reproductive medicine

MDPI

Systematic Review

Use of Laughter Therapy for In Vitro Fertilization: A Systematic Review

Daniela Rodríguez-García [1], Claudio-Alberto Rodríguez-Suárez [1,2,*] and Héctor González-de la Torre [1,2]

[1] Nursing Department, Faculty of Healthcare Science, University of Las Palmas de Gran Canaria (ULPGC), 35016 Las Palmas de Gran Canaria, Spain; daniela.rodriguez106@alu.ulpgc.es (D.R.-G.); hector.gonzalez@ulpgc.es (H.G.-d.l.T.)

[2] Research Support Unit, Insular Maternal and Child University Hospital Complex, Canary Health Service, 35016 Las Palmas de Gran Canaria, Spain

* Correspondence: claudioalberto.rodriguez@ulpgc.es

Abstract: Background/Objectives: In vitro fertilization (IVF) is an assisted reproductive technique for women and couples experiencing difficulties in achieving a spontaneous pregnancy, often due to stressors that negatively affect fertility. Humor can be beneficial in these stressful situations, helping to reduce symptoms of anxiety and depression. The primary aim was to analyze the effectiveness of laughter therapy in increasing pregnancy rates in women undergoing IVF. The secondary aims were to identify different types of laughter therapy interventions and evaluate their benefits. Methods: A systematic review was conducted using Medline, Web of Science, Scopus, Cinahl, ProQuest and Lilacs, with the search terms "laughter", "laughter therapy", "fertilization in vitro" and "fertilization". Intervention studies published in English, Spanish, or Portuguese were included, with no limits on the date of publication. Studies with other designs, those conducted with animals and grey literature were excluded. The quality of the included studies was assessed using the Joanna Briggs Institute critical appraisal tools. Results: In total, n = 3 studies (1 randomized clinical trial and 2 quasi-experimental) were included, evaluating pregnancy rates and symptoms of depression and anxiety. The interventions included clowns performing magic tricks and interpreting comic situations. Additionally, they incorporated hand clapping, breathing exercises, childlike playfulness, drinking milk, muscle relaxation exercises, candles, and music. Conclusions: This review does not provide clear evidence on the effectiveness of laughter therapy in increasing pregnancy success in IVF. Although it may have some positive effects in reducing symptoms of depression and anxiety, it is important to note that while the reduction of these symptoms may enhance the emotional well-being of patients, it has not been demonstrated to directly lead to an increase in pregnancy rates. Laughter therapy is an innovative, non-pharmacological intervention that is simple, non-invasive, easy to implement and cost-effective; however, the number of available studies is insufficient. More research is needed to provide better and higher-quality evidence using rigorous designs to evaluate this intervention in IVF clinical practice.

Keywords: laughter therapy; laughter; fertilization; in vitro fertilization; systematic review

Citation: Rodríguez-García, D.; Rodríguez-Suárez, C.-A.; González-de la Torre, H. Use of Laughter Therapy for In Vitro Fertilization: A Systematic Review. *Reprod. Med.* **2024**, *5*, 252–262. https://doi.org/10.3390/reprodmed5040022

Academic Editor: Paolo Ivo Cavoretto

Received: 14 August 2024
Revised: 18 October 2024
Accepted: 31 October 2024
Published: 2 November 2024

1. Introduction

Infertility is defined as the inability of a woman or couple to achieve pregnancy after 12 months of regular sexual intercourse without the use of any contraceptive method [1]. However, up to 90% of couples who have unprotected sexual intercourse will conceive within one year [2]. Coping with various assisted reproduction techniques involves exposure to different stressors that can negatively affect fertility [1]. Infertility significantly impacts emotional health, interpersonal relationships and sense of identity, and can be influenced by various factors affecting both men and women [2]. These factors include biological and physiological characteristics such as genetic and hormonal disorders, or

advanced age. Stress and chronic diseases, such as diabetes and hypertension, are also predisposing factors [1]. Specific factors in women include polycystic ovary syndrome, uterine fibroids and endometriosis. In men, factors include post-testicular impairment or testicular dysfunction. Both genders may experience issues such as hypogonadotropic hypogonadism, hyperprolactinemia, primary ciliary dyskinesia and cystic fibrosis [1,2]. Additionally, a sedentary lifestyle, overweight, obesity and habits such as smoking and alcohol consumption negatively influence infertility [2]. Sexually transmitted infections can also contribute to infertility [1,2].

