



Research Article

Anxiety and Depression Symptoms among Infertile Couples Undergoing ART in Latvia: A Cross-Sectional Non-Randomized Single-Centre Study

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Abstract

Aim: The aim of the study was to evaluate the presence of anxiety and depression among infertile couples undergoing infertility treatment in Latvia. **Materials and methods:** In this cross-sectional study we compared anxiety and depression symptoms in couples diagnosed with primary infertility (111 women and 55 male), evaluating male and female symptoms separately and together. The level of anxiety and depression were measured using Generalized Anxiety Disorder Scale (GAD-7) and Patient Health Questionnaire-9 (PHQ-9). **Results:** Upon assessing anxiety and depression level scores mild anxiety is predominantly observed in couples undergoing ART cycles for the first time, accounting for 44.6%, compared to those undergoing it for the 2nd and 3rd time, where the prevalence is equal and stands at 40.7%. Conversely, a noteworthy trend is discerned in patients undergoing ART multiple times, revealing a higher prevalence of moderate and severe anxiety, at 18.6% and 9.3%, respectively. The highest prevalence of depression symptoms is observed in individuals undergoing their second ART cycle and beyond. Particularly noteworthy is the substantial proportion of these patients, with 36.0% experiencing mild and 17.7% experiencing moderate depression symptoms. **Conclusions:** The experience of undergoing artificial reproductive technology treatment multiple times is associated with heightened prevalence of depression and anxiety among infertile couples. These conclusions highlight the importance of addressing mental health aspects in the context of infertility and ART cycles.

Keywords: Anxiety; Depression; Infertility; Assisted reproductive treatments

Introduction

Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse [1]. It is well known that it affects both genders equally. According to statistics the causes for infertility in 30%-40% are solely attributed

to the female factor, 40-50% to male factor and another 15-30% present as unexplained [2]. Occurrence of infertility globally, stands at 17.5% and it can result in considerable emotional burden, social judgement, and financial challenges, contributing to the emergence of psychosocial distress [3].

Based on demographical data from the European Union, the average age of women giving birth to their first child was reported as 29.4 years in 2019 [14]. In the context of Latvia, the mean age of child conception is comparatively lower than the European

average, registering at 27.3 in 2019 and gradually increasing to 27.7 in 2021 [15]. This trend indicates a rising concern of infertility in Latvia as well.

Even though both female and male factors are attributed equally to appearance of infertility, there exists a substantial volume of studies justifying female infertility as a factor leading to development of stress [4].

Within the realm of mental health disorders linked to infertility, anxiety and depression emerge as primary concerns, with anxiety displaying a notable prevalence among females [5-7,10]. Moreover it is known that the levels of anxiety are positively correlated with the levels of depression [8].

Many previous studies tried to collect information regarding risk factors for development of symptoms like education, employment status, length of infertility and number of ART cycles. However, only the number of assisted reproductive treatments (ART) has shown strong correlation with increased female anxiety levels. Moreover, it has shown that during ART women are more likely to develop psychological issues than their spouses [9].

Among male partners within infertile couples, there is a recognized prevalence of depression, erectile dysfunction, and challenges in sexual relationships [11].

Nonetheless, men undergoing Assisted Reproductive Technology (ART) treatment do not appear to be vulnerable to the onset of psychiatric disorders, such as depression, if fatherhood is not achieved [12].

Notably, the prevalence of depression among infertile men in the Middle East is significantly higher when compared to Western countries, highlighting a crucial topic that cannot be overlooked in this specific region [13].

All earlier research describes the prevalence of psychological distress of infertile couples among different countries excluding Latvia. Hence, accessing data on Latvian couples is valuable, particularly for exploring and understanding regional and cultural differences.

Additionally, there is a paucity of research examining the potential interdependence of couples with infertility and the potential for one partner to influence the mental well-being of the other during infertility treatment.

Materials and Methods

Participants - study sample selection

The study was conducted in iVF Riga clinic, where 181 patients agreed to participate in the study. Recruitment involved reaching out to potential participants via clinic's administration and

doctors to capture a diverse pool of patients. A random sampling technique was used to select participants. Before the study was conducted the research paper objectives underwent a thorough ethical review by the Rīga Stradiņš University (RSU) Research Ethics Committee to ensure compliance with established ethical standards, and approval was granted prior to the commencement of the study.

