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Worldwide prevalence, risk factors and psychological impact of infertility among women: a systematic review and meta-analysis

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ABSTRACT

Objectives To assess the prevalence, risk factors and psychological impact of infertility among females. This review summarises the available evidence, effect estimates and strength of statistical associations between infertility and its risk factors.

Study design Systematic review and meta-analysis.

Data sources MEDLINE, CINAHL and ScienceDirect were searched through 23 January 2022.

Eligibility criteria The inclusion criteria involved studies that reported the psychological impact of infertility among women. We included cross-sectional, case–control and cohort designs, published in the English language, conducted in the community, and performed at health institution levels on prevalence, risk factors and psychological impact of infertility in women.

Data extraction and synthesis Two reviewers independently extracted and assess the quality of data using the Joanna Briggs Institute Meta-Analysis. The outcomes were assessed with random-effects model and reported as the OR with 95% CI using the Review Manager software.

Results Thirty-two studies with low risk of bias involving 124 556 women were included. The findings indicated the overall pooled prevalence to be 46.25% and 51.5% for infertility and primary infertility, respectively. Smoking was significantly related to infertility, with the OR of 1.85 (95% CI 1.08 to 3.14) times higher than females who do not smoke. There was a statistical significance between infertility and psychological distress among females, with the OR of 1.63 (95% CI 1.24 to 2.13). A statistical significance was noted between depression and infertility among females, with the OR of 1.40 (95% CI 1.11 to 1.75) compared with those fertile.

Conclusions The study results highlight an essential and increasing mental disorder among females associated with infertility and may be overlooked. Acknowledging the problem and providing positive, supportive measures to females with infertility ensure more positive outcomes during the therapeutic process. This review is limited by the differences in definitions, diagnostic cut points, study designs and source populations.

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Strengths and limitations of this study

- ► Meta-analysis of studies according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.
- ► Joanna Briggs Institute Meta-Analysis for assessing the quality of included studies.
- ► Only studies with a low risk of bias were included in the analyses.
- ► Heterogeneity and subgroup analyses were performed.
- ► The search was restricted to English-language articles only.

INTRODUCTION

Infertility is defined by the World Health Organization (WHO) as the inability to conceive after 1 year (or longer) of unprotected intercourse.[1] It is classified as primary or secondary. Primary infertility is denoted for those women who have not conceived previously.[2] In secondary infertility, there is at least one conception, but it fails to repeat.[2] In 2002, the WHO estimated that infertility affects approximately 80 million people in all parts of the world.[3] It affects 10%–15% of couples in their lifetime.[4 5] The prevalence of infertility is concerned, it is high (up to 21.9%): primary infertility at 3.5% and secondary infertility at 18.4%.[6] It is generally accepted that infertility rates are not estimated correctly. The reasons could hinder the measurement of the prevalence, imperfect measurement methods, and unknown kinds of infertility resulting from cultural biases.[7]

Infertility is a multidimensional stressor requiring several kinds of emotional adjustments.[4] It is associated with dysfunction in sexual relationships, anxiety, depression, difficulties in marital life and identity problems.[8] The impact of infertility may be long-lasting, even beyond the initial period of childlessness has passed.[9 10] In the general population, major depression is two to three times as

common among women as among men.[11] In the United States, the 12-month prevalence of any mood disorder is 14.1% in females and 8.5% in males, whereas any anxiety disorder is 22.6% in females and 11.8% in males.[12] Thus, depression is one of the most common negative emotions associated with infertility,[13 14] which the local social and cultural context may influence.

Determining the psychological impact of infertility among women worldwide provides a better assessment than discrete primary studies. Identifying this impact helps gain a clear understanding of the issue and serves as a basis for an appropriate preventive strategy. In addition, it applies to primary prevention that could potentially prevent conditions affecting adverse psychological well-being. We aimed to perform a systematic review and meta-analysis on infertility among females with regard to its pooled prevalence, risk factors and psychological impact in observational studies conducted worldwide. This review will summarise the available evidence, effect estimates, and strength of statistical associations between infertility and its risk factors.