In vitro fertilization (IVF) is a form of assisted reproductive technology (ART) used to help women and couples who struggle to achieve spontaneous pregnancy [3,4]. ART encompasses various techniques, including different insemination methods such as conventional IVF (cIVF) and intracytoplasmic sperm injection (ICSI), as well as different embryo transfer stages (cleavage stage vs. blastocyst stage) and transfer protocols (fresh cycles vs. frozen embryo transfer (FET) or freeze–thaw cycles (TEC)). Each of these approaches uniquely affects reproductive outcomes, including fertilization, implantation and live birth rates. In cIVF, sperm and eggs are combined in a culture dish, allowing for natural fertilization to occur, whereas ICSI involves the direct injection of a single sperm into an egg. ICSI often results in higher fertilization rates, particularly in cases of male factor infertility, as it bypasses issues such as poor sperm motility or morphology [5,6]. Other ART techniques involve fertilizing eggs outside the body in a controlled laboratory environment, followed by the transfer of embryos into the woman's uterus to achieve pregnancy, often in conjunction with controlled ovarian stimulation [7,8]. The stage of embryo transfer is a critical factor in determining reproductive success. Cleavage stage transfers, performed on Day 2 or 3, result in lower implantation rates compared with blastocyst transfers, which occur on Day 5 or 6. Blastocyst transfers allow for more precise embryo selection and better synchronization with the uterine environment, leading to higher clinical pregnancy rates, though they are associated with a slightly increased risk of monozygotic twinning [5,6]. Regarding transfer protocols, FET occurs in the same cycle as egg retrieval, whereas TEC involves freezing embryos for future transfer during either a natural menstrual cycle or a hormonally regulated (programmed) cycle. Studies suggest that TEC can lead to comparable, if not superior, pregnancy and live birth rates compared with fresh transfers, due to better endometrial receptivity in TEC cycles [5,6]. Additionally, TEC is linked with a lower risk of ovarian hyperstimulation syndrome (OHSS), a common complication associated with ovarian stimulation during fresh cycles [6]. The success rates of TEC protocols may vary depending on the type of cycle. Natural freeze–thaw cycles tend to yield higher pregnancy rates due to more physiologically conducive uterine conditions that closely mimic natural implantation windows. Programmed freeze–thaw cycles, which allow for precise control over the timing, might show slightly lower success rates due to reduced endometrial receptivity [5,6].

IVF represents a significant medical and technological advancement; however, this often leads patients to develop high expectations regarding its efficacy, with the implicit assumption that their fertility issues will be resolved [8]. Despite technological advances and improvements in IVF, comprehensive psychological assessment remains crucial to ensure that patients receive full care and support throughout the process [9]. These expectations are frequently influenced by social and cultural factors, and, when not met, they become significant stressors for the couple. Many couples have turned having a child into a life goal necessary for completing the life cycle and fulfilling themselves as adults [8,9]. Consequently, infertility imposes an emotional burden on both the woman and her partner, not only due to the uncertainty but also because of repeated treatment cycles, possible failures, ambiguous diagnoses and high economic costs. In the clinical context of infertility, IVF and embryo transfer are associated with elevated stress levels, particularly when natural methods or other fertility treatments fail to achieve a desired pregnancy [1]. It is important to implement stress-coping strategies and targeted psychotherapy to better manage stress and anxiety, potentially increasing pregnancy rates [9].

There are many non-pharmacological alternatives for stress management, pain reduction and anxiety relief in IVF, such as breathing exercises, yoga, music therapy, massage, spiritual practices and aromatherapy. Laughter therapy, in particular, can be used for both preventive and therapeutic purposes [10]. Through humorous and individualized interventions that increase the frequency of laughter, individuals can reduce symptoms of depression and anxiety, directly improving their mood and mental health in response to stressful events [11]. Laughter therapy also has the potential to positively alter perceptions of the hospital environment [10]. Current evidence demonstrates that spontaneous laughter is associated with a greater reduction in cortisol levels compared with usual activities, suggesting that laughter could serve as an adjunctive medical therapy to improve well-being [12].

This review sought to answer the following research question: What is the effectiveness of laughter therapy in women undergoing in vitro fertilization? The primary aim was to analyze the effectiveness of laughter therapy in increasing pregnancy rates in women undergoing IVF, while the secondary aims were to identify the types of laughter therapy interventions and evaluate their benefits.

2. Materials and Methods

Design: A comprehensive review was carried out following the methodology outlined by the Joanna Briggs Institute (JBI) [13]. The decision to utilize the JBI methodology was informed by its broader and more inclusive framework, which facilitates the assessment of quality essential for generating comprehensive insights. The findings are presented in line with the criteria of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [14].

Since this systematic review aimed to assess the effectiveness of an intervention, the research question was formulated using the Population, Intervention, Comparison and Outcomes (PICO) framework [15], where the P was infertile women, I was laughter therapy, C was other traditional or non-pharmacological therapies, and O was pregnancy rate, depression and anxiety. The review protocol was registered with the international prospective register of systematic reviews (PROSPERO) under the registration number CRD42024573428.

Sources of information: The initial step involved locating prior publications on the topic of interest by conducting searches in the PROSPERO and Google Scholar® databases to address the research question. Following this preliminary assessment, comprehensive searches were carried out in the databases Medline (PubMed), SCI Expanded (Web of Science (WOS)), Scopus (Scopus-Elsevier), Cihahl (EbscoHOST), ProQuest and Lilacs (Virtual Health Library).

