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REVIEW

Global prevalence of major depressive disorder, generalized anxiety, stress, and depression among infertile women: a systematic review and meta-analysis

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Abstract

Background In recent years, the global prevalence of infertility has increased among women (Talmor and Dunphy, Best Pract Res Clin Obstet Gynaecol 29(4):498–506, 2015) and is considered as a public health concern. One of the impacts of infertility is mental health problems in the patients, which can lead to complications such as stress, anxiety, and depression. The aim of this study is to investigate the global prevalence of major depressive disorder, general anxiety, stress, and depression in infertile women through a systematic review and meta-analysis.

Methods To identify studies that have reported the prevalence of major depressive disorder, generalized anxiety, stress, and depression in infertile women, the PubMed, Scopus, Web of Science, Embase, ScienceDirect, and Google Scholar repositories were systematically searched. Articles published up until February 2023 were included, while no lower time limit was imposed in the search strategy. Heterogeneity of studies was examined using the I^2 test and, thus, random-effects model was used to perform the analysis. Data analysis was conducted within the Comprehensive Meta-Analysis (v.2) software.

Results In the review of 44 studies with a sample size of 53,300 infertile female patients, the overall prevalence of major depressive disorder (clinical depression), generalized anxiety, stress, and depression was found to be 22.9%, 13.3%, 78.8%, and 31.6% respectively. It was also found that mental health complications are more prevalent among infertile women in Asia (continent).

Conclusion Considering the prevalence of mental disorders among infertile women, health policymakers can use the results of the present meta-analysis to pay more attention to the mental health of infertile women and devise suitable interventions and programs to reduce and prevent the spread of psychological disorders among infertile women.

Keywords Infertile women · Depression · Major depression · Stress

Abbreviations

GAD	Generalized anxiety disorder
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis

Background

Infertility, in the field of reproductive health, is considered a global concern, and is one of the most common chronic disorders, regardless of age [1, 2]. Infertility refers to the inability to reproduce; as a definition, infertility is when the female or male reproductive systems fail to conceive after 12 months or more of regular unprotected sexual intercourse [3].

Infertility affects millions of people of reproductive age around the world and affect their communities [4]. Estimates show that 48 million couples worldwide have infertility problems [4]. Most couples have an identifiable cause for infertility, while the cause among the rest is unexplained [4, 5].

The main reason for this is related to the stigma around women not having children, especially in cultures that consider this aspect as the main goal of life and the defining role of women. On the other hand, still in many developing and developed societies, a woman is considered a complete person only when she becomes a mother; therefore, women with infertility are socially isolated, neglected, more prone

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to divorce, and severely reduced in dignity [6]. They feel a reduction in their ego and value, which can lead to feelings of guilt and that their lives are meaningless [7–9].

Although some women cope with infertility and yet have a positive and profound life [10], the experience of infertility is associated with a wide range of psychological problems such as depression [11, 12], stress, anxiety [13, 14], low self-esteem [15, 16], low psychological adjustment [17], feelings of fear, anger, shame, jealousy, loneliness, despair, emotional instability, insufficient sexual influence, and sexual dysfunction [18]. Infertility patients face complex challenges that fall in the biological, psychological, social, and moral domains [19]. Accordingly, most infertile women have higher levels of stress, anxiety, and depression [20, 21], in such a way that anxiety and depression in infertile women are comparable to what is experienced among cancer patients [22].

Considering the high rate of infertility globally, and the prevalence of problems related to mental health in infertile people, especially the high prevalence of stress, anxiety and depression in women with infertility, as well as the importance of mental health of infertile women, we decided to conduct a systematic review and meta-analysis on the global prevalence of major depressive disorder, general anxiety, stress and depression among women with infertility. It is strongly believed that the findings from this meta-analysis can provide useful insights for health policymakers to devise appropriate intervention programs.

Methods

We conducted our initial search in January 2023 using the PubMed, Web of Science, Google Scholar, Scopus, ScienceDirect and Embase databases. The keywords of infertile women, barren women, sterile women, generalized anxiety disorder, GAD, major depression, stress, and anxiety and their combinations were used to undertake the searches. To maintain the comprehensiveness of the searches, no restrictions was placed upon year of publication of articles. Subsequently, information from the identified articles were transferred into the EndNote reference management software. Additionally, reference lists used in the identified articles were manually reviewed to ensure that gray and previously unfound, yet relevant, studies are also included. The searches were last updated in February 2023.

Inclusion and exclusion criteria

The inclusion criteria for study selection were:

1. Studies that reported the prevalence of major depressive disorder, generalized anxiety, stress, and depression in women with infertility,
2. Studies with their full text available, and
3. Studies that provided sufficient data (sample size, prevalence).

Exclusion criteria were:

1. Case reports and case series studies,
2. Review studies of any sort,
3. Duplicates, and
4. Studies with insufficient data (lack of information about prevalence and sample size).

Study selection

The study selection was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Initially, studies that were repeated in different databases were excluded from the systematic review, and only one copy was retained. The initial screening took place by reviewing the titles and abstracts of the studies, and irrelevant articles were removed based on the inclusion and exclusion criteria. Then, the full texts of the remaining articles were evaluated based on inclusion and exclusion criteria, and similarly, irrelevant studies were omitted. To avoid bias, all the steps of reviewing sources and data extraction were completed by two researchers independently. If there was a difference of opinion between the two researchers (reviewers) in some of the articles, consensus was achieved with the support of a third reviewer.