Initially, individuals classified as experiencing infertility, both women and men (referred to as the infertile group), underwent a comprehensive briefing regarding the study's objectives.

Following this, a detailed medical history was collected from each participant carried out by the clinic's reproductologist and andrologist. Both primary and secondary admitted patients participated in the study.

The inclusion criteria were thoroughly assessed, necessitating a personal diagnosis of infertility, i.e. patient's inability to achieve conception despite regular sexual intercourse for a duration exceeding 12 months, abstention from contraceptive use within the previous 12 months, a lack of successful conception, and no history of pregnancy (indicating primary infertility) for either the individual itself or their spouse. Informed written consent to partake in the study was an essential prerequisite for inclusion. Exclusion criteria were logically determined and encompassed individuals with mental health conditions, those undergoing treatments with drugs potentially impeding sexual function, individuals with diagnosed organic causes of sexual disorders, and those who incompletely filled out the required questionnaire.

A total of 181 infertile patients and/or their spouses (123 women and 58 men) agreed to participate in the study (actual sample). Due to the failure to satisfy all inclusion criteria, 3 men classified as fertile, along with 4 infertile women and 4 fertile women, were deemed ineligible for participation and were consequently excluded from the study.

The exclusion reasons were positive personal psychiatry history (5 patients) and lacking personal and spouses' infertility diagnosis (8 patients), some of them overlapping.

For the final analysis, 170 participants (115 women and 55 men) completed the questionnaires and fulfilling all criteria were enrolled in the study.

The research cohort was subsequently categorized into four subgroups based on either personal infertility diagnosis or that of their partner. The data has been stratified by gender, resulting in the following groups: Men experiencing infertility, men in good reproductive health but partnered with individuals facing infertility, women with infertility, and women in good reproductive health but partnered with individuals experiencing infertility.

The categorization was conducted to assess whether there are variations in psychological symptoms not just between genders diagnosed with infertility but also to explore the possibility that individuals without infertility may exhibit positive symptoms influenced by their partner's diagnosis.

Procedures

The research instrument utilized was a survey voluntarily and confidentially completed by the research participants. This survey encompassed several sections, including a section addressing socio-demographic factors such as age, location status (local or international patients), education, and travel time to the clinic (ranging from 30 minutes to over 3 hours). Another section focused specifically on infertility aspects, including the duration, the partner's infertility diagnosis, and the number of assisted reproductive technology (ART) cycles. Additionally, the questionnaire featured a detailed component in the form of self-assessment tools: the Latvian iteration of the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7), which assessed the occurrence and severity of depression and anxiety.

Patient Health Questionnaire-9

The PHQ-9 is a 9-item self-report questionnaire designed to measure depression and its severity in the general and clinical (psychiatric) population [16].

PHQ-9 is a brief and easy method to measure depressive symptoms with good psychometric properties, suitable for routine use in patients with infertility [17].

The PHQ-9 enquires about the frequency of challenges experienced by respondents over the past two weeks. Participants rate each item on a 4-point Likert-type scale, ranging from 0 (not at all) to 3 (nearly every day). The cumulative score can vary from 0 to 27, with elevated scores indicative of increased levels of depression.

Assessed depression severity level may include following results: lack of depression (0-4), mild depression (5-9), moderate depression (10-14), moderately severe depression (15-19) and severe depression (20-27) [18].

General Anxiety Disorder-7

The 7-item Generalised Anxiety Disorder Scale (GAD-7) is a practical self-report anxiety questionnaire and a reliable

tool to measure anxiety in primary care, as well as in the general population [19]. GAD-7 consists of 7 questions about the frequency of challenges experienced by respondents over the past two weeks. The evaluated level of anxiety severity can be categorised into different outcomes: minimal anxiety (0-4), mild anxiety (5-9), moderate anxiety (10-14), severe anxiety (15-21) [19-21].

Statistical analysis

Data was analyzed using SPSS version 26 (IBM, Armonk, NY, USA). The Kolmogorov–Smirnov statistics were applied to test age distribution among genders. The distribution of variables was examined using descriptive analyses. Mean, median and standard deviation were reported for continuous variables, and frequency was reported for categorical variables. The categorical comparisons among the studied groups were conducted using the Chi-square test. The comparison of fertility duration, depression, and anxiety scores between fertile and infertile groups, was conducted using the Mann-Whitney U test. Values of *p* less than 0.05 indicated significant differences.