Search strategies: Searches were conducted between March and July 2024 using the MeSH terms: “laughter therapy”, “laughter”, “fertilization” and “in vitro fertilization” and the entry terms, using the Boolean operators AND/OR. Methodological filters were applied as needed. Specifically, the search in Scopus employed search field limits focused on the TITLE-ABS-KEY (title–abstract–keywords) fields, while the search in WOS utilized the TS (topic) field. This approach was adopted to enhance the precision of the literature retrieval process, facilitating the identification of records that were pertinent to the specific research domain. Conversely, the TX (text) field was included in Cinahl to facilitate searches across the entire article. The searches were conducted by one of the authors (D.R.-G.) and verified by a second one (C.-A.R.-S.) following the PRISMA-S extension for searching [16]. The final search strategy was adapted to each of the selected databases, as shown in Table 1.

Eligibility criteria: Included studies published in Spanish, English or Portuguese that investigated the use of laughter therapy within the context of IVF. Only experimental intervention studies were considered; randomized clinical trials (RCTs) and quasi-experimental studies (including pre–post designs with or without a control group) were included. No restrictions were placed on the year of publication. Studies were excluded if they focused on other traditional or non-pharmacological interventions, were review articles (narrative, scoping or systematic) or employed quantitative observational, analytical or descriptive de-

signs. Additionally, case studies, qualitative designs, non-research publications, protocols, studies conducted on animals and grey literature were also excluded.

Table 1. Search strategies in each of the databases.

Database and Date	Search Strategies
Medline (PubMed) 25 March 2024	((“Laughter”[MeSH]) OR (“laughter therapy”[MeSH] OR “therapy, laughter” OR “laughter yoga” OR “yoga, laughter”)) AND ((“fertilization in vitro”[MeSH] OR “in vitro fertilization” OR “in vitro fertilizations” OR “test-tube fertilization” OR “fertilization, test-tube” OR “fertilizations, test-tube” OR “test tube fertilization” OR “test-tube fertilizations” OR “fertilizations in vitro” OR “test-tube babies” OR “babies, test-tube” OR “baby, test-tube” OR “test tube babies” OR “test-tube baby”) OR (“fertilization”[MeSH] OR “fertilizations” OR “fertilization, delayed” OR “delayed fertilization” OR “delayed fertilizations” OR “fertilizations, delayed” OR “fertilization, polyspermic” OR “fertilizations, polyspermic” OR “polyspermic fertilization” OR “polyspermic fertilizations” OR “conception” OR “conceptions”))
SCI Expanded (Web of Science) 25 March 2024	TS = (“laughter” OR “laughter therapy”) AND TS = (“fertilization in vitro” OR “fertilization” OR “conception”)
Scopus (Scopus-Elsevier) 25 March 2024	TITLE-ABS-KEY (“laughter”) OR TITLE-ABS-KEY (“laughter therapy”) OR TITLE-ABS-KEY (“yoga, laughter”) AND TITLE-ABS-KEY (“fertilization in vitro”) OR TITLE-ABS-KEY (“fertilization”) OR TITLE-ABS-KEY (“conception”)
Cinahl 5 July 2024	TX (“Laughter” OR “Laughter Therapy”) AND TX (“fertilization in vitro” OR “fertilization” OR “conception”)
ProQuest 5 July 2024	“In vitro fertilization” and “laughter therapy”
Lilacs (Virtual Health Library) 25 March 2024	(“In vitro fertilization” OR “fertilization”) and (“laughter therapy” or “laughter”)

Screening process: Following the searches, duplicate records were removed, and the remaining records were screened on the basis of their titles and abstracts. Full-text articles of the selected records were then retrieved to evaluate their eligibility according to the inclusion and exclusion criteria. Screening was carried out through a peer review process (C.-A.R.-S. and D.R.-G.) and, in the case of discrepancies, a third author decided (H.G.-d.l.T.). The quality of the studies was evaluated using the suitable JBI critical appraisal tools for each research design. A score of more than 50% on the items included in each tool was considered indicative of good quality (for RCTs with 13 items, a score of $\geq$7 was deemed indicative of good quality, while for quasi-experimental studies with 9 items, a score of $\geq$5 was considered to reflect good quality). A pilot phase was conducted with a sample of records to verify the suitability of the process.

Definition of the study variables: The primary research outcome was pregnancy rates, while the secondary outcomes were symptoms of depression and anxiety. However, data on depression and anxiety symptoms were extracted from all studies, irrespective of their designation as primary or secondary outcomes. Furthermore, additional outcomes reported in the studies, whether primary or secondary, were also extracted, even if they were not initially included in the review.

Data extraction: Bibliometric variables related to the affiliations of the studies, along with variables concerning the statistical scores, were extracted. Additionally, the following information was collected: country and year of publication, design of the study, main and additional outcomes, instruments used to measure the effectiveness of laughter therapy, characteristics of the interventions (including type, setting and session duration) and details about the study population. For continuous quantitative variables, statistical data such as mean scores and standard deviations were extracted, whereas percentages and frequencies were extracted for qualitative variables. The *p*-values were also extracted to test the hypothesis contrasts, along with effect sizes when available. Data extraction was carried out individually by two authors (C.-A.R.-S. and D.R.-G.), with discrepancies resolved by a third one (H.G.-d.l.T.). The Mendeley® reference manager (version 2.121.0) was used for data management. An initial phase for the extraction process was conducted using a sample of articles.