Quality evaluation

To evaluate the quality of the remaining articles, a checklist appropriate for the inspection of observational studies was adopted. The Strengthening the Reporting of Observational Studies in Epidemiology checklist (STROBE) consists of six headings including: title, abstract, introduction, methods, results, and discussion. An article scored a point once a subheading was fulfilled, and accordingly articles with a score of 16 and above were considered to be of average and high methodological quality, respectively. Articles with a score below 16 were deemed to be of poor quality and were therefore excluded from our work.

Data extraction

Data extraction was completed by two researchers using a different pre-prepared checklist. This checklist includes the following headings: first author's name, year of publication, study location, sample size, age group of women, prevalence of different disorders, and study instrument(s).

Statistical analysis

The reported results from the selected studies were extracted into the Comprehensive Meta-Analysis (CMS v.2) software, and the heterogeneity of the studies was examined through the I^2 test. Publication bias was assessed using the Egger's test at a significance level of 0.05 and corresponding Funnel plots were drawn.

Results

Following the searchers, 453 articles were found from the selected databases and 2 further possible related articles were identified through manual search, and details of all found articles were transferred into the EndNote reference management software. Subsequently, 128 articles were

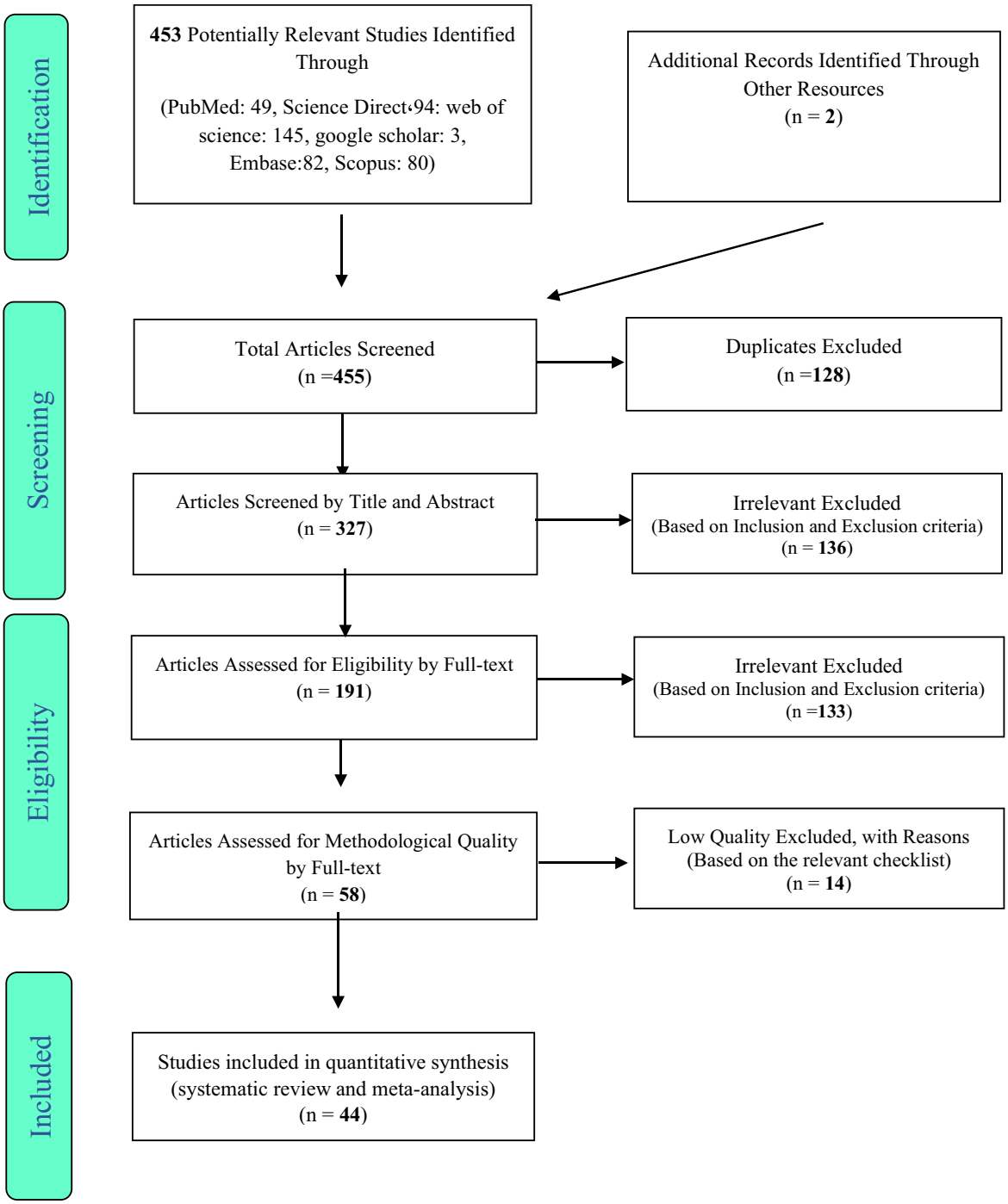

Fig. 1 PRISMA flow diagram for study selection

excluded due to duplication. In the screening phase, titles and abstracts of the studies were reviewed and 136 articles were excluded based on the inclusion and exclusion criteria. In the eligibility evaluation stage, a further 133 articles were excluded through the review of full texts and in accordance with the inclusion and exclusion criteria. In the quality evaluation phase, through the study of the full text of the articles and based on the scores obtained from the STROBE checklist, studies that had poor methodological quality were excluded, and finally 44 studies were included for final evaluation. The information of these 44 studies is reported in (Fig. 1) and Tables 1, 2, 3, 4.

