A Two-centre Study of Psychiatric Morbidity among Infertile Chinese Women in Hong Kong

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Objectives: To study the psychiatric morbidity of infertile females versus fertile females in Hong Kong using validated psychometric tests and to investigate the intrinsic demographic factors related to psychological morbidity that arises from infertility.
Methods: A two-centre cross-sectional observational study was conducted of consecutive infertile patients who attended an infertility clinic and fertile controls who attended the nurse-led smear clinic from 1 June 2014 to 30 November 2014. Socio-demographic and clinical data were collected. Psychometric status was assessed by a 12-item General Health Questionnaire, Beck Depression Inventory, and State-Trait Anxiety Inventory (STAI).
Results: Analysis of 245 valid questionnaires revealed a significantly higher median STAI score in infertile women compared with their fertile counterparts (58 vs. 50, p=0.001). More infertile women had tertiary education or above (37.4% vs. 14.3%, p=0.01) and more were in full-time employment compared with fertile controls (71.6% vs. 41.0%, p=0.002). The prevalence of housewives was double among the controls (46.2% vs. 20.6%, p=0.002). More infertile women lived in private housing compared with controls (75.5% vs. 50.0%, p=0.001). Subgroup analyses revealed that infertile housewives and those living in private housing scored significantly higher in STAI than their fertile counterparts (p=0.03 and p=0.04, respectively).
Conclusion: Infertile women have a higher predisposition to anxiety disorders and were more career-oriented. Subgroup analyses of possible confounding factors revealed that infertile housewives and private-housing occupants were significantly more prone to anxiety than their fertile counterparts.
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Introduction

Fertility has been viewed as the link between generations and the tie for many to immortality. Infertility is defined as a woman of reproductive age who has not conceived after 1 year of unprotected sexual intercourse[1]. It is a public health issue, with a 10% global prevalence. In Hong Kong, an estimated one in six couples have difficulty conceiving for a variety of reasons[2]. With its emotionally stressful nature and high socio-economic burden, infertility is a life crisis for both men and women. It is not only a gynaecological illness but also a biopsychosocial health problem[3].

Psychiatric Morbidity Associated with Infertility

Much previous research has focused on the psychological distress associated with infertility. Descriptive reports suggest that the experience of infertility can be devastating[3]. Across many cultures, individuals perceive their childlessness as a sign of diminished status, defectiveness, and incompetence. Some women hide their distress from health care providers because of the fear of being stigmatised and criticised[4]. It has been reported that high rates of clinically significant symptoms of depression and anxiety, suicidal tendency, and a strong conceptualisation of grief affect people with infertility[5]. Intimate partner violence and sexual violence have also been associated with infertility[5]. Another difficult emotional consequence of infertility is the loss of control over one's life[6]. This loss of control may begin prior to a formal diagnosis of infertility; difficulty with conception can challenge a couple's notion that they are in charge of their own reproduction. Since an important part of the

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adult identity is to be capable of reproduction[7,8], infertility becomes the focal point of daily discourse, often to the exclusion of other important aspects of life.

Psychiatric Morbidity and Infertility in Chinese

Distress associated with infertility can be complex, multidimensional, and strongly influenced by sociocultural values. As many Chinese societies are influenced by Confucian teaching where barrenness is regarded as an unfilial offence, infertility can be exceedingly stigmatising and traumatic. In a psychological survey performed in Beijing[9], more than 80% of couples had been tormented by various psychological stresses caused by infertility, and half of the infertile women rated infertility as the most stressful event in their lives. This was viewed as being even more stressful than marital dissolution or the death of a close relative. A local study by Lok et al[10] revealed that 33% of patients who attended an assisted reproductive technology clinic reported a significant level of psychological stress and 8% exhibited moderate to severe symptoms of depression.

A number of previous publications have addressed the psychological impact of infertility and its treatment or treatment failure on infertile women. This current study was designed to investigate the psychological impact of the diagnosis of infertility on infertile women and compare their level of psychiatric morbidity with that of their fertile counterparts in Hong Kong. Our objective was to assess the severity of psychological morbidity among these women using validated psychometric tests and to identify the associated intrinsic demographic factors. A better understanding of the psychological impact of infertility in Hong Kong women will enable the formulation of a more tailored psychological intervention.