3. Results

In total, n = 466 records were identified. After removing duplicates (n = 108) and grey literature (n = 119), n = 239 records were screened by title and abstract. Of these, n = 228 were excluded for not meeting the inclusion criteria, while n = 11 were retrieved for full-text evaluation. After the critical appraisal process, n = 3 studies were included in the review, as shown in the flow diagram in Figure 1.

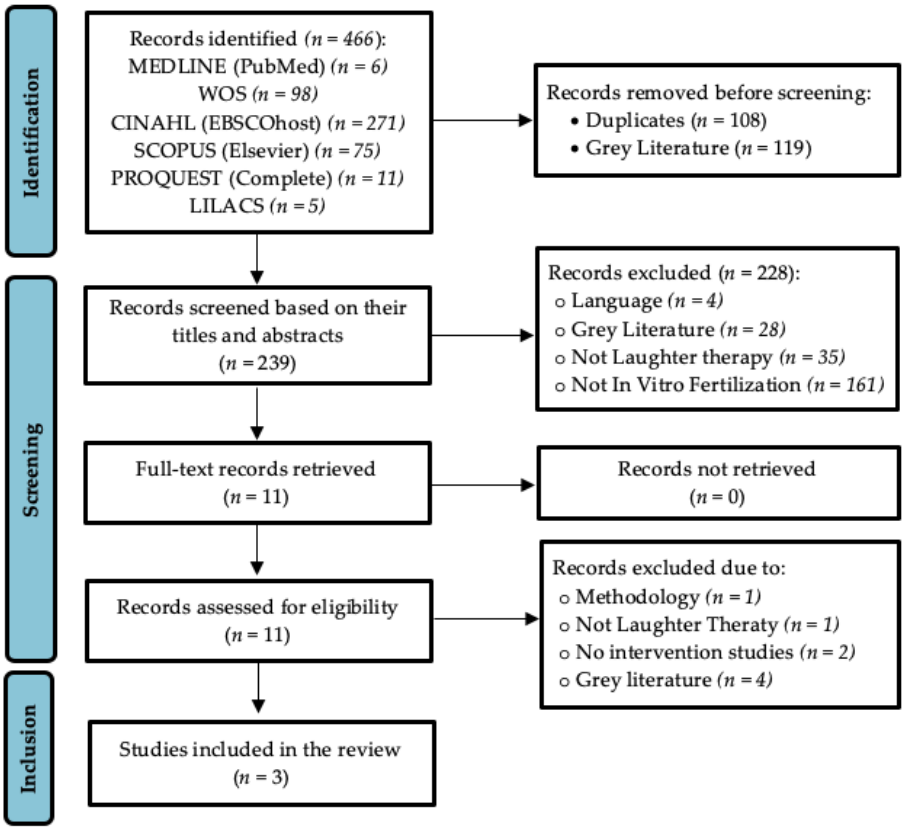

Figure 1. PRISMA flow diagram (Source: ref. [14]).

In the full-text critical appraisal process, n = 1 studies were excluded for the methodology, n = 3 for the inclusion criteria, and n = 4 for grey literature (Supplementary Table S1). The critical appraisal process of the included studies is shown as Supplementary Table S2.

Regarding the design of the studies, an RCT (n = 1) and quasi-experimental studies (n = 2) were included. Table 2 shows an overview of the general characteristics of each study, including the authors, years of publication, countries, study designs, clinical settings, aims, outcomes and conclusions.

Clinical information regarding the study population and sample, instruments used, interventions and the main statistical and clinical results were extracted. Results related to depression were measured using the Beck Depression Inventory (BDI) [17] and those of anxiety used the State Trait Anxiety Inventory (STAI) [17,18], alongside pregnancy rates [17,19]. Additionally, results on the subjective perception of anxiety were reported [18]. The laughter therapy interventions included hand clapping, breathing exercises, childlike playfulness, drinking milk, muscle relaxation exercises, candles and music [17], a clown (involving jokes and magic tricks) and a film showing the clown performing the same routine [18], and a medical clown performing magic tricks and interpretating comic situations [19], as shown in Table 3.

Table 2. General characteristics of the included studies.

Author (Year), Country	Design Clinical Setting	Study Aims, Main/Additional Outcomes	Conclusions
Kiyak and Kocoglu (2021), Turkey [17]	RCT [1]. Private IVF [2] center.	To examine the effect of progressive muscle relaxation exercises and laughter therapy on the mental health and treatment outcomes of women undergoing IVF. Outcomes: pregnancy, depression, and anxiety.	Women undergoing IVF treatment who received progressive muscle relaxation and laughter therapy demonstrated psychological changes; however, the treatment did not affect medical outcomes.
Friedler et al. (2017), Israel [18]	Quasi-experimental. IVF unit of a medical center.	To compare the evaluation of exposure to medical clown interventions versus humorous film interventions in women undergoing IVF and embryo transfer. Outcome: anxiety.	Physiological and emotional responses were more favorable in the medical clown interventions than in the humorous films.
Friedler et al. (2011), Israel [19]	Quasi-experimental IVF unit of a medical center.	To evaluate the impact of medical clown interventions on pregnancy rates in women undergoing IVF and embryo transfer. Outcome: pregnancy.	Women who received a visit from the medical clown had higher pregnancy rates than control group women.