Table 1 Summary of characteristics of included studies related to the prevalence of stress in women with infertility

Author	Year	Country	Age range	Sample size	Prevalence of stress in infertile women	Instrument
Teklemicheal et al. [23]	2022	Ethiopia	20–48	96	92.71%	COMPI-FPPS[a]
Xiaoli et al. [24]	2016	China	23–41	81	53.06%	WHOQOL-100[b]

[a]Copenhagen Multi-Centre Psychosocial Infertility–Fertility Problem Stress Scales

[b]World Health Organization Quality of Life

Table 2 Summary of characteristics of included studies related to the prevalence of major depression in women with infertility

Author	Year	Country	Age range	Sample size	Prevalence of MD in infertile women	Instrument
Carvalho et al. [30]	2021	Brazil	35.89 ± 5.20	90	9.9%	(M.I.N.I.)[a] Brazilian version 5.0.0, DSM IV[b]
Volgsten et al. [26]	2018	Sweden	38.3 ± 3.9	278	5.7%	(PRIME-MD)[c] based on DSM-IV
Al-Asadi et al. [25]	2015	Iraq	16–45	251	68.9%	(ICD-10)[d]
Saffarieh et al. [31]	2020	Iran	18–46	30	16.7%	BDI[e], STAI[g]
Holley et al. [32]	2015	USA	23–52	174	39.1%	Composite International Diagnostic Interview Major Depression module, a structured diagnostic interview
Chen et al. [33]	2004	Taiwan	24–45	112	17%	MINI
Osman et al. [34]	2022	Egypt	18–59	371	30.2%	PHQ-9[g]

[a]Mini International Neuropsychiatric Interview

[b]Diagnostic and Statistical Manual of Mental Disorders, version 4

[c]Primary Care Evaluation of Mental Health Disorders

[d]Interactional Classification of Diseases-Version 10

[e]Beck Depression Inventory

[f]State–Trait Anxiety Inventory

[g]Patient Health questionnaire

Table 3 Summary of characteristics of included studies related to the prevalence of general anxiety disorder in women with infertility

Author	Year	Location	Age	Sample size	Prevalence of GAD IN infertile women	Instrument
Carvalho et al. [30]	2021	Brazil	35.89 ± 5.20	90	8.9%	(M.I.N.I.) Brazilian version 5.0.0, DSM IV
Volgsten et al. [26]	2018	Sweden	38.3 ± 3.9	278	1.8%	(PRIME-MD) based on DSM-IV
Gui et al. [35]	2021	China	24–48	693	21.8%	GAD-7[a]
Aghanwa et al. [36]	1999	Nigeria	…	37	2.7%	PSE[b] and clinical evaluation
Chen et al. [33]	2004	Taiwan	24–45	112	23.2%	MINI
Shabani et al. [27]	2010	Iran	…	353	44.1%	GHQ[c] and interviews

[a]Generalized Anxiety Disorder

[b]Present State Examination

[c]General Health Questionnaire

Table 4 Summary of characteristics of included studies related to the prevalence of depression in women with infertility

Author	Year	Location	Age	Women sample size	Prevalence of depression IN infertile women	Instrument
Cui et al. [37]	2021	China	22–47	536	27.9%	HADS[a]
Yangin et al. [38]	2015	Turkey	19–43	102	26.5%	BDI
Dong et al. [39]	2021	China	21–44	715	19.3%	PHQ-9
Jin et al. [40]	2013	China	22–41	460	14.8%	ZAD[b]
Lakatos et al. [41]	2017	Hungary	33.30 ± 4.85	134	44.8%	BDI
Huang et al. [42]	2019	China	35.7 ± 5.29	97	30%	BDI-II
Naab et al. [43]	2013	Ghana	30–39	203	53%	CES-D[c]
Sakulsaengprapha et al. [44]	2019	Thailand	36.5 ± 4.6	421	3%	HADS
Drosdzol et al. [45]	2009	Polish	29.8 + 4.1	206	35.4%	BDI
Aghanwa et al. [36]	1999	Nigeria	…	37	27%	PSE clinical evaluation
Crawford et al. [46]	2017	North Carolina	…	416	41%	NIH PROMIS (short form)[d]
Kato et al. [47]	2021	Japan	24–46	513	54%	QIDS[e]
Czyżkowska et al. [48]	2016	Poland	18–40	50	78%	BDI
Bondade et al. [49]	2018	India	26.73 ± 4.23	100	25%	DSM-5
Alhassan et al. [50]	2014	Ghana	30.5 ± 6.3	100	62%	BDI
Audier-Bourgain et al. [51]	2021	France	24–42	61	8.2%	HADS
Holley et al. [32]	2015	USA	23–52	174	24%	CESD
Cho et al. [52]	2019	Korea	36.16 ± 4.55	118	37.3%	BDI
Khan et al. [53]	2020	Pakistan	28.46 ± 7.68	160	75%	HADS
Suna et al. [54]	2016	Turkey	20–40	30	23.3%	BDI
Salomão et al. [55]	2018	Brazil	32–38	140	11.42%	HADS
Domar et al. [56]	1992	…	…	338	37%	BDI
Domar et al. [56]	1992	…	…	338	25%	CES-D
Sulyman et al. [57]	2019	Nigeria	19–43	207	25.6%	HADS
Li et al. [58]	2021	China	20–37	202	59.9%	SDS[f]
Peyvandi et al. [59]	2011	Iran	18–48	200	62%	BDI
Carreño Meléndez et al. [60]	2007	Spain	19–42	240	32.1%	SDS
Deeks et al. [61]	2010	Australia	…	22	67.7%	HADS
Sezgin et al. [62]	2016	Turkey	21–47	100	33%	HADS
Wright et al. [63]	1991	Canada	29.5 ± 4.5	449	23.2%	Psychiatric Symptom Inventory
Alosaimi et al. [64]	2015	Saudi Arabia	31.5	206	26.2%	MINI
Herbert et al. [65]	2010	Australia	…	1031	26.7%	CES-D10
Sejbaek et al. [29]	2013	Denmark	…	42,915	2.6%	ICD-8, ICD-10
Upkong et al. [66]	2006	Nigeria	24–46	112	42.9%	BDI
Dadhwal et al. [28]	2022	India	29.21 ± 3.74	150	58% (only dep), 24% (dep + anx)	HDRS[g]
Shabani et al. [27]	2010	Iran	…	353	30.4%	GHQ and interviews