Results

Sociodemographic characteristics

In this study, 170 infertile individuals participated, comprising 145 females and 35 males. The results reveal homogeneity in age across genders, with a mean age of 36.8 years (\pm SD 5.0) for females and 36.8 years (\pm SD 6.0) for males. The study showed a wide range of infertility durations (1 to 20 years in total) and observed differences between genders. The average duration of infertility for males was 4.9 years (median of 3.0 years, \pm SD 5.3), while females had an average infertility duration of 4.7 years (median of 4.0 years, \pm SD 3.6).

Gender categorization based on fertility resulted in the formation of four subgroups:

23.5% constituted infertile males (IM), 8.8% comprised fertile males with infertile spouses (FM), 55.9% represented infertile females (IF), and 11.8% consisted of fertile females with infertile spouses (FF). Subsequently, each subgroup underwent systematic analysis regarding factors such as smoking, alcohol, psychiatric disorders among relatives, education status, travel time to the hospital, and the number of Assisted Reproductive Technology (ART) cycles (Table 1).

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Variable	Females			Males		
	IF	FF	X2 test	IM	FM	X2 test
Education						
Primary education	0	0	NS	5,0 (7)	0	NS
Secondary education	22.1 (21)	35.0 (7)		42.5 (17)	33.3 (5)	
Higher education	77.9 (74)	65.0 (13)		52.5 (21)	66.7 (10)	
Patient status						
Local	84.2 (80)	75.0 (18)	NS	85.0 (34)	60.0 (9)	p<0.05
International	15.8 (15)	25.0 (5)		15.0 (6)	40.0 (6)	
Travel time to the hospital						
< 30 minutes	33.7 (32)	35.0 (7)	NS	22.5 (9)	13.3 (2)	NS
30-60 minutes	29.5 (28)	25.0 (5)		25.0 (1)	53.3 (8)	
>60 minutes	36.8 (35)	40 (8)		52.5 (21)	33.3 (5)	
Smoking						
Yes	15.8 (15)	30.0 (12)	NS	30.0 (12)	26.7 (4)	NS
No	84.2 (80)	70.0 (28)		70.0 (28)	73.3 (11)	
Alcohol						
Yes	23.2 (22)	20.0 (4)	NS	30.0 (12)	33.3 (5)	NS
No	76.8 (73)	80.0 (26)		80.0 (28)	77.7 (10)	
Psychiatric disorders among relatives						
Yes	3.2 (3)	10.0 (2)	NS	5.0 (2)	20.0 (3)	p<0.01
No	96.8 (92)	90.0 (18)		95.0 (38)	80.0 (12)	
Number of ART cycles						
None	6,3 (6)	5.0 (1)	p<0.05	27.5 (11)	6.7 (1)	NS
First	41.4 (39)	35.0 (7)		27.5 (11)	53.3 (8)	
Second	12.6 (12)	40.0 (8)		20.0 (8)	13.3 (2)	
Third	14.7 (14)	15.0 (3)		17.5 (7)	13.3 (2)	
More than three	25.3 (24)	5.0 (1)		7.5 (3)	13.3 (2)	
Total	100 (95)	100 (20)		100 (40)	100 (15)	
Data are presented as percentages, with total numbers in brackets. FI: Female Infertile; FF: Female Fertile; MI: Male Infertile; MF: Male Fertile; ART: Assisted Reproductive Technology.						

Table 1: Characteristics of the Study Population.

It is worth noting that a significant proportion of the entire cohort, specifically 69.4%, had notable academic achievements, holding either bachelor's or master's degrees, when detailing the educational status of the participants. A more detailed breakdown reveals that within the participant groups, 77.9% of infertile women, 65% of fertile females, 52.5% of infertile men, and 66.7% of fertile men boasted a higher education background.

There was a remarkable statistical distinction in the occurrence of psychiatric disorders among relatives, revealing a higher prevalence within the Male Fertile (FM) group ($p < 0.01$).

Within the Male Fertile (FM) group, a notable 20.0% of participants reported the presence of psychiatric disorders among their relatives. This contrasts with the Infertile Male (IM)

participants, where a lower proportion, specifically 5.0%, reported psychiatric disorders among their relatives.

