ORIGINAL ARTICLE

Identification of associated risk factors for the severity of generalized anxiety disorder among Iranian infertile people: An ordinal regression analysis with a flexible link function

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Background: Generalized anxiety disorder (GAD) is a common disorder in infertile people. The aim of this study was the identification of associated risk factors for the severity of GAD in infertile people using an ordinal model with a flexible link function. **Materials and Methods:** This cross-sectional study was conducted on 1146 individuals with a couple's infertility problem selected from an infertility center in Tehran, Iran. Data collected using self-administered questionnaires include demographic/clinical information and GAD-7. We used a Bayesian-ordered symmetric power logit (splogit) model to identify the risk factors for the severity of GAD. Furthermore, we implemented standard ordinal models to compare with the ordered splogit model. **Results:** Female gender (B coefficient 0.48, 95% credible interval [CrI]: 0.34–0.62), longer duration of infertility (B coefficient 0.03, 95% CrI: 0.01–0.04), previous treatment failure (B coefficient 0.17, 95% CrI: 0.03–0.30), and self-cause of infertility (B coefficient 0.12, 95% CrI: 0.01–0.23) were associated factors with the severity of GAD. The splogit model had a better fit and performance to determine the associated risk factor for the severity of GAD as compared to standard models. It provided more precise estimates of risk factors and one more significant risk factor. **Conclusion:** Infertile people with female gender, longer duration of infertility, failure in previous treatments, and self-cause infertility are more likely to experience higher severity levels of GAD and require additional psychological, and support interventions. Furthermore, it can be argued that the ordinal splogit model is more powerful to identify the associated risk factors for the severity of GAD.

Key words: Anxiety, Bayesian analysis, generalized anxiety disorder-7, infertility, risk factors

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INTRODUCTION

Infertility is the failure to become pregnant after 1 year or more of regular sexual intercourse without using protected methods.[1,2] Annually, an estimated 60–80 million couples are affected by infertility worldwide.[3] Infertility is an unpleasant and stressful occasion in the life of a person and may lead to psychological disorders such as depression and anxiety in both men and women.[4]

Generalized anxiety disorder (GAD) is one of the psychological disorders which is often happening in infertile people.[5] People with GAD experience extreme, persistent, and unrealistic worry about different events or activities.[6] The current estimate of the prevalence of GAD in the general population is about 1.6%–5.0%.[7] Although there is a lack of information about the prevalence of GAD among infertile people, most studies which are limited to some infertility centers suggest a much higher of GAD prevalence in the infertile population than the general population.[8,9] GAD is highly comorbid with major depression, other anxiety disorders, and also physical disorders such as diabetes, peptic ulcer disease, and irritable bowel syndrome, cardiac, and other somatic symptoms.[10,11] Patients with

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GAD commonly experience lower levels of two dimensions of physical and psychological aspects of health-related quality of life, including physical functioning, role physical, role emotional, bodily pain, general health, vitality, social functioning, and mental health.[10] Studies show that the direct and indirect costs of GAD are very high,[12] and the comorbidity between GAD and other psychiatric disorders results in an increase of around 65% in the direct economic costs.[13] Moreover, as the severity of GAD increases, so does the financial burden.[14]

In people with GAD, levels of symptom severity may impact on the levels of physical functioning.[7,15] Furthermore, the likelihood of full remission, the treatment plan of GAD, and choice of drug(s) depend on the severity of the problem.[16,17] In infertile people, more severity levels of anxiety could lead to higher cortisol level and therefore lower successful pregnancy rate in infertility treatments.[18]

Not with standing the importance of GAD in infertile people and its negative consequences, there is little information about it in this group. Identification of associated risk factors for the severity of GAD in this population may aid clinicians to obtain a more accurate understanding of GAD among infertile people and identifying patients at greater demand for psychological support and treatments.

In clinical practice and research, GAD-7 is one of the most common rating scales used for screening, diagnosis, and severity assessment of GAD. In GAD-7, the clinically meaningful GAD severity levels are defined as an ordinal scale based on predetermined threshold values to denote normal, mild, moderate, and severe levels.[5,19] Ordinal regression models with traditional link functions including probit, logit, and complementary log-log (cloglog) are most commonly using methods for the analysis of such data in the statistical literature. In recent years, it has been proposed the using of flexible link functions in the modeling of the ordinal dependent variables to avoid link misspecification, the bias in the parameter estimations and inferior fit in the model.[20] Evaluation of the usefulness of recently proposed ordinal models in health researches could be valuable to determine the best method for model fitting and parameter estimation.

The current study was an effort to identify the associated risk factors for the severity of GAD as one of the most common psychological disorders in infertile people using an ordinal model with a flexible link function.