[1] RCT, randomized clinical trial; [2] IVF, in vitro fertilization.

Table 3. Interventions and results of the included studies.

Author (Year), Design	Population and Sample	Instruments	Interventions	Statistical and Clinical Results
Kiyak and Kocoglu (2021), RCT [1] [17]	*N* = 141 IG [2] = 71 CG [3] = 70 Women with primary or secondary infertility	Beck Depression Inventory (BDI): 21 items measuring symptoms of depression. Items scores between 0 (absence of symptoms) and 3 (severity of symptoms) points. State–Trait Anxiety Inventory (STAI): 20-item scale to measure the presence of anxiety symptoms, scores between 20–80. <40: Asymptomatic or minimal symptoms. >40: Moderate or severe symptoms.	Total 40 min; 3–4 sessions/week. First: Laughter therapy 15–20 min in 4 sections: 1. Hand clapping and warm-up exercise (clap hands keeping the hands parallel to each other. The touch of fingers and palms stimulates the acupressure points and increases the energy level. Hands clap in a 1-2, 1-2-3 rhythm, and the song Ho-Ho, Ha-Ha-Ha is sung with the clapping gesture. This is repeated three times). 2. Deep breathing exercises. 3. Childlike playfulness (singing and dancing between laughter and breathing exercises to instill childlike playfulness in the mind). 4. Laughter exercise (at the leader's instruction, they say "Hmmm. . ." and pour the milk from one glass to the other and pour it back into the other glass, say "Hmmm. . .", and then everyone laughs and pretends to drink milk. This exercise is repeated four times). Second: Muscle relaxation exercises 15–20 min accompanied by candles and music.	BDI (depression): Before: IG: Mean = 12.31 (*SD* [4] = 7.61) CG: Mean = 11.50 (*SD* = 8.75) *t*-Test: 0.585 (*p*-value: 0.559) After: IG: Mean = 8.44 (*SD* = 6.43) CG: Mean = 11.57 (*SD* = 8.57) *t*-Test: −2.446 (*p*-value: 0.016) Cohen's *d*: 0.35 95% *CI* (0.018, 0.68) STAI (anxiety): State anxiety (temporary): Before: IG: Mean = 43.75 (*SD* = 5.84) CG: Mean = 43.11 (*SD* = 5.67) *t*-Test: 0.651 (*p*-value: 0.516) After: IG: Mean = 43.34 (*SD* = 5.37) CG: Mean = 41.96 (*SD* = 4.76) *t*-Test: 1.613 (*p*-value: 0.109) Cohen's *d*: 0.09 95% *CI* (−0.23, 0.642) Trait anxiety (longstanding): Before: IG: Mean = 46.73 (*SD* = 6.22) CG: Mean = 47.71 (*SD* = 5.07) *t*-Test: −1.021 (*p*-value: 0.309) After: IG: Mean = 45.63 (*SD* = 5.05) CG: Mean = 47.93 (*SD* = 4.91) *t*-Test: −2.732 (*p*-value: 0.007) Cohen's *d*: 0.173 95% CI (0.504, 0.156) Pregnancy rates: Negative: IG (*n* = 21): 39.6% CG (*n* = 24): 54.5% Positive: IG (*n* = 32): 60.4% CG (*n* = 20): 45.5% χ^2 = 2.153 (*p*-value: 0.142) Cohen's *d*: 0.149

Table 3. *Cont.*

Author (Year), Design	Population and Sample	Instruments	Interventions	Statistical and Clinical Results
Friedler et al. (2017), Quasi-experimental [18]	*N* = 295 IG (clown) = 101 IG (film) = 99 CG = 95	STAI (anxiety): 20-item scale to measure the presence of anxiety symptoms, scores between 20–80. <40: Asymptomatic or minimal symptoms. >40: Moderate or severe symptoms. Subjective evaluation questionnaire: Four items response on a Likert scale: 1 (not at all); 10 (very much): 1. Reduced my anxiety level? 2. Bothered me? 3. Helped to distract me? 4. Made the time more pleasant? 5. Would it be a good idea to include the clown/movie as part of the fertility treatment? (response options: "yes", "no").	IG (clown): Jokes and magic tricks in an interactive way. IG (film): A 10 min film played showing the clown performing the same routine as used for the clown IG. Both treatments were performed in the recovery room after the embryo transfer for 10 min.	STAI (anxiety): Before: IG (clown): Mean = 44 (*SD* = 45.8) IG (film): Mean = 50 (*SD* = 51.5) CG: Not reported *p*-value: 0.43 After: Not measured. Subjective evaluation questionnaire: Responses to the question: 1. Reduced my anxiety level? IG (clown): Mean = 10 (IQR [5]: 6, 10) IG (film): Mean = 8 (IQR: 4, 9) *p*-value: 0.01 (Wilcoxon test) 2. Bothered me? IG (clown): Mean = 1 (IQR: 1, 1) IG (film): Mean = 1 (IQR: 1, 1) *p*-value: 0.08 (Wilcoxon test) 3. Helped to distract me? IG (clown): Mean = 10 (IQR: 8, 10) IG (film): Mean = 9 (IQR: 6, 10) *p*-value: 0.04 (Wilcoxon test) 4. Made the time more pleasant? IG (clown): Mean = 10 (IQR: 8, 10) IG (film): Mean = 10 (IQR: 7, 10) *p*-value: 0.07 (Wilcoxon test) 5. Would it be a good idea to include the clown/movie as part of the fertility treatment? Yes responses: Clown, *n* = 67 Film, *n* = 62 *p*-value: 0.35
Friedler et al. (2011), Quasi-experimental [19]	*N* = 219 IG = 110 CG = 109	Serum hCG [6] measurement.	Medical clown after the embryo transfer session. A routine based on magic tricks and interpretation of comic situations was performed (12–15 min)	Pregnancy rates: IG (*n* = 40, 36.4%) CG (*n* = 22, 20.2%) *p*-value: 0.008 OR = 2.67 (95% CI: 1.36, 5.24) *p*-value: 0.004