Within the female cohort, a notable significance emerged in the distribution of the number of ART cycles ($p < 0.05$), indicating a higher proportion of first-time cycles within the Infertile Females (IF) group.

Anxiety and depression among female and male

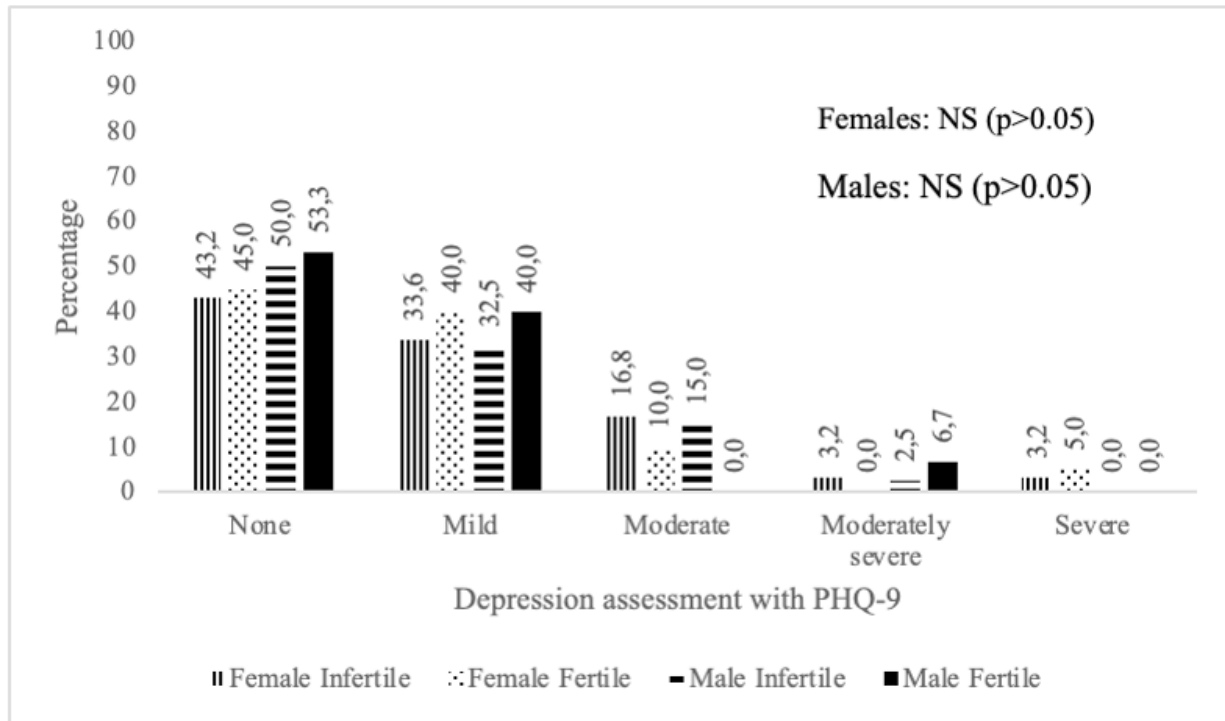
The mean anxiety score among infertile females was statistically significantly higher than that of fertile females ($p < 0.05$). Detailed characteristics of depression and anxiety, as assessed through the Patient Health Questionnaire (PHQ) and Generalised Anxiety Disorder (GAD-7) scales, among both fertile and infertile females and males. (Table 2)

Scale	Groups	Mean	Median	Min	Max	SD	Mann-Whitney U test
PHQ-9	FI	6.4	5.0	0	27	5.0	NS
	FF	6.1	5.5	0	22	4.8	
	MI	5.1	4.5	0	19	4.2	NS
	MF	4.7	4.0	0	16	4.0	
GAD-7	FI	7.1	6.1	0	21	4.7	$p < 0.05$
	FF	6.3	5.9	0	21	4.4	
	MI	5.5	4.0	0	19	4.3	NS
	MF	5.1	5.0	0	12	4.2	

PHQ: Patient Health Questionnaire; GAD: Generalised Anxiety Disorder scale; FI: Female Infertile; FF: Female Fertile; MI: Male Infertile; MF: Male Fertile; SD: Standard Distribution