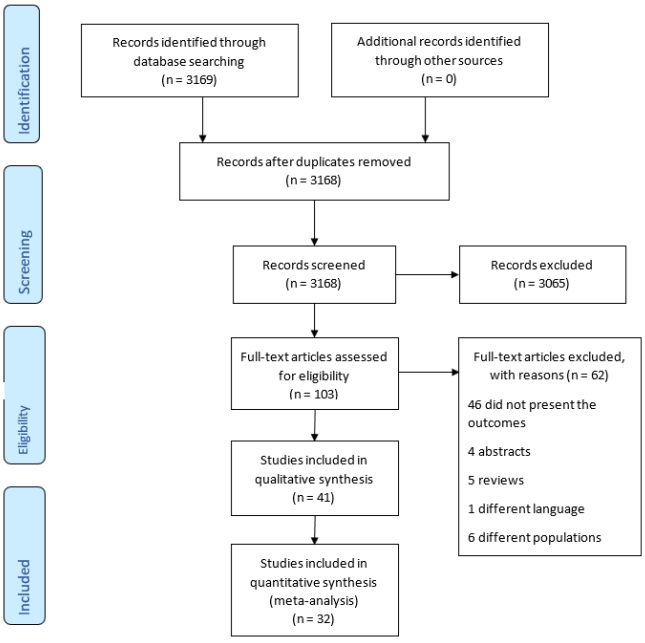


Figure 1 Flow diagram showing the included studies for systemic review and meta-analysis on the prevalence, risk factors and psychological impact of infertility among women.

MATERIALS AND METHODS

Study design and search strategy

A systematic review and meta-analysis of studies were conducted to assess the psychological impact of infertility among women. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15]

A systematic search was performed in MEDLINE (PubMed), CINAHL (EBSCOhost) and ScienceDirect. The search was done using text words such as "infertility," "prevalence," "risk factor," "psychology," "mental," "quality of life," "anxiety, "depression" and "stress." The search terms were flexible and tailored to various electronic databases (online supplemental file). All studies published from the inception of these databases until 23 January 2022 were retrieved to assess their eligibility for inclusion in this study. The search was restricted to full-text and English-language articles. To find additional potentially eligible studies, reference lists of included citations were cross-checked.

Eligibility criteria

The inclusion criteria involved studies that reported the psychological impact of infertility among women. Studies with cross-sectional, case-control and cohort designs, published in the English language, conducted in the community, and performed at health institution levels were included. Case series/reports, conference papers, proceedings, articles available only in an abstract form, editorial reviews, letters of communication, commentaries, systematic reviews and qualitative studies were excluded.

Study selection and screening

All records identified by our search strategy were exported to the EndNote software. Duplicate articles were removed. Two independent reviewers screened the titles and abstracts of the identified articles. The full text of eligible studies was obtained and read thoroughly to assess their suitability. A consensus discussion was held in the event of a conflict between the two reviewers, and a third reviewer was consulted. The search method is presented in the PRISMA flow chart showing the studies that were included and excluded with reasons for exclusion (figure 1).

Quality assessment and bias

A critical appraisal was undertaken to assess data quality using the Joanna Briggs Institute Meta-Analysis for cross-sectional, case–control and cohort studies.[16] Two reviewers performed bias assessments independently. The risk of bias was considered low when more than 70% of the answers were 'yes,' moderate when 50%–69% of the answers were 'yes,' and high when up to 49% of the answers were 'yes'. Studies that showed a high and moderate risk of bias were excluded from the review.

Data extraction process

Two reviewers independently extracted data using the NVivo software (V.12). The process included the first author, publication year, study location, study design and setting, study population, sample size, psychological impact, infertility definition and data in calculating effect estimates for psychological impact.

Result synthesis and statistical analysis

The outcomes were reported as the odds ratio (OR) and 95% confidence interval (CI). The analysis was performed using the Review Manager software (V.5.4; Nordic Cochrane Centre, Copenhagen, Denmark). A

random-effects model was employed to pool data. The I^2 statistic was used to assess heterogeneity, with a guide as outlined: 0%–40% might not be important; 30%–60% may represent moderate heterogeneity; 50%–90% may represent substantial heterogeneity, and 75%–100% may represent considerable heterogeneity.[17] A subgroup analysis was performed based on countries (developed and developing) and comorbidity (presence and absence of comorbidity) if an adequate number of studies were available. Funnel plots were used to assess publication bias if indicated.