[a]Hospital Anxiety and Depression Scale

[b]Zung Self-Rating Depression Scale

[c]Center for Epidemiologic Studies for Depression

[d]National Institutes of Health Patient Reported Outcomes Measurement Information System

[e]Quick Inventory of Depressive Symptomatology

[f]Self-Rating depression Scale

[g]Hamilton Depression Rating Scale

In the studies included in Table 1, the highest prevalence of stress among infertile women (92.71%) is related to the study of Teklemicheal et al. in 2022 which used the Copenhagen Multi-Centre Psychosocial Infertility–Fertility Problem Stress Scales (COMPI-FPPS) tool in the age group of 20–48 years [23]; and the lowest prevalence Stress in infertile women (53.06%) is reported by Xiaoli et al.'s study in 2016 which used the WHOQOL-100 tool (World Health Organization QoL) in the age group of 23 to 41 years [24]. Moreover, the overall pooled prevalence of stress among infertile women is 78.8% (95% CI: 25.8%–97.5%). Two studies used COMPI-FPPS and WHOQOL-100 tools to measure stress, which are presented in Table 1.

In the studies included in Table 2, the highest prevalence of major depression in infertile women (68.9%) is reported in a study by Al-Asadi et al. in 2015 which used the ICD-10 tool in the age group of 16 to 45 years [25]. The lowest prevalence of major depression in infertile women (5.7%) reported in the study of Volgsten et al. in 2018 which adopted the Primary Care Evaluation of Mental Disorders (PRIME-MD) tool based on DSM-IV in an average age group of 38.3 ± 3.9 years [26]. In our meta-analysis, the overall pooled prevalence of major depression among infertile women is found as 22.9% (95% CI: 11%–41.6%).

In the studies included in Table 3, the highest prevalence of generalized anxiety disorder in infertile women (44.1%) is related to a study conducted by Shabani et al. in 2010 which had adopted the General Health Questionnaire (GHQ) and diagnostic calculation [27]; the lowest prevalence of generalized anxiety disorder in infertile women (1.8%) is reported in Volgsten et al. which was conducted in 2018 using the PRIME-MD tool based on DSM-IV in an average age of 38.3 ± 3.9 years [26]. In our meta-analysis, the overall pooled prevalence of generalized anxiety disorder in infertile women is found to be 13.3% (95% CI: 6.5%–25.3%).

In the studies included in Table 4, the highest prevalence of depression in infertile women (78%) is related to the work of Czyżkowska et al. in 2016 which used the BDI tool [48]; the lowest prevalence of depression in women with infertility (2.6%) is in the study of Sejbaek et al. This study was in 2013 using the ICD-8 and ICD-10 tools [29]. In our meta-analysis, the overall pooled prevalence of depression in infertile women is 31.6% (95% CI: 21%–44.6%).

Stress

In the review of 2 studies with a total sample size of 177 people, the I^2 heterogeneity test showed high heterogeneity (I^2: 96.5), and therefore random-effects method was adopted to analyze the results. Based on the meta-analysis, the prevalence of stress among infertile women is found as 78.8% (95%CI: 25.8%–97.5%) (Fig. 2). It should be noted that it was not possible to check the publication bias in the studies due to the presence of only 2 studies in this category.

Major depression

In the review of 7 studies with a sample size of 1306 people, the I^2 test showed high heterogeneity (I^2: 97.3), and accordingly, random-effects method was adopted to analyze the results. Based on the meta-analysis, the pooled prevalence of major depression in infertile women is found to be 22.9% (95%CI: 11%–41.6%) (Fig. 3). Test of publication bias using the Egger's test showed the absence of publication bias among the studies (p: 0.179) (Fig. 4).