[1] RCT, randomized clinical trial; [2] IG, intervention group; [3] CG, control group; [4] SD, standard deviation; [5] IQR, interquartile range; [6] hCG, human chorionic gonadotropin.

4. Discussion

The use of non-pharmacological therapies in the context of IVF has been minimally studied; however, beneficial therapeutic effects have been reported with other interventions in the field of obstetrics and gynecology, such as hysteroscopy [20], breast biopsy [21] and colposcopy [22]. In this regard, the screening process revealed that the majority of available publications have focused on fertility techniques other than IVF (*n* = 161). Furthermore, several studies exploring alternative therapies include interventions beyond laughter therapy (*n* = 36). In contrast, studies specifically examining laughter therapy in IVF are very limited, consisting of only one RCT and two quasi-experimental studies, all conducted in Turkey and Israel between 2011 and 2021. These studies demonstrated some methodological limitations and issues with outcome reporting. In this context, although they did not focus on laughter therapy, studies with qualitative designs are also scarce [8,23]. Moreover, no observational studies on laughter therapy in the clinical setting of IVF have been identified.

This review aimed to evaluate the effectiveness of laughter therapy in patients undergoing IVF, particularly in relation to increasing the pregnancy rates, and to identify its impact on symptoms of depression and anxiety. IVF can lead to adverse symptoms in women, including anxiety, depression and perceived stress, which can disrupt immune homeostasis at the mother–fetus interface. This disruption affects blastula hatching, maternal endometrial receptivity and the psycho-neuro-immuno-endocrine network, ulti-

mately influencing the proliferation, invasion and vascular remodeling of the embryonic trophoblast and reducing the success rate of embryo transfer [24]. According to Zhou et al., this situation exacerbates psychological distress, creating a vicious cycle. The use of cognitive-behavioral therapies, acupuncture, yoga and other psychological interventions before and after IVF has been shown to interrupt this cycle, improve pregnancy rates and reduce anxiety and depression [24].

Specifically, in the context of other non-pharmacological therapies, Mahmoud et al. [25] studied the effectiveness of music therapy in relation to assisted reproductive technologies. They found that music therapy significantly reduced anxiety scores compared with the CG (I^2 = 50%, *MD* = −3.09, 95% CI [−5.57, −0.61], p = 0.01). In this regard, Hullender Rubin et al. [26] also reported significant effects of acupuncture on state anxiety (I^2 = 68%, *SMD* = −0.21, 95% CI [−0.39, −0.04], p = 0.01). However, related to the clinical pregnancy rates, Hullender Rubin et al. [26] showed that the music therapy group experienced an increase compared with the CG, although the result was not statistically significant (I^2 = 0%, RR = 1.08, 95% CI [0.94, 1.26], p = 0.28). Similarly, Wang et al. [27] found significant effects on pregnancy rates (I^2 = 66%, RR = 1.31, 95% CI [1.13, 1.52], p = 0.0004), while Yang et al. [28] observed a lesser effect (I^2 = 26.3%, RR = 1.42, 95% CI [1.31, 1.54], p = 0.142).

In the context of laughter therapy interventions, in relation to depression, only Kiyak and Kocoglu [17] assessed these symptoms using the BDI following sessions with hand clapping, breath exercises, childlike playfulness, drinking milk, muscle relaxation exercise, and candles and music, with a significant decrease in the intervention group (IG) symptoms (p = 0.016) with a medium effect size (Cohen's d: 0.35) according to Rendón-Macías [29]. Also in the clinical field of gynecology, but in pregnant women before delivery, Zhu et al. [30] compared different non-pharmacological therapies (music, massage, yoga and exercise), among which laughter therapy was not included, to assess depressive symptoms, obtaining low-quality evidence with very heterogeneous studies, indicating that all of them had protective effects, although music therapy might be the most effective intervention (I^2 = 92%, SMD = −1. 63, 95% CI [−2.28, −0.77], p = 0.0002). Regarding the instruments used to assess depressive symptoms, according to Coutiño-Escamilla et al. [31], the most commonly used test to measure depressive symptoms in women affected by breast cancer and to evaluate the use of non-pharmacological therapies are the Center for Epidemiologic Studies—Depression Scale (CES-D), followed by Hospital Anxiety and Depression (HADS) and Profile of Mood States (POMS), while the least used one was BDI.