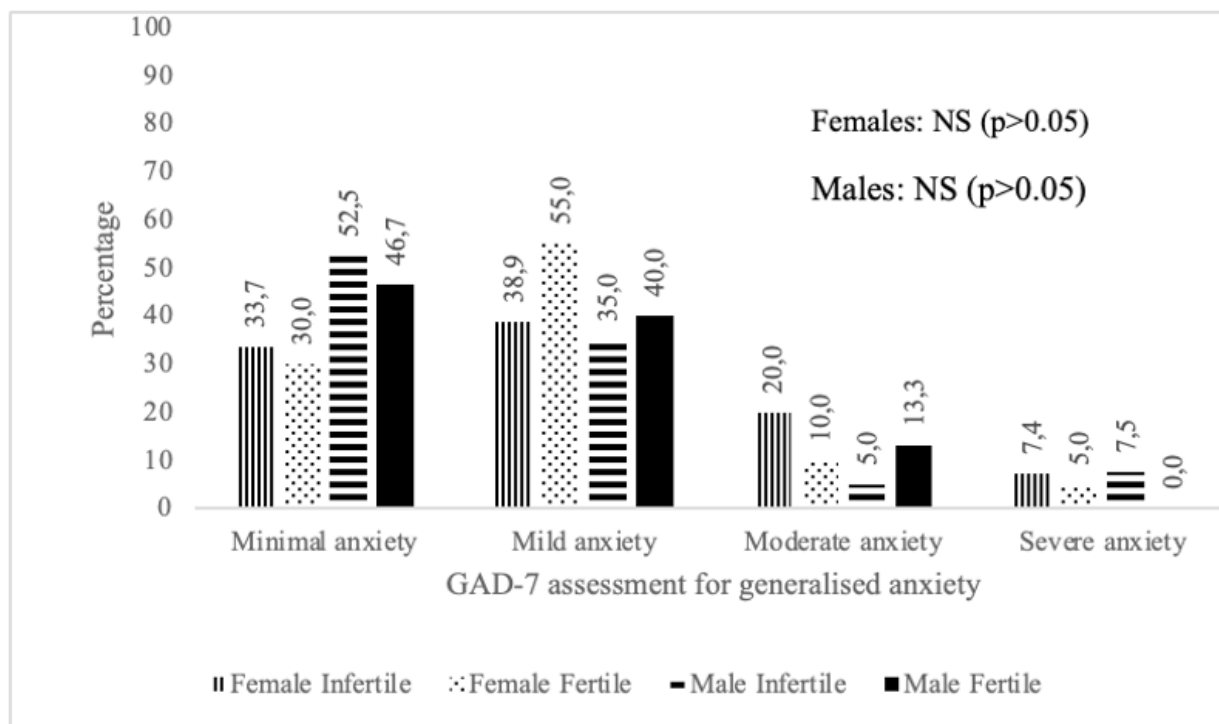
Table 2: Characteristics of Depression and Anxiety in PHQ and GAD among Fertile and Infertile Females and Males.

Among all respondents, 4 individuals (2.4%) demonstrated mild depression, 5 (2.9%) exhibited moderately severe depression, 24 (14.1%) showed moderate depression, and 25 (24.7%) displayed severe depression. The distribution of depression based on gender among fertile and infertile respondents. (Graph 1)



Graph 1: Gender-based Distribution of Depression in Fertile and Infertile Respondents.

Among all respondents, 11 individuals (6.5%) exhibited mild anxiety, 25 (47.0%) showed moderate anxiety, and 68 (40.0%) displayed severe anxiety. Distribution of anxiety based on gender among fertile and infertile respondents is presented in Graph 2.



Graph 2: Gender-based Distribution of Anxiety in Fertile and Infertile Respondents.

Depression and anxiety and number of ART cycles

A statistically significant distinction was observed in the prevalence of depression and anxiety among all patients undergoing ART cycles. Specifically, when assessing patients’ scores on the PHQ-9 and GAD-7 scales, noteworthy variations were identified based on the number of ART cycles. Participants undergoing ART for the 2nd or 3rd time exhibited higher absolute values of depression and anxiety symptoms, reflected in the PHQ-9 scale [6.2 ± 5.4] and the GAD-7 scale [7.1 ± 5.3] (Table 3)