RESULTS

Characteristics of included studies

A total of 3169 articles were retrieved through an electronic search using different search terms. Forty-eight duplicate records were removed. Of the 3168 articles screened for eligibility, 3065 were excluded by their title and abstract evaluation. The full text of 103 articles was searched. Subsequently, 62 articles were excluded: 46 did not present the main outcomes, 6 were performed in different populations, 5 were review articles, 4 had only abstracts and 1 was published in a non-English language (figure 1). A total of 41 studies underwent quality assessment, of which nine had moderate and high risk of bias.

Finally, 32 studies with low risk of bias were explored in the review: 22 were cross-sectional, 8 were case–control and 2 were cohort studies. Different countries were involved. Five studies were conducted in Iran,[18–22] four in Turkey,[23–26] three in Italy,[27–29] three in America,[30–32] three in Sweden,[33–35] two in India,[36 37] two in the Netherlands,[38 39] one in Finland,[9] two in Africa,[40 41] one in Saudi Arabia,[42] one in Japan,[43] two in China[44 45] one in Pakistan[46] and two in Greece.[47 48] The smallest sample size was 87,[47] and the largest was 98 320.[39] Overall, this study included 124 556 women (table 1).

Prevalence

Of the included studies, 20 were conducted in a hospital-based setting, 4[9 23 33 37] in a community-based setting and 2[18 46] in both hospital-based and community-based settings. A slight difference in the prevalence of infertility was observed in the review. A lower prevalence (10.4%) of infertility[9] was observed in a community-based setting, and a higher prevalence (79.3%)[44 47] was noted in a hospital-based setting. The overall pooled prevalence of infertility was 46.25% (95% CI 37.73% to 54.77%; I^2=100%). Twenty-four articles were included for the estimation of pooled prevalence of infertility among females (figure 2). The funnel plot was asymmetry with smaller studies and lower prevalence being missing on the left side. The results of the assessment of bias based on the funnel plot asymmetry were not shown but available on request. Out of this, nine were used for the estimation of pooled prevalence of primary infertility.

The overall pooled prevalence of primary infertility was 51.5% (95% CI 32.74% to 70.26%; I^2=100%) (figure 1). The lowest prevalence (18%) of primary infertility was reported in a hospital-based study,[27] and the highest prevalence (91.1%) was observed in both community- and hospital-based studies conducted in Iran[18] (figure 2).

Risk factors of infertility

In this study, risk factors such as age, body mass index (BMI), smoking and family income were evaluated for their association with infertility. Five studies were included to assess age older than 35 years as a risk factor for infertility regarding the association between age and infertility among females.[9 18 32 37] The pooled meta-regression analysis showed no significant difference in the occurrence of infertility in females aged 35 years or older compared with those younger than 35 years, with the odds being 1.10 (95% CI 0.83 to 1.45; I^2=41%). Similarly, there was no association between BMI and infertility in four studies,[9 32–34] with odds of 1.11 (95% CI 0.91 to 1.36; I^2=66%). However, smoking was found to be significantly related to infertility in three studies,[9 33 34] with the odds being 1.85 (95% CI 1.08 to 3.14; I^2=94%) times higher compared with those who do not smoke (figure 3). There was no difference observed (OR 0.85; 95% CI 0.59 to 1.23; I^2=34%) regarding the association between low income and infertility in five studies.[9 20 24 37 46]

The psychological impact of infertility

In this study, psychological impact—including distress, depression and anxiety—was evaluated. Four studies were included to assess the distress caused by infertility.[9 20 39 43] The pooled meta-regression analysis showed a statistical significance between infertility and psychological distress among females, with the odds being 1.63 (95% CI 1.24 to 2.13; I^2=57%) (figure 4).

Eight studies were included to assess the association between depression and infertility among females.[9 19 29 30 32–35] Four studies showed significant[9 30 34 35] associations, and four showed no significant[19 29 32 33] associations. The pooled meta-regression analysis showed a statistical significance between depression and infertility among females, with the odds being 1.40 (95% CI 1.11, 1.75; I^2=50%) compared with those fertile. However, there was no association between anxiety and infertility in the six studies,[9 19 29 32–34] with a pooled meta-regression analysis of OR 1.68 (95% CI 0.71, 3.98; I^2=98%) (figure 4).