Methods and Materials

Subjects and Controls

In Hong Kong, reproductive technology techniques can be provided only to partners who are married[11]. In our study, infertile Chinese women who attended the infertility clinic at the Pamela Youde Nethersole Eastern Hospital (PYNEH) and the Prince of Wales Hospital (PWH) were recruited. The PYNEH is a regional hospital that serves Hong Kong Island East and offers level 2 infertility treatment such as ovulation induction and intrauterine insemination. The PWH is a university-affiliated hospital that serves the New Territories in Hong Kong and provides level 3 infertility treatment including in-vitro fertilisation. Patients seen at the infertility clinics are largely referred by primary care physicians, private sector specialists, and the Family Planning Association. Patients who were non-Chinese, unwilling to participate, or who had a history of psychiatric or chronic disease(s) were excluded from the study.

Healthy married fertile women who attended the nurse-led smear clinic at the PWH served as controls. These women had treated cervical pathology and were currently stable and attending regular Pap smear surveillance at the nurse-led smear clinic. Those who were non-Chinese, unwilling to participate, or who had a history of infertility or psychiatric or chronic disease(s) were excluded from the study.

Study Design

This was a cross-sectional observational study. After obtaining institutional review board approval at both PYNEH and PWH, patients were given an explanation of the aim and process of the study, including all psychometric tests and interviews to be conducted. Written informed consent was obtained. All participants were requested to complete a set of questionnaires that requested socio-demographic and clinical data (Appendix) and three psychometric self-rating scales: 12-item General Health Questionnaire (GHQ-12), Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAI). The results were compared among the two groups.

The socio-demographic data (age, years of marriage, education level, employment status and family income) and clinical data (type, cause and duration of infertility, history of fertility treatment received, obstetric history and history of psychiatric illness) were collected.

General Health Questionnaire

The GHQ is an extensively used self-reported questionnaire for the detection and measurement of psychiatric morbidity in a general clinical setting[12]. The GHQ-12 is the shortest version and comprises only 12 questions. The questionnaire focuses on two major areas: inability to carry out normal functions and the appearance of new and distressing phenomena. The caseness threshold is 4 for the GHQ-12. The validated Chinese version of GHQ-12 was used[13].

Beck Depression Inventory

The 21-item BDI is one of the most widely used and reliable questionnaires for detecting depression as well as its intensity in normal populations[14]. A score of ≥12 is associated with depression. The validated Chinese version was used[15].

State-Trait Anxiety Inventory

The STAI has been widely applied to assess a patient's vulnerability to be anxious (Trait Anxiety scale) and current anxiety level (State Anxiety scale)[16]. A total score of ≥39 for the State Anxiety scale has been suggested to detect clinically significant symptoms. The Chinese validated version was used[17].

Sample Size Calculation

Based on a local study published in 2002[10], 33% of infertile Hong Kong Chinese women who attended an ART clinic scored above an arbitrary cutoff in the GHQ. Assuming half of these high scorers fulfilled the appropriate diagnosis of a psychiatric disorder, the anticipated prevalence was 16.5%. If the anticipated rate is 4 times higher than that of the normal fertile controls as described in previous literature[18], with a case-to-control ratio of 4:1, 152 subjects and 38 controls were required with a 80% power at a 5% significance level.

Two-sample Proportion Test

The sample size for subject (n0) and control group (n1) were calculated based on the formula:

$$n_0 = \frac{(z_{\alpha/2} + z_{1-\beta})^2[kp_1(1-p_1) + p_2(1-p_2)]}{k(p_1 - p_2)^2}$$

where α denotes the significance level (0.05); β as 1-power (assuming the power being 80%); n1 as k (control-to-case ratio, 1:4) x n_0; p_1 as sample prevalence rate of the subject group (16.5%); and p2 as sample prevalence rate of the control group (16.5% / 4 = 4.125%). With power of 80% and the case-to-control ratio of 4:1, the total required sample size was 190 (i.e. 152 subjects and 38 controls).

Statistical Analyses

All statistical analyses were performed using PASW Statistics 18, release version 18.0.0 (SPSS Inc., Chicago [IL], US). For categorical data, the Chi-square test and Fisher's exact test were used according to the data pattern. For continuous data with a highly skewed distribution, a non-parametric test (i.e. Mann-Whitney *U* test) was used. The critical level of statistical significance was set at 0.05.

Correlation analyses of demographic variables in psychometric test scores were done. For continuous data with a highly skewed distribution, a non-parametric test (i.e. Spearman's rho correlation test) was used. Spearman's rho correlation coefficient of >0.4 in the absolute value and a p value of <0.05 was regarded as statistically significant.