MATERIALS AND METHODS

Study design

A cross-sectional study was conducted from May to August 2017 at the Infertility Treatment Center of Royan Institute in Tehran, Iran. Participants of the study were men or women with couple's infertility problem which met the following inclusion criteria: (a) the willingness to participate in the study; (b) age >18 years; and (c) ability to reading, writing, and understanding Persian. A total of 1146 eligible people completed and returned questionnaires. Data collection was conducted using the GAD-7 questionnaire. Information about demographic/clinical factors including gender, age, educational level, infertility duration, infertility cause, history of abortion, and failure of previous treatment was also collected.

Generalized anxiety disorder-7 questionnaire

The Gad-7 is a measurement scale to assess the respondents' anxiety symptoms for the past 2 weeks. It contains 7 Likert scale items from 0 (not at all) to 3 (nearly every day) and can be used to determine the risk of GAD based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria. Scores for the whole scale range from 0 to 21, and a higher total score reflects more severe symptoms of GAD. A cut-off point of 10 is typically employed for clinical diagnosis of GAD, and cut-off points of 5, 10, and 15 describe mild, moderate, and severe anxiety symptoms, respectively. The reliability and validity of the Persian version of GAD-7 in the Iranian infertility population were assessed by Omani-Samani *et al*.,[5] with a Cronbach alpha of 0.876.

Ethics

The study was approved by the Iranian Ethics Committee of Royan Institute (Approval number: IR.ACECR.ROYAN.REC.1395.187), and written informed consent to participate in the study was obtained from all individuals.

Statistical analysis

Data analyses were done using GNU PSPP (a free alternative to SPSS) and R version 3.5.0. Continuous and categorical variables were summarized as mean ± standard deviation (SD) and frequency (percentage), respectively. Categorical data were compared between categories of GAD using the Kruskal–Wallis test. Correlation between severity of GAD and continuous variables were assessed using the Spearman's rank-order correlation. Furthermore, a simple ordinal regression model was performed on potential risk factors for the severity of GAD and those with $P < 0.2$ were subjected to multivariate analysis. Multivariate analysis was conducted using a Bayesian ordinal splogit model, and a 95% credible interval (CrI) not including zero was considered as the statistical significance.

Ordered symmetric power logit model

Let Y denotes the severity level of GAD (1 = no/minimal, 2 = mild, 3 = moderate, and 4 = severe) and J represents the number of severity levels (here $J = 4$). Postulating the existence of a latent (unobserved) variable associated with

each response is a natural way for statistical inference about an ordinal model.[14] The latent variable can be modeled as a linear function of the covariates as follows:[21,22]

$$w_i = x_i^{'}\beta + \epsilon_i$$

For each individual i, x_i is the values of a set of predictor variables, β is a vector of coefficients of the predictors, $E(\epsilon \mid x_i) = 0$, $\epsilon_i \sim F$ and F is a cumulative distribution function (cdf). The response variable is determined by discretization of the data into J ordered categories through a series of unknown thresholds which can be stated mathematically as:

$$y_i = j \text{ if } \gamma_{j-1} < w_i \leq \gamma_j$$

where $-\infty = \gamma_0 < \gamma_1 < \ldots < \gamma_{j-1} < \gamma_j = \infty$. To guarantee that the parameters of the model are identifiable and without loss of generality, γ_1 can be fixed at 0. The probability of observed $y_i = j$, conditional on x_i, β, and $\gamma = (\gamma_1, \ldots \gamma_{J-1})'$ can expressed as

$$P(y_i = j) = F(\gamma_j - x_i'\beta) - F(\gamma_{j-1} - x_i'\beta)$$

Therefore, the likelihood function for the model can be written as

$$f(y \mid \beta, \gamma) = \prod_{i=1}^{n}\prod_{j=1}^{J}\left[F\left(\gamma_j - x_i^{'}\beta\right) - F\left(\gamma_{j-1} - x_i^{'}\beta\right)\right]^{I\{y_i = j\}}$$

where $I\{y_i = j\}$ is the indicator function that takes the value 1 if $y_i = j$, and 0 otherwise. The probability of observing $y_i = j$ is associated with the F-distribution. The distribution behind the splogit model is a flexible distribution that permits for both positive and negative skewness and also enables detecting the measure of skewness required.[18] The cdf of splogit distribution can be written as

$$F(w) = F_0^r\left(\frac{w}{r}\right)I_{(0,1]}(r) + \left[1 - F_0^{\frac{1}{r}}(-rw)\right]I_{(1,+\infty)}(r)$$

where F_0 is a logit baseline distribution.