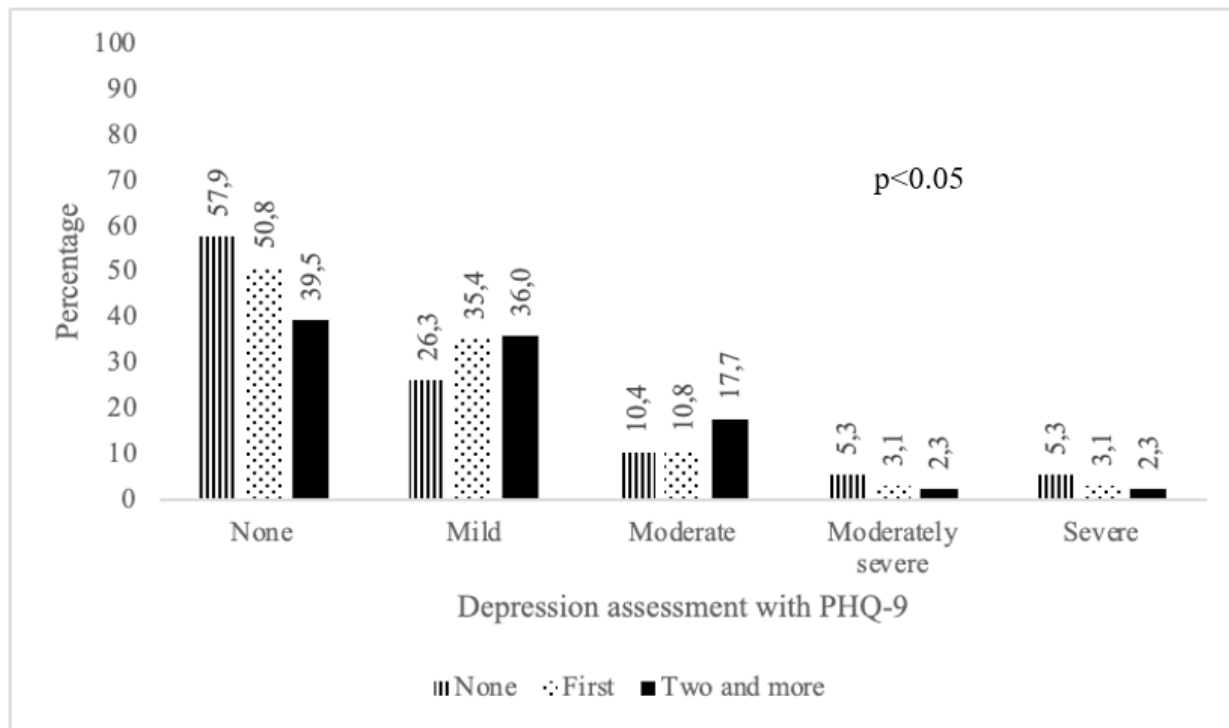
Scale	ART	Mean	Median	Min	Max	SD	Mann-Whitney U test
PHQ-9	None	5.1	3.0	0	18	4.7	p<0.05
	First	5.0	4.0	0	19	3.8	
	Two and more	6.2	5.5	0	27	5.4	
GAD-7	None	5.9	4.0	0	15	5.3	p<0.05
	First	5.5	5.0	0	15	3.0	
	Two and more	7.1	7.0	0	21	5.3	

PHQ: Patient Health Questionnaire; GAD: Generalised Anxiety Disorder scale; ART: Assisted reproductive technologies; SD: Standard Distribution.

Table 3: Characteristics of Depression and Anxiety in PHQ and GAD among ART patients.