Regarding anxiety, the studies conducted by Kiyak and Kocoglu [17] and Friedler et al. [18] used the STAI. Likewise, in the international context, the scale most used to measure preoperative anxiety is the STAI, which was used by 28.19% [32]. Kiyak and Kocoglu [17] reported significative post-intervention changes using hand clapping, breath exercises, childlike playfulness, drinking milk, muscle relaxation exercises, and candles and music for longstanding trait anxiety (p = 0.007), although with small effect sizes (Cohen's d: 0.173) [27]. In contrast, temporary state anxiety (p = 0.109, Cohen's d: 0.09) was not significative. Friedler et al. [18] reported no post-intervention measures of anxiety for either the IG (clown and a film clown) or CG.

The pregnancy rate reported by Kiyak and Kocoglu [17] indicated a higher percentage of participants in the IG (60.4%) with a positive pregnancy outcome compared with the CG (45.5%). However, the effect size was very small (Cohen's d = 0.149) and not statistically significant (p = 0.142). In other words, the observed difference in pregnancy rates between the groups could be due to chance, indicating that the impact of the laughter therapy intervention on pregnancy outcomes is minimal. Meanwhile, Friedler et al. [19] reported a pregnancy rate of 36.4% in the IG, which was significantly higher than the 20.2% observed in the CG. The difference between the IG and CG was statistically significant (p = 0.008), suggesting that the intervention had a meaningful effect on pregnancy rates. The intervention demonstrated at least a moderate positive effect, with the odds of achieving pregnancy being 2.67 times higher in the IG compared with the CG (OR: 2.67; 95% CI [1.36, 5.24]; p = 0.004). These findings suggest that laughter therapy had a significant and positive

impact on pregnancy rates. Overall, the study by Friedler et al. [19] did not evaluate depression and anxiety, which prevents any association of these factors with pregnancy rates. Conversely, the findings from Kiyak and Kocoglu [17] suggest that the intervention was particularly effective in reducing depression and, to a lesser extent, trait anxiety. However, it was considered to have little to no impact on state anxiety or pregnancy rates.

Regarding additional outcomes reported by Friedler et al. [18], an ad hoc questionnaire was used to assess the participants' subjective opinions. The results were not statistically relevant but indicated a favorable perception among women towards the use and implementation of clowns and clown films, with preferences for in-person clown interventions during IVF procedures. In a related study, Agüero-Millán et al. [33] compared various interventions and found significative differences ($\chi^2 = 118.37$, $p = 0.000$). They observed that virtual reality and clowns are more commonly used with children, while massage, music and videos are more frequently used with adults.

The main limitation of this systematic review is the heterogeneity observed in the interventions, methodologies and results, which has hampered the ability to compare and synthesize the findings effectively. When interventions, methodologies and outcomes exhibit substantial variability across studies, direct comparisons or aggregations of the results through meta-analysis become challenging. Heterogeneity can stem from variations in the study designs, participant demographics, intervention protocols, outcome measurements and statistical methodologies. This lack of uniformity undermines the capacity to derive clear and generalizable conclusions, as statistical techniques, particularly meta-analyses, depend on the comparability of datasets to accurately assess the overall effects. Consequently, high levels of heterogeneity can lead to inconsistent findings and hinder the interpretation of results [34]. Additionally, the lack of statistical results in some studies has hampered the meta-analysis of the outcomes. Further limitations include the exclusion of articles published in languages other than Spanish, English or Portuguese, which may have led to the omission of relevant research findings. Moreover, the scarcity of international studies on laughter therapy in IVF settings is a constraint, given the potential influence of social and cultural factors on responses to humor. Cultural differences in humor could influence the results of studies involving humor-based laughter therapy, which could affect individuals' responses. For example, some cultures may prefer slapstick or physical comedy, while others might lean toward wordplay or sarcasm. Moreover, in cultures where laughter holds a significant cultural value, humor-based therapies may exhibit enhanced effectiveness. Conversely, in societies with more conservative views toward humor or where emotional expression is socially constrained, the effectiveness of such interventions may be reduced or display greater variability [34]. Cultural differences in humor can play a critical role in the effectiveness of laughter-based interventions. Researchers must account for these differences when designing studies and interpreting results, ensuring that the humor used in interventions is culturally appropriate and resonant with the participants, considering how the cultural context may affect emotional and physiological responses to humor [12,34].

Despite these limitations, a notable strength of this review is that all the selected studies are either experimental or quasi-experimental with a CG. This design allows for the evaluation of pre–post-intervention quantitative results on pregnancy rates, depression and anxiety for both the experimental group and CG.

5. Conclusions

This review does not provide clear evidence regarding the effect of laughter therapy on increasing pregnancy success rates in IVF. However, it suggests that laughter therapy may have some positive effects in reducing symptoms of depression and anxiety in patients undergoing IVF treatment. It is important to note that while the reduction in these symptoms may enhance the emotional well-being of patients, it has not been demonstrated to directly lead to an increase in pregnancy rates. The available studies are insufficient to thoroughly evaluate this non-pharmacological therapy in the IVF clinical setting, as

they are few in number and heterogeneous, limited to interventions involving relaxation exercises, games, magic tricks and clowns.