Subgroup analyses of potential confounding demographic factors were performed to eliminate their effect on psychometric test scores. For continuous data with a highly skewed distribution, a non-parametric test (i.e. Mann-Whitney *U* test) was used. The critical level of statistical significance was set at 0.05.

Results

A total of 245 valid questionnaires were collected during the period 1 June 2014 to 30 November 2014. The Figure shows the recruitment of participants in this study. In the infertile arm, 58 women attending the PYNEH infertility clinic and 178 attending the PWH infertility clinic were approached, of whom 22 did not satisfy the inclusion criteria and nine refused to participate as they

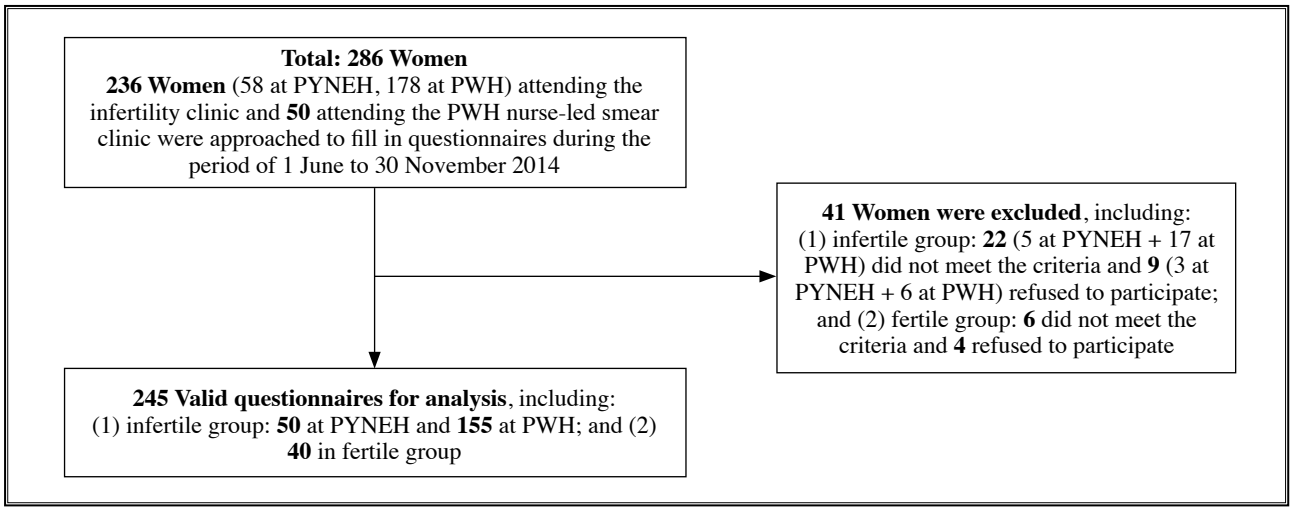

Figure. Recruitment of participants

Abbreviations: PWH = Prince of Wales Hospital; PYNEH = Pamela Youde Nethersole Eastern Hospital

were unwilling to disclose personal information to the researchers. A final total of 205 infertile women were thus recruited. In the fertile arm, 50 fertile women attending the nurse-led smear clinic at PWH were approached, of whom six did not satisfy the inclusion criteria and four refused to participate as they were unwilling to disclose personal information to the researchers. A total of 40 fertile controls were thus recruited. Table 1 shows the women's socio-demographic and clinical data. The median age was 34 years in infertile women and 35 years in the control group; no statistical difference in age was noted between the two groups (p=0.78). Approximately 93% of the infertile women were nulliparous and 85% of the fertile controls had at least one child (p<0.001). A history of termination of pregnancy was present in six of the nulliparous controls. The rate of miscarriages was similar between the two