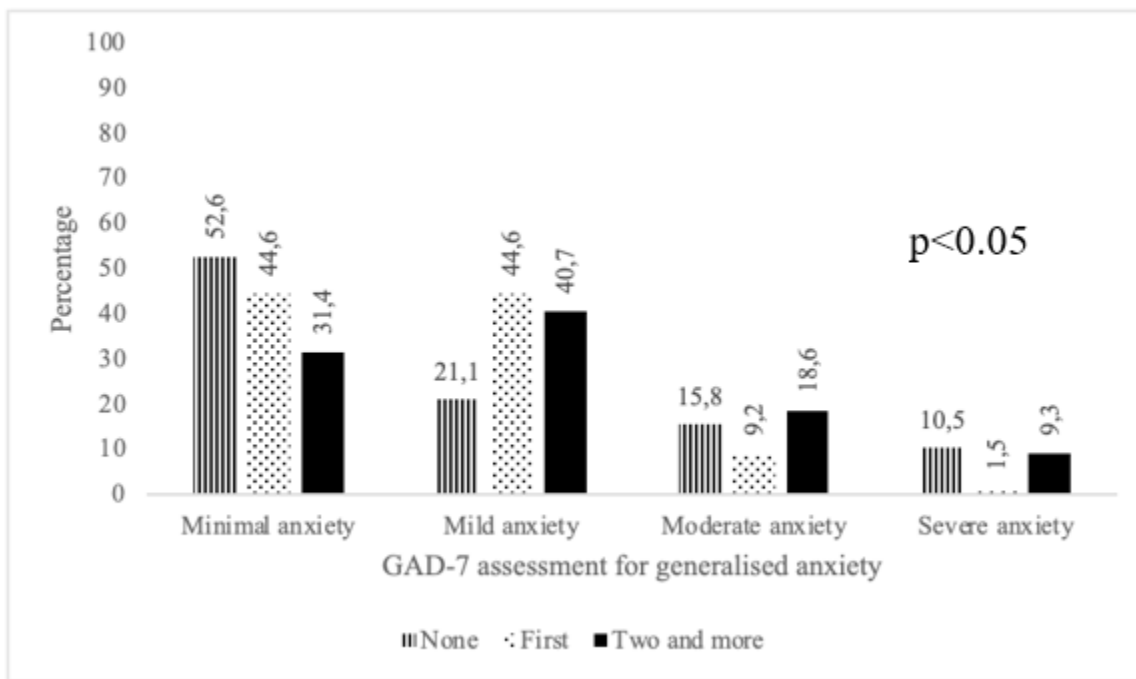
Subsequently, recognizing the observed patterns, a more in-depth investigation was undertaken to assess the nuanced levels of depression and anxiety relative to the duration of undergoing ART cycles (Graphs 3 and 4)

It can be inferred that individuals undergoing ART cycles for the 2nd and 3rd time exhibit a higher prevalence of mild and moderate depression symptoms, measuring at 36.0% and 17.7%, respectively. This contrasts with patients undergoing ART for the first time or those who have not undergone it at all. ($p < 0.05$) (Graph 3)



Graph 3: Distribution of Depression among ART patients.

In analyzing anxiety level scores among couples undergoing Assisted Reproductive Technology (ART) cycles, a noticeable trend emerges. Specifically, it appears that mild anxiety is more prevalent in couples experiencing their initial ART cycle, accounting for 44.6% of cases. In contrast, those undergoing ART for the second or third time exhibit a slightly lower incidence of mild anxiety, collectively totaling 40.7%. However, a compelling observation arises when focusing on individuals who have undergone ART multiple times. This subgroup demonstrates a higher prevalence of moderate to severe anxiety, with 18.6% experiencing moderately severe anxiety and 9.3% reporting severe anxiety. This suggests that as couples engage in multiple ART cycles, there is an escalation in the likelihood of encountering anxiety levels beyond the mild range, potentially reflecting the cumulative emotional impact of the fertility treatment journey. ($p < 0.05$) (Graph 4)



Graph 4: Distribution of Anxiety among ART patients.

Discussion

In the context of this cross-sectional study, our primary objective was to explore the prevalence of anxiety and depression symptoms among infertile couples undergoing fertility treatments in Latvia. Additionally, we sought to identify the risk factors associated with the development of psychological symptoms in this population. Furthermore, we aimed to gain a comprehensive understanding of the demographic characteristics of infertile patients in Latvia for improved contextualization of our findings.

Our study reveals a notable trend within our sample of infertile couples, highlighting a prevalent inclination toward higher educational attainment. This observed association aligns cohesively with findings reported in previous studies [22-24].

This discovery has been systematically expounded upon, attributing it to a distinct correlation observed between elevated levels of educational accomplishment and lifestyles centred around career pursuits. This interconnectedness is suggested to play a role in postponing the commencement of parenthood, thereby potentially exerting an influence on fertility rates. One of the key findings of this study included that the mean anxiety score among infertile females was higher than that of fertile females with partners experiencing infertility. Earlier other publications also emphasized women commonly encounter anxiety, mood fluctuations, preoccupation, irritability, despondency, as well

as feelings of guilt and emotional distress, irrespective of the underlying cause [5, 25,26].

