$, in a sample of infertile women including all causes of infertility.

For assessment of psychiatric disorders Chen et al 2004 used Mini-International Neuropsychiatric Interview (MINI) and found that 40.2% of infertile women before a new course of ART had a psychiatric disorder. Guerra et al 1998 found that 24% of the assisted reproduction patients had a psychiatric disorder and 33% had psychological dysfunction.

After the cycle of treatment was completed, 38 (44.19%) scored ≥ 4 on GHQ i.e. 7 women turned positive for psychiatric morbidity signifying deterioration of the psychiatric wellbeing of 8.14% of the sample. As the success rate per treatment cycle in the current study was only 11.63%, this deterioration could be attributed to treatment failure. This is in agree with results of Lok et al 2002 who found that following failed treatment further 10% of his sample scored above GHQ cut off.

As high frequencies of anxiety and depression were reported in infertile women and in assisted reproduction clinics (Chen et al. 2004, Anderson et al, 2003), these symptoms were explored in the sample before and after treatment.

In the present study, 27 women (31.4%) had depressive symptoms as assessed by BDI and of them

9.31% had moderate to severe symptoms in comparison to Lok et al 2002 who found that 8% of infertile women had BDI score of 20 or more signifying moderate to severe depression before treatment.

Domar et al 1992 found that 37% of infertile women scored in the depressed range on the BDI, of them 28% had mild/moderate scores, 7.2% had moderate /severe scores and 1.2% had extremely severe scores. When Chen et al, 2004 used MINI, he found that 17% of the infertile women attending ART cycle had major depressive disorder and 9.8% had dysthymic disorder. Also Meller et al 2002 used structured clinical interview (SCID) and found that 32% of women with unexplained infertility had current major depression and 63% had definite history of depression.

At the end of the treatment cycle, 31 (36.05%) women had depressive symptoms signaling an increase of 4.7% with the main rise in the group of moderate depression. This is in agree with the results of Verhaak et al 2002 who found that after a first failed treatment cycle, women showed an increase in depression (13% showed clinically relevant forms of depression). Also Lok et al 2002 and Newton et al, 1990 reported the same findings regarding BDI scores after failed treatment.

During an ART cycle, although stress is noticeable in different stag-

es of treatment it reaches a significantly high level after failure. Negative result is intimately connected to a feeling of loss, which may provoke an important depression (Franco et al 2002 and Lok et al 2002).

In the current study : it was found that, 29 (33.72%) women had anxiety symptoms as assessed by HAMA before treatment. This in accordance with Anderson et al, 2003 who found that about a quarter of the infertile women attending the assisted reproduction clinics had a high level of anxiety and Chen et al, 2004 who used MINI and found that 28.6% of the infertile women attending ART cycle had anxiety disorders.

At the end of the treatment cycle, 35 women (40.7%) had anxiety symptoms signaling an increase of 7% with the main rise in the group of moderate anxiety. This was in agree with the findings of Verhaak et al 2002 and Newton et al, 1990.

Although general considerations can be made about the stress level during ART, the experience of the patient with infertility is personal and unique. Each patient reacting differently to stress based on her personality and life experience. Matsubayashi et al 2004 and Guz et al, 2003 found that infertile women who were suffering of lack of husband's support and faced with negative reactions from their husbands, their husbands' families or their so-

cial environment scored higher for anxiety and depression. Cultural factors may play some role in the mood of infertile women. In traditional Eastern culture the family is usually valued more than the individual. The meaning of an individual's life often includes the extension of the family by giving birth to offspring. Infertile women in the East may suffer from more stress and anxiety than those in the West (Chen et al 2004).

After completion of the current treatment cycle, the post treatment BDI and HAMA scores were significantly higher than the corresponding scores at baseline. This was for the whole sample and for the group of unsuccessful treatment. Women who got pregnant had significantly lower post treatment BDI scores. HAMA scores decreased but the differences were not statistically significant, this could be explained by the expected worries about fate of the pregnancy.

Verhaak et al 2002 found no differences between pre- and posttreatment levels of anxiety and depression after a successful treatment.

Women with primary infertility were associated with more psychiatric morbidity and significantly higher post treatment BDI and HAMA mean scores. This was in agree with Newton et al, 1990 who found that women without children were a subgroup particularly vulnerable to the

stress of failure.

On the other hand, Souter et al, 2002 and Domar et al 1992 found no significant association between parity and psychological score.

Women with higher number of previous treatment cycles were associated with more psychiatric morbidity and significantly higher post treatment BDI and HAMA mean scores. This is in accordance with Guerra et al, 1998 who reported that Psychiatric morbidity was significantly associated with the number of treatment cycles and Boivin et al 1995 who concluded that it was the number of treatment failure experiences per se rather than the actual time spent in treatment that is the critical factor affecting the distress experienced by patients. Also Souter et al, 2002 reported that GHQ-12 scores significantly increased with number of clinical attendances. They attributed this to the possibility that women who attend for the first time feel positive about the possibility of treatment and have not received any bad news about investigations or their prognosis.

On the contrary, Chen et al, 2004 and Lok et al 2002 concluded that history of previous assisted reproduction treatment were not risk factors for psychiatric morbidities in the assisted reproduction clinic.

In the present study, No statistically significant correlations were

found between the post treatment BDI and HAMA mean scores and demographic factors or duration of infertility ($P > 0.05$).

These results support the findings of Chen et al, 2004 who reported that demographic features were not risk factors for psychiatric morbidities in the assisted reproduction clinic.

However, Guz et al, 2003 found that age and duration of infertility were inversely correlated with depression and anxiety. These results may indicate that the patients are able to accept the problem as they grow older and the longer infertility persists. Also, Souter et al, 2002 reported that GHQ-12 scores significantly decreased as the patient's age increased.

Chiba et al.1997 reported that the duration of infertility plays an important role in the development of depression with longer duration of infertility associated with more depression and Guerra et al, 1998 reported that psychiatric morbidity was significantly associated with length of infertility.

Domar et al, 1992 found that women with a 2- to 3-year history of infertility had significantly higher depression scores compared with women with infertility durations of < 1 year or > 6 years.

This study assessed psychiatric

symptoms and not disorders, need to be replicated on a bigger sample using more refined diagnostic criteria to assess accurately the prevalence and pattern of psychiatric disorders in women with unexplained infertility specially those attending assisted reproduction treatment.

Conclusion :

Depression and anxiety symptoms are common in women with unexplained infertility seeking as-

sisted reproduction. Failure of treatment is associated with significant deterioration of these symptoms. Clinicians offering assisted reproduction treatment should be aware of the high prevalence of psychiatric morbidity in their patients and to ensure the appropriate psychological support for them. Special care is highly recommended for the women with failed treatment especially those with primary infertility and multiple previous treatment cycles.

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