Table 1. Demographic characteristics of participants*

Characteristic	Infertile group (n=205)	Control group (n=40)	p Value
Age (years)	34 (32-37)	35 (32-37)	0.78
Parity			<0.001
0	190 (92.7)	6 (15.0)	
1	15 (7.3)	17 (42.5)	
2	0	15 (37.5)	
≥3	0	2 (5.0)	
No. of previous miscarriage			0.90
0	172 (83.9)	34 (85.0)	
1	22 (10.7)	4 (10.0)	
2	8 (3.9)	1 (2.5)	
≥3	3 (1.5)	1 (2.5)	
No. of previous abortion			<0.001
0	179 (87.3)	17 (42.5)	
1	18 (8.8)	10 (25.0)	
2	6 (2.9)	11 (27.5)	
≥3	2 (1.0)	2 (5.0)	
Family income (HK$)	25,000 (15,000-40,000)	21,500 (14,750-30,000)	0.18
Missing data	18	10	
Education level			0.01
Primary	6 (3.0)	3 (8.6)	
Secondary	118 (59.6)	27 (77.1)	
Tertiary or above	74 (37.4)	5 (14.3)	
Missing data	7	5	
Employment status			0.002
Full-time	146 (71.6)	16 (41.0)	
Part-time	8 (3.9)	3 (7.7)	
Unemployed	8 (3.9)	2 (5.1)	
Housewife	42 (20.6)	18 (46.2)	
Missing data	1	1	
Living place			0.001
Public housing	49 (24.5)	19 (50.0)	
Private	151 (75.5)	19 (50.0)	
Missing data	5	2	

* Continuous variables are shown as median (interquartile range) and analysed by Mann-Whitney *U* test. Categorical variables are shown as No. (%) and analysed by Pearson Chi-square test or Fisher's exact test

Table 2. Comparisons of psychometric assessment between infertile and fertile women*

	Infertile group (n=205)	Control group (n=40)	p Value
GHQ-12			
Total score	1 (0-3)	2 (0-4)	0.21
Score <4	153/202 (76)	29 (72)	0.66
Score ≥4	49/202 (24)	11 (28)	
Missing data	3	-	
BDI			
Total score	5 (1-11)	6 (0-17)	0.75
Score <12	152/193 (79)	25/39 (64)	0.05
Score ≥12	41/193 (21)	14/39 (36)	
Missing data	12	1	
STAI			
Total score	58 (51-65)	50 (46-57)	0.001
Score <39	4/198 (2)	2 (5)	0.25
Score ≥39	194/198 (98)	36 (95)	
Missing data	7	2	

Abbreviations: BDI = Beck Depression Inventory; GHQ-12 = 12-item General Health Questionnaire; STAI = State-Trait Anxiety Inventory

* Continuous variables are shown as median (interquartile range) and analysed by Mann-Whitney *U* test. Categorical variables are shown as No. (%) and analysed by Pearson Chi-square test or Fisher's exact test. Percentages were calculated with exclusion of missing data

groups: 16.1% of infertile women and 15% of the controls (p=0.90). A history of termination was present in 12.7% of the infertile women, significantly less compared with 57.5% of the controls (p<0.001). Family income was comparable between the two groups with a median of HK$25,000 per month in infertile subjects compared with HK$21,500 in the controls.

The majority of the women from the two groups scored below the cutoff value of GHQ-12 and BDI (GHQ-12 score <4: 76% in the infertile group vs. 72% in the controls; BDI score <12: 79% vs. 64%), and were not statistically different (Table 2).

Up to 98% of infertile women scored above the STAI cutoff value of 39, indicating presence of clinically significant anxiety symptoms. A significantly higher STAI median (interquartile range) score was noted compared with the controls (58 [51-65] vs. 50 [46-57], p=0.001) [Table 2].

Correlation analyses of demographic variables and STAI scores were performed. The results are presented as Spearman's rho correlation coefficient and shown in Table 3. Since none of the demographic variables were positively or negatively correlated with the STAI score to a statistically significant level, subgroup analyses were performed after matching for education level, occupational status, and housing arrangement between the infertile and fertile groups to eliminate the effect of these factors on the STAI score.

The infertile women were more highly educated with 37.4% having a tertiary education compared with 14.3% in the control group (p=0.01, Table 1). Participants with only primary level education (n=9) were excluded because the sample size was too small. Subgroup analysis

Table 3. Correlations between State-Trait Anxiety Inventory scores and continuous variables

Variable	Score
Age	r= –0.049 (p=0.45, n=236)
Parity	r= –0.171 (p=0.01, n=236)
No. of previous miscarriage	r= –0.031 (p=0.63, n=236)
No. of previous abortion	r= –0.225 (p<0.001, n=236)
Family income	r=0.147 (p=0.03, n=210)
Education level	r=0.159 (p=0.02, n=226)

of education level–matched participants showed no significant difference in the median STAI score among the two groups (p=0.11, Table 4). The infertile group, regardless of their education level, scored higher in median STAI scores when compared with the controls, although no statistical difference was demonstrated.