Priors, computational issues, and assessment of splogit model

We assigned a normal prior on β and a truncated normal prior distribution on γ. We used a mean 0 and a large diffuse SD 1000 for normal priors, reflecting the lack of information. Jiang *et al*.[23] proposed a proper gamma prior with mean 1 and reasonable large variance for the power parameter r of the splogit model. In this study, we assigned the power parameter r with a Gamma (α_r, α_r) prior distribution, where $\alpha_r = 2$. The program Just Another Gibbs Sampler (JAGS) was used to perform all the Bayesian computations using the R2jags providing interface utilities. For more details on the sampling method see Jiang *et al*.[23] Assessment of the ordered splogit model was performed using the deviance information criteria (DIC) in comparison to the traditional models including probit, logit, and complementary log-log. The model with the smallest value of DIC was chosen as the best model.

RESULTS

Table 1 presents descriptive statistics of the characteristics of the study's participants.

Findings indicated that 19.5% of males and 36.6% of females with couple's infertility problem had moderate to severe levels of GAD. Simple ordinal regression showed that age, duration of infertility, sex, previous treatment failure, and cause of infertility had a significant relationship with the GAD severity ($P < 0.2$). We showed only the results of the ordinal logit model in Table 2. The ordered splogit model had the smallest DIC value and therefore the best fit among ordinal models. Furthermore, we obtained more precise estimates of predictors (narrower 95% CrI) and one more significant predictor under the splogit model. Table 2 shows the posterior mean of regression coefficients, 95% CrI, and the DIC values for the ordinal models.

The results showed that people who experienced a longer duration of infertility suffered higher severity levels of GAD (B coefficient 0.03, 95% CrI: 0.01–0.04). Females were more likely to experience higher severity levels of GAD than males (B coefficient 0.48, 95% CrI: 0.34–0.62). Furthermore, individuals with previous treatment failure were more likely to have higher severity levels of GAD (B coefficient 0.17, 95% CrI: 0.03–0.30). On the other hand, results demonstrated that people with self-cause of infertility had higher levels of GAD than others (regression coefficient 0.12, 95% CrI: 0.01–0.23). We found no significant relationship between age and the severity levels of GAD (regression coefficient – 0.01, 95% CrI:-0.02–0.01). The bold-faced values in Table 2 indicate statistically significant results.

DISCUSSION

The present study was developed to identify associated risk factors for the severity of GAD. The results showed that individuals with longer infertility duration suffered from higher severity levels of GAD. This finding supports previous researches conducted by Yang *et al*.[24] and Ramezanzadeh *et al*.[25] However, some studies demonstrated that there is no association between the duration of infertility and anxiety or depression.[26,27] People with longer infertility duration may repeatedly refer to physicians and receive different treatments and so fluctuate between hope and hopelessness and experience more concern and anxiety about the difficulty of having a baby.[28]

Table 1: Characteristics of the participants in the present study

Predictors	GAD severity level				*P*
	No/minimal anxiety	Mild	Moderate	Severe	
Age (years), mean±SD	33.10±5.49	32.72±5.38	32.08±5.75	32.67±5.83	0.070†
Duration of infertility (years), mean±SD	5.12±3.87	5.05±3.65	5.96±4.50	6.70±4.65	<0.001†
Sex, *n* (%)					
Male	289 (58.5)	161 (49.1)	81 (37.0)	28 (26.7)	<0.001*
Female	205 (41.5)	167 (50.9)	138 (63.0)	77 (73.3)	
Educational level, *n* (%)					
Primary	104 (21.0)	54 (16.5)	53 (24.2)	27 (25.7)	0.368*
Secondary	157 (31.8)	99 (30.1)	80 (36.5)	34 (32.4)	
University	233 (47.2)	175 (53.4)	86 (39.3)	44 (41.9)	
History of abortion, *n* (%)					
No	356 (72.1)	233 (71.0)	154 (70.3)	77 (73.3)	0.840*
Yes	138 (27.9)	95 (29.0)	65 (29.7)	28 (26.7)	
Previous treatment failure, *n* (%)					
No	272 (55.1)	169 (51.5)	94 (42.9)	41 (39.0)	<0.001*
Yes	222 (44.9)	159 (48.5)	125 (57.1)	64 (61.0)	
Cause of infertility, *n* (%)					
Male factor	186 (37.7)	123 (37.5)	80 (36.5)	48 (45.7)	0.059*
Female factor	90 (18.2)	68 (20.7)	46 (21.0)	15 (14.3)	
Both	80 (16.2)	59 (18.0)	48 (21.9)	21 (20.0)	
Unexplained	138 (27.9)	78 (23.8)	45 (20.6)	21 (20.0)	

**P* value based on the Kruskal-Wallis test; †*P* value based on the Spearman rank correlation test. GAD=Generalized anxiety disorder; SD=Standard deviation