Generalized anxiety disorder (GAD)

In the review of 6 studies with a sample size of 1563 people, the I^2 test showed high heterogeneity (I^2: 95.9), and accordingly, random-effects method was adopted to analyze the results. Based on the meta-analysis, the pooled prevalence of generalized anxiety disorder among infertile women is 13.3% (95% CI: 6.5%–25.3%) (Fig. 5). Test of publication

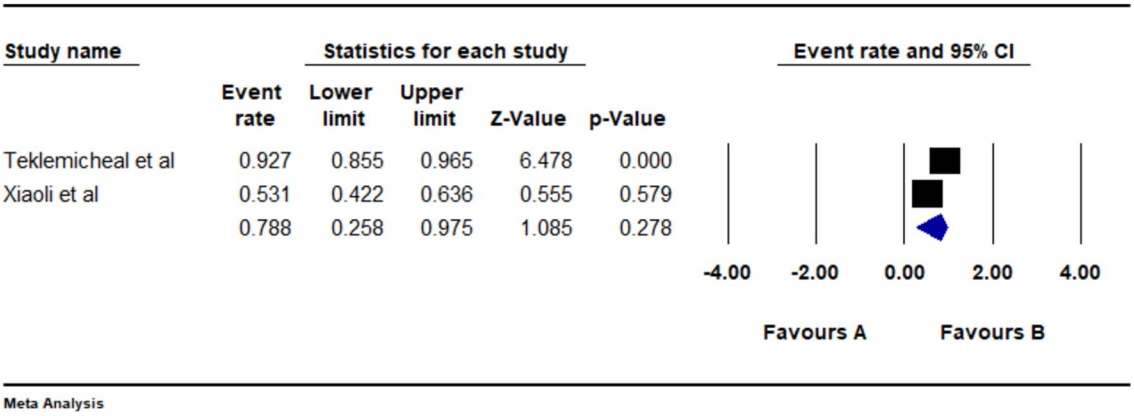

Fig. 2 Forest plot of prevalence of stress in infertile women based on random-effects method

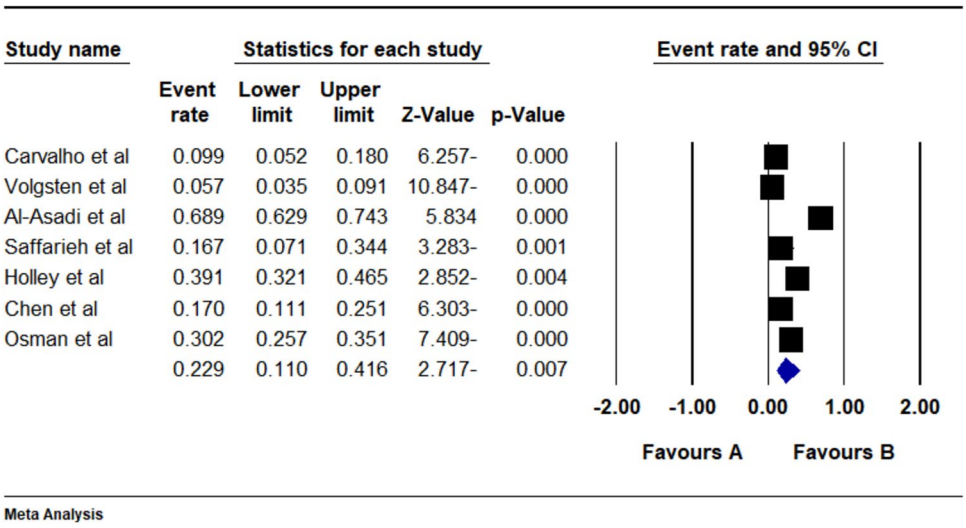

Fig. 3 Forest plot of prevalence of major depression based on random-effects method

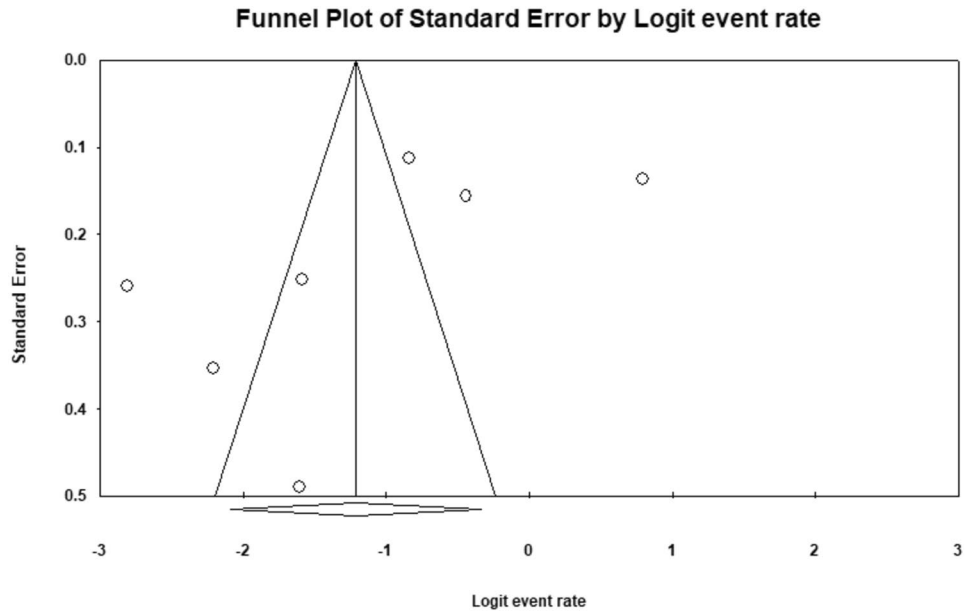

Fig. 4 Funnel plot for assessing publication bias in the reviewed studies related to major depression

bias using the Egger's test showed the absence of publication bias in the studies (p: 0.191) (Fig. 6).