Employment was also statistically different between the two groups (p=0.002); the majority of the infertile subjects had a full-time job compared with the control group (71.6% vs. 41.0%) whilst the controls were mostly housewives (46.2% vs. 20.6% in the infertile group). Subgroup analysis in the full-time employed participants showed no significant difference in the median (interquartile range) STAI score (57.5 [51-64.25] in the infertile group vs. 53.5 [47-57.75] in the control group, p=0.10). Nonetheless analysis of the housewife population revealed that infertile housewives had significantly more anxiety than fertile housewives (59 [51-66.75] in the infertile group vs. 50 [46.5-66] in the control group, p=0.03) [Table 4]. Subgroup analysis of the part-time employed (n=11) and unemployed participants (n=10) was excluded because their sample size was too small. The types of housing arrangement were statistically different between the infertile and control groups. Significantly more infertile women lived in private housing (75.5%) than public housing (24.5%). This is in contrast to the 50% split in the fertile controls (p=0.001) that is consistent with the normal distribution for the general population of Hong Kong[19]. The median (interquartile range) STAI score was significantly higher in the infertile private housing occupants than their fertile counterparts (58 [51-65] in the infertile group vs. 50 [47-57.5] in the control group, p=0.04) [Table 4].

Discussion

In this study, we analysed the psychiatric morbidity of infertile women using three validated psychometric tests. We used the GHQ-12, BDI, and STAI to assess the level of psychiatric stress, depression tendency and anxiety symptoms. No significant difference was noted between the two groups for GHQ-12 and BDI; thus our study cannot demonstrate a positive association between infertility and depression. That depression is not always recognised in infertile patients possibly because they are reluctant to report depressive symptoms to their clinician. It has been reported that these patients prefer to appear well-adjusted, presumably because they fear that fertility treatment will be denied or postponed if psychiatric problems are revealed[20,21].

Up to 98% of infertile participants scored above the cutoff value of STAI revealing that they were displaying clinically significant anxiety symptoms. This finding is in line with previous studies that showed infertility to be associated with anxiety[22,23]. With this high STAI score in both groups, our results showed that Hong Kong women of

Table 4. Subgroup analysis of State-Trait Anxiety Inventory scores*

	Infertile group	Control group	p Value
Education level			
Secondary	(n=118)	(n=27)	
	57 (50.75-64)	50 (46.75-58.25)	0.06
Tertiary	(n=74)	(n=5)	
	60 (53.5-66.5)	53 (44-61)	0.11
Employment			
Housewife	(n=42)	(n=18)	
	59 (51-66.75)	50 (46.5-66)	0.03
Full-time	(n=146)	(n=16)	
	57.5 (51-64.25)	53.5 (47-57.75)	0.10
Living place			
Public housing	(n=49)	(n=19)	
	56 (50.75-63)	50 (46-59)	0.11
Private housing	(n=151)	(n=19)	
	58 (51-65)	50 (47-57.5)	0.04

* Continuous variables are shown as median (interquartile range) and analysed by Mann-Whitney *U* test

reproductive age are vulnerable to psychological morbidity, especially anxiety. The reason behind this observation is nonetheless beyond the scope of this study. The finding that clinically significant anxiety is very common in women of reproductive age encouraged us to consider the incorporation of STAI as an essential assessment tool for infertility patients to identify those patients at risk. Links have been suggested between anxiety, depression, the hypothalamic-pituitary-adrenal axis (e.g. anxiety-induced hyperprolactinaemia) and failure to conceive; psychological intervention aimed at reducing anxiety might increase the likelihood of conception[24-26].

Comparison of infertile subjects with controls revealed a significantly higher median STAI score in the former. Nonetheless before we can conclude that infertility is a significant factor underlying increased anxiety, subgroup analysis was performed to correct three apparent confounding factors that differed significantly between the infertile and control groups. These were education level, employment status, and housing type. Our analysis of these matched cohorts also showed significant differences in the STAI levels, consolidating the concept that infertility is a stress-inducing condition.

Infertile women had a higher education level and a higher proportion were in full-time employment. Our findings are consistent with the widely observed global trend of infertile women being more career-oriented[27]. In our subgroup education level–matched cohort analysis, we did not demonstrate a statistically significant difference between the two groups; nonetheless the median STAI score in the infertile group tended to be higher. This observation agrees with the findings of previous studies that infertile patients are more anxious than the normal population[24,28].