DISCUSSION

Infertility is a worldwide public health agenda affecting an individual's personal, social and economic life and the family as a whole. This study was conducted to determine the pooled prevalence and risk factors of infertility among females. In this meta-analysis, the pooled prevalence of infertility and primary infertility among females was 45.85% (95% CI 37.12% to 54.57%) and 51.5% (95% CI 32.74% to 70.26%), respectively. The prevalence of infertility among females in this study is higher than in a review conducted in 2007 (between 3.5% and 16.7%).[49] It

Table 1 Summary of research articles included in this systemic review and meta-analysis of infertility (n=32)

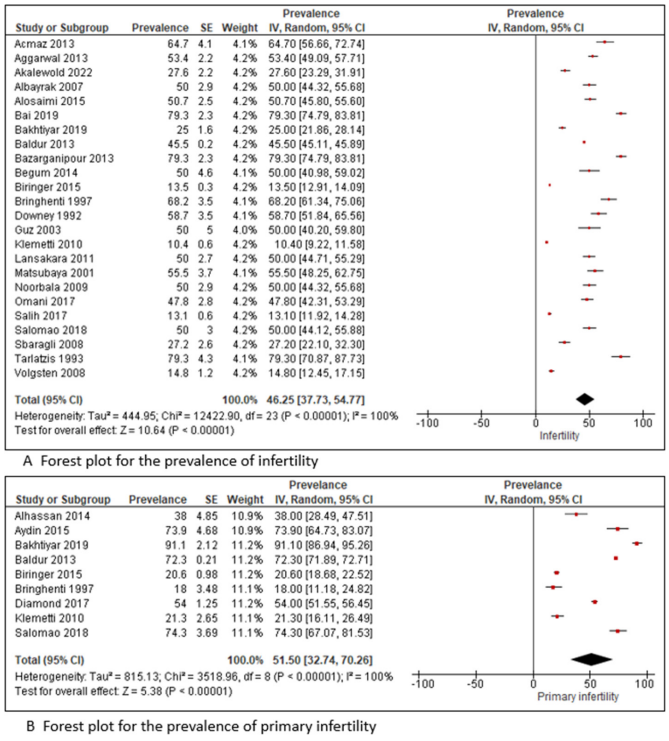
No	Authors	Study area	Study design	Sample size	Female infertility	Quality assessment (%)
1	Aggarwal *et al*, 2013[36]	India	Cross-sectional	500	267	87.5
2	Albayrak and Günay, 2007[23]	Kayseri, Turkey	Cross-sectional	300	150	87.5
3	Biringer *et al*, 2015[33]	North Trondelag, Sweden	Cross-sectional	12 584	1696	100
4	Klemetti *et al*, 2010[9]	Finlad	Cross-sectional	2291	239	100
5	Bakhtiyar *et al*, 2019[18]	Lorestan, Iran	Case control	720	180	70
6	Alhassan *et al*, 2014[40]	Ghana	Cross-sectional	100	100	87.5
7	Alosaimi *et al*, 2015[42]	Riyadh, Saudi Arabia	Cross-sectional	406	206	100
8	Matsubaya *et al*, 2001[43]	Tokai, Japan	Cross-sectional	182	101	87.5
9	Açmaz *et al*, 2013[24]	Kayseri, Turkey	Cross-sectional	133	86	87.5
10	Bai *et al*, 2019[44]	Ningxia province, China	Cross-sectional	740	380	100
11	Bazarganipour *et al*, 2013[19]	Kashan, Iran	Cross-sectional	300	238	100
12	Begum and Hasan, 2014[46]	Karachi, Pakistan	Cross-sectional	120	60	87.5
13	Volgsten *et al*, 2008[35]	Sweden	Cross-sectional	825	122	88.9
14	Bringhenti *et al*, 1997[27]	Italy	Cross-sectional	179	122	87.5
15	Lansakara and Wickramasinghe, 2011[37]	Colombo, Sri Lanka	Cross-sectional	354	177	87.5
16	Noorbala *et al*, 2009[20]	Tehran, Iran	Cross-sectional	300	150	87.5
17	Salih Joelsson *et al*, 2017[34]	Sweden	Cross-sectional	3583	468	100
18	Aydin *et al*, 2015[25]	Istanbul, Turkey	Cross-sectional	88	88	87.5
19	Tarlatzis *et al*, 1993[47]	Greece	Cohort	87	69	81.8
20	Ramezan *et al*, 2004[21]	Tehran, Iran	Cross-sectional	370	370	87.5
21	Aarts *et al*, 2011[38]	Netherlands	Cross-sectional	472	472	87.5
22	Baldur *et al*, 2013[39]	Denmark	Cohort	98 320	44 773	100
23	Diamond *et al*, 2017[31]	United states	Cross-sectional	1594	1594	87.5
24	Downey and McKinney, 1992[30]	New York City	Case control	201	118	80
25	Fassino *et al*, 2002[28]	Italy	Case control	172	172	90
26	Guz *et al*, 2003[26]	Turkey	Case control	100	50	80
27	Omani *et al*, 2017[22]	Tehran, Iran	Cross-sectional	312	149	100
28	Salomão *et al*, 2018[32]	Brazil	Case control	280	140	80
29	Sbaragli *et al*, 2008[29]	Siena, Italy	Case control	302	82	100
30	Akalewold *et al*, 2022[41]	Ethiopia	Cross-sectional	409	66	100
31	Kleanthi *et al*, 2021[48]	Greece	Case control	177		90
32	Peng *et al*, 2021[45]	China	Case control	450		100