Depression

In the review of 36 studies with a sample size of 51,636 people, the I^2 test showed high heterogeneity (I^2: 99.4), and therefore, random-effects method was used to analyze the results. According to our meta-analysis, the pooled prevalence of depression among women Infertility is 31.6% (95% CI: 21%–44.6%) (Fig. 7). Assessment of publication bias using the Egger's test indicated the existence of publication bias in the studies (p: 0.000) (Fig. 8).

Discussion

Infertility is considered as a concern for women in several communities and cultures, where there is a strong emphasis on women being mothers or wives [67–69]. Accordingly, there are numerous cases where a woman's infertility has an impact on her marriage and life [70]. Since pregnancy and the role of mother are viewed as specific to women, social expectations from women are also higher compared to men. Moreover, the fear of social stigma of infertility is greater among women [71]. Considering these, infertility is deemed as a personal crisis that can cause severe mental and emotional stress and pressure on

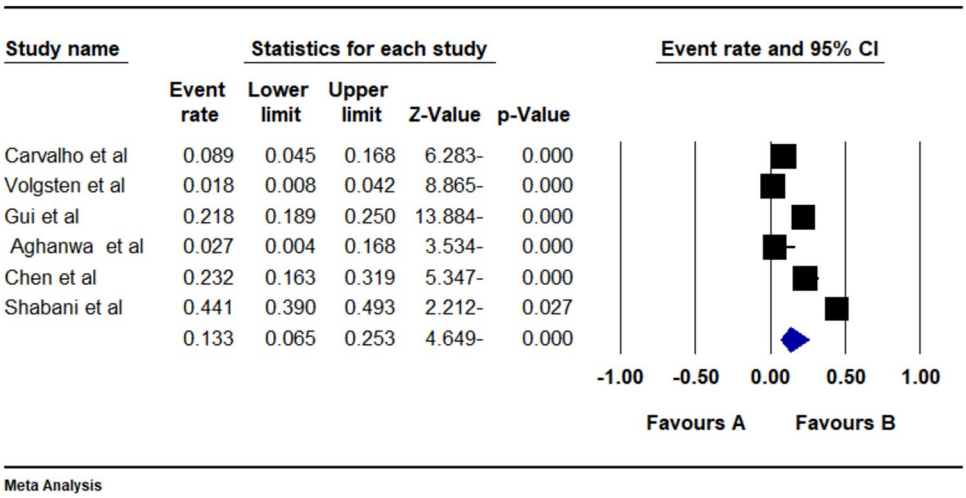

Fig. 5 Forest plot of prevalence of generalized anxiety disorder based on random-effects method

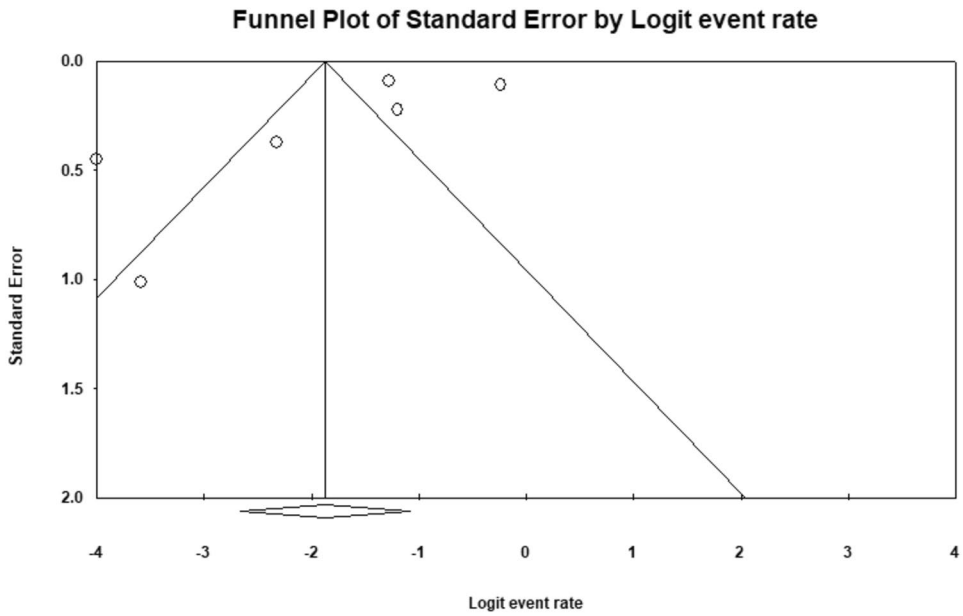

Fig. 6 Funnel plot for assessing publication bias in the reviewed studies related to GAD

couples and can negatively impact their mental health in various ways [72].