In the course of conducting this study, assessing men and their psychological responses to infertility diagnoses posed notable challenges. It is crucial to note that during the questionnaire selection phase, a significant number of male participants could not be included due to incomplete questionnaire submissions. Particularly, a substantial deficiency was observed in responses related to PHQ-9 and GAD-7, indicating a substantial issue wherein male patients may feel reluctant or uncomfortable sharing symptoms of anxiety and/or depression. This underscores the importance of exploring strategies to enhance male engagement in expressing psychological aspects during infertility assessments, as their perspectives contribute significantly to a comprehensive understanding of the emotional dimensions associated with fertility challenges.

Prior research has underscored a heightened susceptibility to depression symptoms among male patients facing infertility in the Middle East region [13,27]. However, our study, focused on the Latvian patients specifically, revealed no statistically significant findings, primarily attributed to the limited number of respondents. This scarcity of data may be indicative of existing societal stigmas surrounding male mental health and it is a common phenomenon in ART literature [29].

Earlier investigations in the European region concerning psychological symptoms linked to male infertility have yielded controversial findings.

In our study, a statistically significant difference emerged in the occurrence of depression and anxiety across all individuals undergoing Assisted Reproductive Technology (ART) cycles. Notably, variations in patients' scores on the PHQ-9 and GAD-7 scales were evident, particularly in relation to the number of ART cycles they had undergone. In our study, it was observed that individuals undergoing Assisted Reproductive Technology (ART) cycles for the first time showed a higher prevalence of anxiety (44.6%) compared to those with prior cycles, irrespective of gender. Interestingly, patients undergoing ART for the second time or more demonstrated a higher prevalence of moderate anxiety (18.6%) and severe anxiety (9.3%). These findings suggest that anxiety levels may vary across different stages of the ART journey, emphasizing the need for targeted support and interventions tailored to the specific experiences of individuals undergoing repeated ART cycles. Engaging in assisted reproductive technology proves to be physically intrusive, emotionally taxing, and financially challenging. The sense of losing control permeates various aspects of a couple's life, potentially impacting the overall success of the fertilization process [26].

The emerging depression and anxiety symptoms among infertile patients are explained in previous studies. With inability to conceive naturally can evoke feelings of shame and embarrassment in infertile couples. When suspicions arise regarding infertility issues, it is crucial to avoid assigning or reinforcing blame. Infertility should be acknowledged as a shared challenge for the couple, requiring a collective approach for resolution [28].

Upon investigating depression symptoms within couples facing infertility and considering the number of ART cycles, a notable trend becomes apparent. The highest prevalence of depression symptoms is observed in individuals undergoing their second ART cycle and beyond. Particularly noteworthy is the substantial proportion of these patients, with 36.0% experiencing mild and 17.7% experiencing moderate depression symptoms, as indicated by the PHQ-9 scale.

Aligning with our findings, a comprehensive prospective longitudinal cohort study revealed that 56.5% of women and 32.1% of men scored within the clinical range for depressive symptomatology [31]. Furthermore, the study demonstrated that depression rates were elevated for both women and men who remained infertile compared to those who achieved success in their fertility treatments. This corroborates the significance of understanding and addressing the psychological well-being of individuals undergoing fertility treatments, particularly those facing repeated cycles, and emphasizes the need for targeted mental health support throughout the infertility journey.

Main limitations of this study were lack of male respondents and reliance on self-reported mental health instruments possessing a limitation, as these instruments reflect subjective evaluations rather than clinical diagnoses. Future research should consider these limitations and explore strategies to address them, potentially incorporating clinical assessments to enhance the validity of mental health evaluations.

Conclusions

The experience of undergoing artificial reproductive technology treatment multiple times is associated with heightened prevalence of depression and anxiety among infertile couples. In conclusion, it is noteworthy that the initial ART cycle may elicit mild anxiety symptoms in infertile couples, while engaging in two or more cycles appears to be associated with a heightened susceptibility to the development moderate and severe anxiety and of depressive symptoms. These conclusions highlight the importance of addressing mental health aspects in the context of infertility and ART, emphasizing the need for personalized support and interventions tailored to the specific challenges individuals and couples may face during their fertility journey.

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Statements and Declarations

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