The quality assessment was performed based on the Joanna Briggs Institute Meta-Analysis for cross-sectional, case–control and cohort studies.

is because most of the sample size for the research articles in this meta-analysis is from an infertility clinic. Regarding primary infertility, it is similar to a review in Africa at 49.9% (95% CI 41.34% to 58.48%).[50]

Various risk factors were assessed in terms of their association with infertility among females. Age was not found to be associated with infertility; however, a study on a sample comprising 7172 couples showed that the odds of being diagnosed with unexplained and tubal factor infertility are almost twice as high in women older than 35 years as those younger than 30 years.[51] There was no association noted between BMI and infertility among females. Vahratian and Smith[52] found that a large proportion of females seeking medical help to become pregnant are obese, and the risk of infertility is three times higher in those obese than nonobese.[53] Smoking is a crucial risk factor for females, and it shows that females who smoke have a 1.8 times higher risk of developing infertility than those who do not. One study pointed toward a significant association with a 60% increase in the risk of infertility among females who smoke cigarettes.[54] A meta-analysis identified the pertinent literature available from 1966 through late 1997 and reported an OR of 1.60 for infertility among females who smoke compared with those who do not across all study designs.[54]

Infertility among females has a vast impact on psychological distress. In the current study, females with infertility have a 1.6 times higher risk of being psychologically

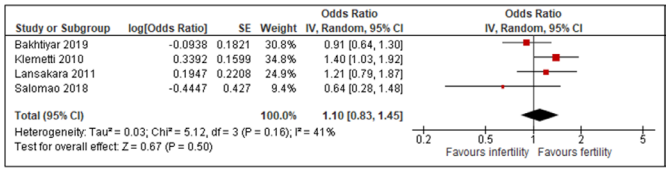


A Forest plot for the prevalence of infertility

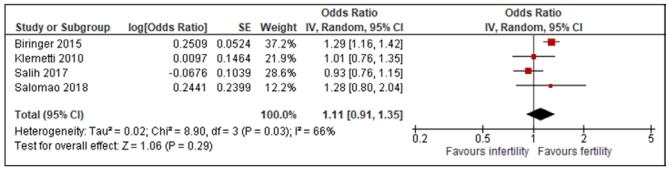
B Forest plot for the prevalence of primary infertility

Figure 2 Forest plot depicting the prevalence of infertility. IV, inverse variance.

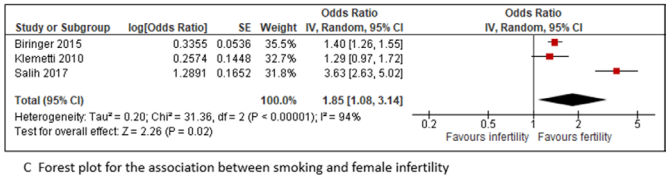
distressed than those fertile. This is similar to a study in Taiwan,[55] which found that 40.2% of the females with infertility suffer from mental disorders. A review of studies conducted in many countries suggested that women endure the major burdens caused by infertility and experience intense anxiety from being blamed for their failure to give birth.[56] Infertility also contributes to the risk of having depression, with females suffering from infertility having a 1.4 times higher chance of being depressed, whereas other studies showed 67.0%[57] and 35.3%[58] of women with infertility were depressed. Recent