Table 2: Simple and multiple ordinal regression model's results on factors related to the severity of generalized anxiety disorder

Predictors	Simple ordinal regression		Multiple ordinal regression, *B* coefficient (95% CrI)			
	Logit		Probit	Logit	Cloglog	Splogit
	B coefficient (95% CI)	*P*				
Age (years)	−0.02 (−0.039-0.001)	0.04	−0.01 (0.03-0.01)	−0.01 (0.03-0.01)	−0.01 (0.02-0.01)	−0.01 (0.02-0.01)
Duration of infertility	0.05 (0.02-0.08)	<0.001	**0.04 (0.01-0.07)**	**0.04 (0.01-0.06)**	**0.03 (0.01-0.05)**	**0.03 (0.01-0.04)**
Sex						
Female	0.77 (0.56-0.99)	<0.001	**0.81 (0.57-1.04)**	**0.72 (0.47-0.97)**	**0.55 (0.38-0.71)**	**0.48 (0.34-0.62)**
Male	1		1	1	1	1
SD						
Yes	0.24 (0.11-0.36)	<0.001	**0.29 (0.06-0.52)**	**0.27 (0.05-0.48)**	**0.20 (0.03-0.36)**	**0.17 (0.03-0.30)**
No	1		1			1
Cause of infertility						
Partner	0.10 (−0.03-0.13)	0.15	−0.02 (−0.29-0.25)	−0.03 (−0.27-0.22)	−0.03 (−0.22-0.16)	−0.02 (−0.17-0.14)
Self	0.08 (−0.01-0.16)	0.09	0.21 (−0.06-0.47)	0.19 (−0.06-0.44)	0.15 (−0.03-0.33)	**0.12 (0.01-0.23)**
Both/unexplained	1		1	1	1	1
Model selection						
DIC			2821.6	2827.5	2758.2	**2722.3**

CrI=Credible interval; SD=Standard deviation; DIC=Deviance information criteria; CI=Confidence interval

Another important finding was that females experienced higher severity levels of GAD than males. This finding was in accordance with findings reported by Galundia[4] and Maroufizadeh *et al*.[29] This relation may be related to the different reaction of men and women toward infertility.[30] On the other hand, in Iranian culture, women may have more encounter with social pressure than men due to frequently consider them as responsible for infertility.[4] Furthermore, it is typical for women to be more influenced because of involving profoundly in investigations and infertility treatment procedures.[4,25] Male infertility evaluation usually initiated after evaluation of infertility in female.[31] On the other hand, the procedures and tests for infertility problems are more complex, invasive, and costly for females than males.[31,32] Moreover, it has been demonstrated that women more involved in the process of trying to have a baby such as treatment seeking, and selection of the tests or therapies they can take when pregnancy attempts are failed, even when the male is the cause of infertility.[33]

We also found that people who have experienced failure in the previous treatments suffered from higher levels

of GAD than others. A study demonstrated that anxiety and depression in patients experiencing infertility and undergoing assisted reproductive technology (ART) increase after infertility treatment failure.[26] Furthermore, a systematic review examined the association between psychological outcomes and having treatment failure in both men and women and showed increased levels of anxiety and depression after an ART treatment failure.[34]

We observed that patients with self-cause of infertility were more likely to experience higher GAD severity levels than others. A similar result was reached by Dhaliwal *et al*.[28] An explanation for this might be that a diagnosis of infertility problem in a man or woman may lead them to feel lacking in self-confidence, and feeling worthless as a spouse, and fear of being abandoned by her/his partner and being alone.[35]

In this study, the ordinal regression models with different link functions were used to determine the risk factors for severity of GAD. The splogit model had a better fit and performance to determine significant factors associated with the severity of GAD as compared to standard models including logit, probit, and cloglog models. It provided more precise estimates of risk factors (narrower 95% Crl) and one more significant risk factor. These results indicated the power of the splogit model for handling the data in this study.

This study provides valuable insights into risk factors for severity levels of GAD among infertile people using a large sample size in both men and women and a validated instrument to assess the severity of GAD. However, it has some limitations: (i) its cross-sectional design provides no evidence for causality, (ii) the study was only conducted in one infertility treatment center in Iran; so, generalizing the results to other populations has to be performed with caution, and (iii) some confounding factors such as having any comorbidity or previous history of psychiatric disorders and using medications were not evaluated within the study.

CONCLUSION

The present study revealed that infertile people with female gender, longer duration of infertility, failure in previous treatments, and self-cause infertility are more likely to experience higher severity levels of GAD and require additional psychological, and support interventions. Moreover, in this study, the ordinal splogit model was more powerful to identify the associated risk factors for the severity of GAD.

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Conflicts of interest

There are no conflicts of interest.

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