The present study was a systematic review and meta-analysis to analyze reported results of relevant literature on the global prevalence of major depressive disorder, generalized anxiety, stress and depression among infertile women. Based on the results of this study, the overall pooled prevalence of major depressive disorder, generalized anxiety disorder, stress, and depression in infertile women is 22.9%, 13.3%, 78.8%, and 31.6%, respectively.

Many studies have reported high prevalence of symptoms of depression, anxiety and stress among infertile women [73–78]. According to a study by Alhassan et al., 62% of infertile women in Ghana suffer from depression [50]. The prevalence of depression among Chinese infertile women is reported 69% [79]. Depression is also highly prevalent among infertile women in Japan and Gambia [80, 81]. Jones et al. (1993) also stated that there is mild to moderate depression in 28.3%, moderate to severe depression in 7.2%, and the most severe form of depression in 1.2% of infertile women [82].

On the other hand, Noorbala et al. argued that 48% of infertile women experience depression [83]. The rate of depression among infertile Bahraini women was reported as 32.5%, whereas this figure in infertile Tunisian women was 46.6% [84]. Similarly, depression rate among infertile Iranian women was 40% [85, 86]. Oddens et al.'s study (1999) stated that 24.9% of infertile women had depression disorders [87]. According to the results of the present study, the overall prevalence of major depressive disorder in infertile women is 22.90% and the prevalence of depression is 31.6%.

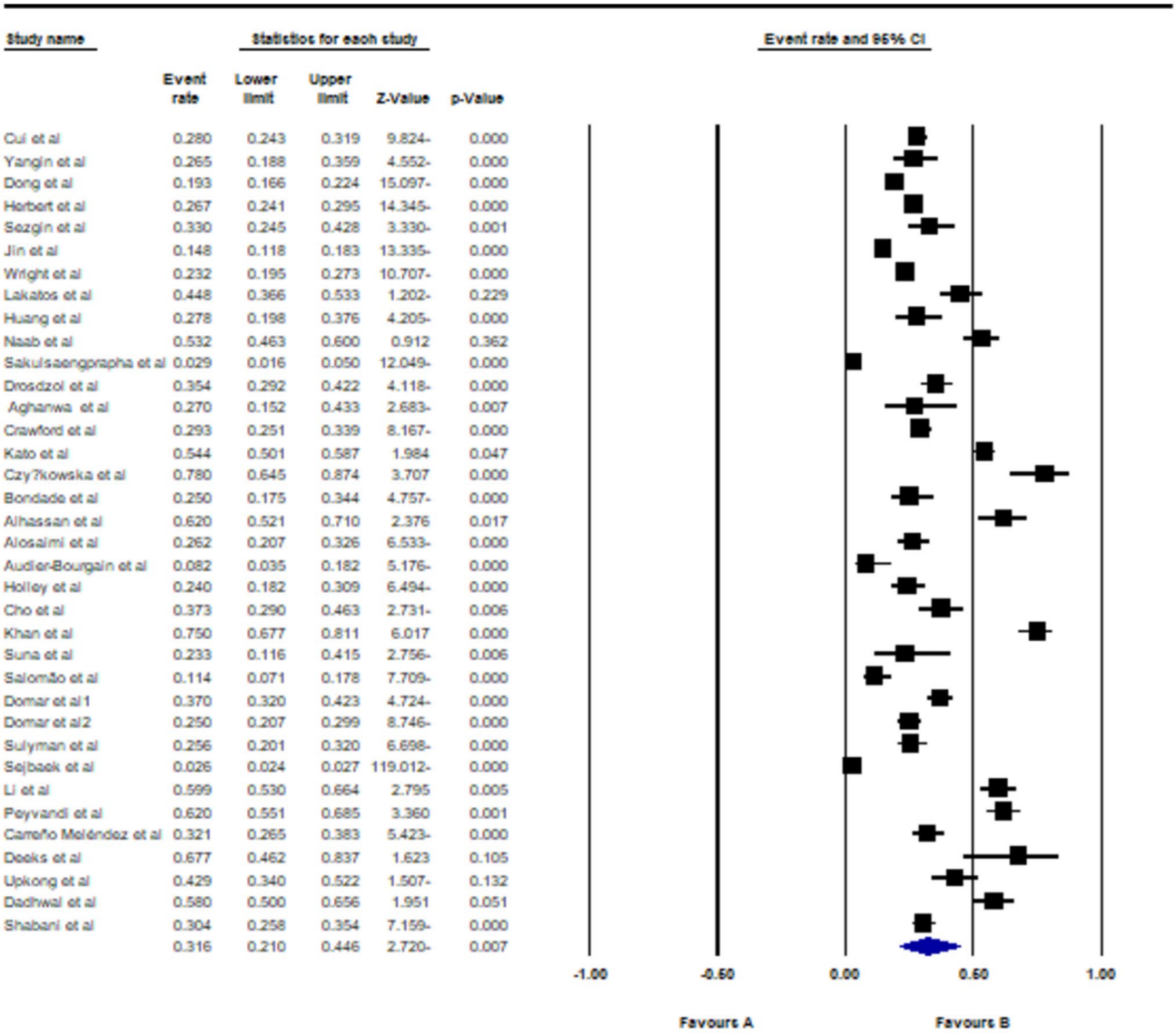

Fig. 7 Forest plot of prevalence of depression based on random-effects method

In some countries, socio-cultural and religious norms allow husbands to have multiple marriages, and a woman's infertility provides them with a reason for this decision. In addition, having a child, a boy, gives women a sense of pride and security for old age, which is why infertility causes many psychological problems for women. However, in developed countries, psychological disorders are less common due to women's legal rights, their participation in professional life and their contribution to the family economy [8, 72, 88]. For this reason, the results of our study provide a lower prevalence of depression disorders reported for some countries, especially developing countries, due to the inclusion of different cultures.