A Forest plot for the association between age and female infertility

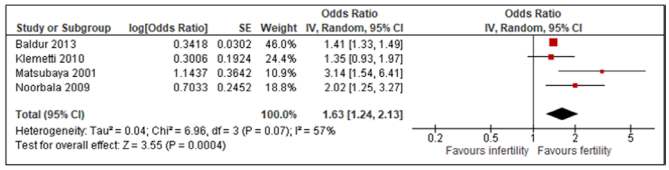


B Forest plot for the association between body mass index and female infertility

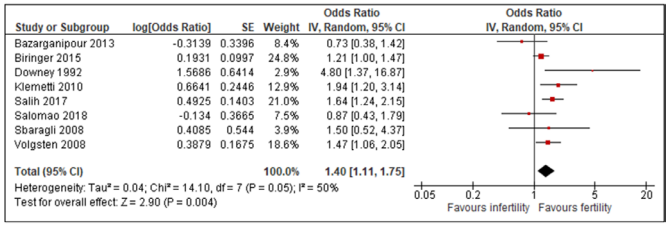


C Forest plot for the association between smoking and female infertility

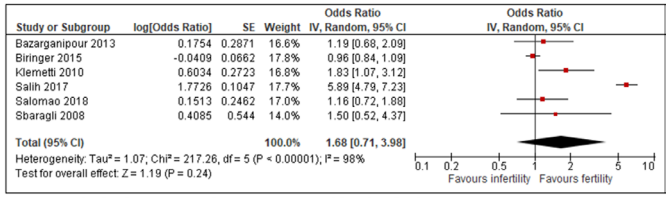
Figure 3 Forest plot depicting the risk factors associated with infertility. IV, inverse variance.



A Forest plot for the association between distress and female infertility



B Forest plot for the association between depression and female infertility



C Forest plot for the association between anxiety and female infertility

Figure 4 Forest plot depicting the psychological impact of infertility. IV, inverse variance.

research has shown that prevalence can range from 11%[35] to 27%[55] and 73%.[57] Another study in Sweden[35] reported that major depression was the most common disorder among couples suffering from infertility, with a prevalence of 10.9% in females and 5.1% in males. It shows that infertility increases the risk of depression. Therefore, it should be considered a serious warning and given a particular focus.

The risk of anxiety in females with infertility is also high. A meta-analysis by Kiani and Simbar[59] showed a pooled prevalence of 36.17% (95% CI 22.47% to 49.87%) among females having anxiety because of infertility. In another systematic review, Sawyer *et al*[60] reported a 14.8% prevalence of anxiety in females with infertility and a prevalence of 14.0% among women in their prenatal and postnatal periods. In most societies, having a child is closely related to a woman's identity. Being a mother is equated with being female,[59] which results in high levels of stress and a sense of worthlessness in those childless.[61] In addition, a female who cannot conceive is at risk of social insecurity and becomes anxious because she foresees a future with no child to take care of them in old age or case of illness.[62]

Strengths and limitations

This study showed the prevalence of infertility worldwide and the risk of psychological problems among such females, including studies from different countries. It also focused on the quantitative aspect of the problem to get a better view of the intervention.

However, this study is not without limitations. The differences in definitions, diagnostic cut points, study designs, and source populations make performing a meta-analysis on infertility difficult. On the contrary, there are diverse

instruments to determine psychological distress, depression and anxiety that make comparing results difficult. Another limitation was the use of various instruments to assess psychological problems in the general population. None of the tools was developed specifically to investigate the incidence of factors concerning females. Although the risk factors identified in this review are not new, calling attention to the psychological impact of infertility is worthwhile.

CONCLUSIONS

This study identified that the risk of psychological distress among females with infertility is 60% higher than that among the general population. Furthermore, the risks of anxiety and depression are 60% and 40% times higher, respectively. These results highlight an important and increasing mental disorder among females that may be overlooked. Psychological distress should concern attending physicians and should be assessed to avoid any unwanted events from happening. Acknowledging the problem and taking positive, supportive measures to help females with infertility ensure more positive outcomes during the therapeutic process.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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