As expected with more career-oriented women, the proportion of those in full-time employment was higher in the infertile group. In contrast, the control group comprised mostly housewives, followed by full-time, part-time, and then unemployed women. Subgroup analysis of all full-time employed participants showed no difference in the STAI median scores between the infertile women and controls. Donkor and Sandall[29] suggested that infertile women with high-level occupations use a problem-focused stress coping strategy, so they experience a lower infertility-related stress. This could explain why the full-time working infertile patients in our study did not show a significantly higher STAI score despite being confronted by an apparent life stressor. We postulate that although the nature of the stressor is very important, the stress-coping mechanism also plays a crucial role in determining the severity of stress manifested.

Subgroup analysis also showed that infertile housewives suffered significantly more anxiety symptoms than fertile housewives. A Japanese group and an Iran group have also demonstrated this phenomenon[24,30]; since housewives are generally expected to manage households and to procreate, it is easy to understand why they are more vulnerable to mental stress secondary to being infertile. Significantly more infertile women (75.5%) lived in private housing compared with the control group. Although they lived in different types of housing estates, the family income for the two groups was similar, and close to the Hong Kong average income[19]. This suggests that their social support and resources were not significantly different. Nonetheless with the astronomical housing price for both rental and private properties in Hong Kong, it is fair to hypothesise that the relative spending power and financial flexibility are lower for those living in private housing. To correct for this potential bias due to their financial flexibility, a subgroup analysis was required. This subgroup analysis showed a statistically significant difference when the median STAI score of private-housing–matched infertile women and controls was compared. This means that by matching the financial burden of the two groups, the difference in the observed median STAI score may be due to the infertility problem endured by the infertile women.

The strength of our study is that it was a two-centre study that involved 245 participants from a diverse background. This contributes to the generalisability of the study. Results generated from the current study can be extrapolated and applied to the population we are serving. Nonetheless there are several limitations. First, measurement of psychiatric morbidity was based on the use of psychometric assessment only. These psychometric tests function as a screening tool and assess the severity of symptoms in a patient with a previously diagnosed psychiatric disorder. Formal assessment is beyond the role of an obstetrician. A clinical psychologist or psychiatrist is required to clinically diagnose and manage individuals with genuine psychiatric disorders. We suggest referral to a clinical psychologist or psychiatrist for women who score above the cutoff level in the psychometric tests so that formal assessment using the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders can be arranged with intervention planned when indicated. Second, although the initial power analysis (80%) deemed our study to have adequate subjects for overall assessment, a larger trial with more patients would allow us to perform

more subgroup analyses in a comprehensive manner since some subgroups could not be properly analysed due to their small case number, for example those with only primary school education (n=9), part-time employed (n=11), or unemployed (n=10). Third, the controls were recruited from one centre only. If a larger trial is to be considered in the future, liaisons with the Family Planning Association of Hong Kong and Maternal and Child Health Centres can be considered as it can enrich the diversity of the controls and be more representative of the general population. Fourth, the magnitude of the effect of infertility duration and previous treatment attempts and/or failure on psychiatric morbidity were beyond the scope of our study. It would be clinically useful to know whether they have an adverse effect on psychiatric wellbeing so that clinicians can identify infertile patients who are more vulnerable to psychiatric morbidity.

Conclusion

In a cohort matched for age, ethnicity, marital status, and family structure, infertile women had a higher predisposition to anxiety disorders than controls, based on the psychometric assessment using STAI. In our study, infertile women had a higher level of education, more were in full-time employment, and more lived in private housing. Correction of these confounding factors was achieved by performing matched subgroup analyses. Infertile housewives and those living in private housing were especially more prone to anxiety than their fertile counterparts. We suggest that a thorough history-taking that addresses these factors is prudent. Since STAI identified a large proportion of infertile patients at risk of clinically significant anxiety, we propose to incorporate STAI as an essential screening tool at the first infertility consultation with consequent referral to a clinical psychologist or psychiatrist if the STAI is abnormally elevated. Infertility is a disease of the body and mind so a holistic approach must be employed to help affected couples. Our aim as health care providers is to help them to endure this stressful experience and accept this harsh diagnosis while providing adequate support and information to enhance their understanding and compliance with the subsequent intense treatment.

Declaration

The authors declared no conflict of interest in this study.

Appendix

Additional material related to this article can be found on the HKJGOM website. Please go to <http://www.hkjgom.org/>, search for the appropriate article, and click on **Full Text (PDF)** following the title.

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