According to literature, patients with infertility experience lower quality of life and higher levels of anxiety [89–92]. Lawson et al., Allen, and Kraaji et al. have shown higher levels of anxiety in infertile women [93–95]. Another study found that 67% of infertile women suffered from anxiety [79]. The prevalence of generalized anxiety disorder in infertile women in Taiwan has been reported as 23.2% [96]. Anxiety was investigated in 130 infertile women in China, and the results showed

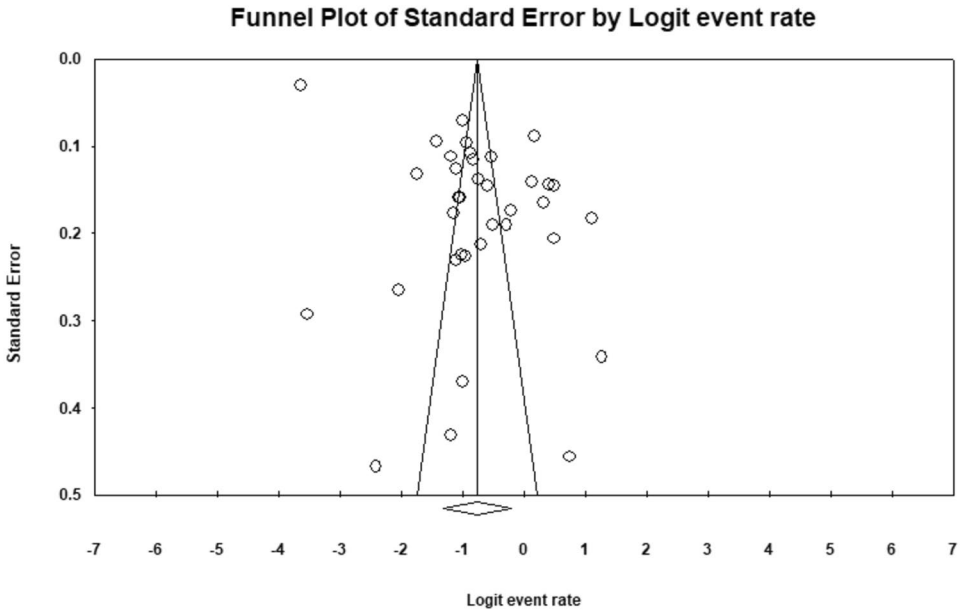

Fig. 8 Funnel plot for assessing publication bias in the reviewed studies related to depression

different levels of psychological stress among 83.8% of infertile women; in addition, moderate or severe types were observed in 25% [97]. In another study, depression and/or anxiety disorders were present in 33% (Hong Kong) [87], and 32% (Scotland) of infertile women [98]. In our study, the overall pooled prevalence of generalized anxiety disorder in infertile women is 13.3%, and the results of these studies are in line with our findings. The lower prevalence of anxiety in our review is due to the fact that we only examined generalized anxiety disorder and did not examine other types of anxiety.

The stress levels of infertile women in developing countries such as Cameroon [99], India [100] and Nigeria [101] have been reported as 84.6%, 80%, and 87.2%, respectively. On the other hand, in developed countries such as Sweden, 30.8% of stress has been reported for infertile women [102]. Similarly, Luk et al., Dooley et al., and El Kissi et al. showed in their studies that stress has a higher prevalence among infertile women [78, 103, 104]. The results of these studies are in line with our findings (78.8%). Since cultural and social issues that cause stress in infertile women is more prevalent in some regions, especially in Asian countries, the results of our research are closer to the studies conducted in the Asia (continent).

There are some limitations in our work. One of the limitations of this study is that several articles were excluded from the review due to their low quality, e.g., by not reporting the prevalence figure. Additionally, the level of anxiety, depression and stress among infertile women can be affected by various factors such as the role of the life partner, economic conditions, etc.

Conclusion

According to the results of the present study, the overall prevalence of major depressive disorder, general anxiety, stress and depression in infertile women is 22.9%, 13.3%, 78.8%, and 31.6%, respectively. According to the results, women suffering from infertility also experience many psychological disorders. In this way, paying attention to the mental health of infertile women is an crucial, and in addition to the treatment of infertility, taking care of the mental health of infertile women is of special importance. Therefore, health policymakers can potentially use the results of the present meta-analysis to gain insights on the prevalence of mental disorders among infertile women. Moreover, policymakers can plan appropriate intervention programs in response to the psychological problems of infertile women.

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Author contributions NS and FB contributed to the design, MM statistical analysis, participated in most of the study steps. MM and RH and AHF and NA and PH prepared the manuscript. All authors have read and approved the content of the manuscript.

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Data availability Datasets are available through the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethics approval was received from the ethics committee of deputy of research and technology, Kermanshah University of Medical Sciences (IR.KUMS.REC.1402.151).

Consent for publication Not applicable.

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