Laughter therapy is an innovative, non-pharmacological intervention that is simple, non-invasive, easy to implement and cost-effective. However, further research is needed to provide higher-quality evidence through rigorous study designs to evaluate its efficacy in IVF clinical practice. Future studies should focus on areas such as larger sample sizes, standardized outcome measures, cultural differences and long-term effects, particularly concerning its impact on increasing pregnancy rates and improving the symptoms of depression and anxiety associated with ART.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/reprodmed5040022/s1. Table S1: Excluded studies. Table S2: Critical appraisal of the included studies.

Author Contributions: Conceptualization, D.R.-G. and C.-A.R.-S.; methodology, D.R.-G., C.-A.R.-S. and H.G.-d.l.T.; validation, D.R.-G., C.-A.R.-S. and H.G.-d.l.T.; investigation, D.R.-G.; resources, C.-A.R.-S. and H.G.-d.l.T.; data curation, D.R.-G., C.-A.R.-S. and H.G.-d.l.T.; writing—original draft preparation, D.R.-G.; writing—review and editing, D.R.-G., C.-A.R.-S. and H.G.-d.l.T.; supervision, C.-A.R.-S. and H.G.-d.l.T.; project administration, D.R.-G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Vander Borght, M.; Wyns, C. Fertility and Infertility: Definition and Epidemiology. *Clin. Biochem.* **2018**, *62*, 2–10. [CrossRef] [PubMed]
2. Carson, S.A.; Kallen, A.N. Diagnosis and Management of Infertility: A Review. *JAMA* **2021**, *326*, 65–76. [CrossRef]
3. Penzias, A.; Bendikson, K.; Butts, S.; Coutifaris, C.; Fossum, G.; Falcone, T.; Gitlin, S.; Gracia, C.; Hansen, K.; La Barbera, A.; et al. Guidance on the Limits to the Number of Embryos to Transfer: A Committee Opinion. *Fertil. Steril.* **2017**, *107*, 901–903. [CrossRef]
4. Rodríguez Martínez, K.; Méndez Vidal, J. Clinical and Therapeutic Factors Influencing the Achievement of Pregnancy among Patients Undergoing In Vitro Fertilization. *Rev. Cubana Endocrinol.* **2015**, *26*, 108–123. Available online: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1561-29532015000200002 (accessed on 1 August 2024).
5. Tocariu, R.; Niculae, L.E.; Niculae, A.Ș.; Carp-Velișcu, A.; Brătilă, E. Fresh versus Frozen Embryo Transfer in In Vitro Fertilization/Intracytoplasmic Sperm Injection Cycles: A Systematic Review and Meta-Analysis of Neonatal Outcomes. *Medicina* **2024**, *60*, 1373. [CrossRef] [PubMed]
6. Bergenheim, S.J.; Saupstad, M.; Pistoljevic, N.; Andersen, A.N.; Forman, J.L.; Løssl, K.; Pinborg, A. Immediate versus postponed frozen embryo transfer after IVF/ICSI: A systematic review and meta-analysis. *Hum. Reprod. Update* **2021**, *27*, 623–642. [CrossRef] [PubMed]
7. Van Voorhis, B.J. Clinical practice. In vitro fertilization. *N. Engl. J. Med.* **2007**, *356*, 379–386. [CrossRef]
8. Glover, L.; McLellan, A.; Weaver, S.M. What does having a fertility problem mean to couples? *J. Reprod. Infant. Psychol.* **2009**, *27*, 401–418. [CrossRef]
9. Veiga, M.C.; Puccio, M.C.; Tamburelli, V. ¿Qué relación existe entre estrés, ansiedad e infertilidad? *Reproducción* **2013**, *28*, 79–89. Available online: https://www.samer.org.ar/revista/numeros/2013/vol_3/revision.pdf (accessed on 1 August 2024).
10. Sun, X.; Zhang, J.; Wang, Y.; Zhang, X.; Li, S.; Qu, Z.; Zhang, H. The impact of humor therapy on people suffering from depression or anxiety: An integrative literature review. *Brain Behav.* **2023**, *13*, e3108. [CrossRef]
11. Akimbekov, N.S.; Razzaque, M.S. Laughter therapy: A humor-induced hormonal intervention to reduce stress and anxiety. *Curr. Res. Physiol.* **2021**, *4*, 135. [CrossRef] [PubMed]
12. Kramer, C.K.; Leitao, C.B. Laughter as medicine: A systematic review and meta-analysis of interventional studies evaluating the impact of spontaneous laughter on cortisol levels. *PLoS ONE* **2023**, *18*, e0286260. [CrossRef] [PubMed]
13. Aromataris, E.; Munn, Z. (Eds.) *JBI Manual for Evidence Synthesis*; JBI: Adelaide, Australia, 2020. Available online: https://synthesismanual.jbi.global (accessed on 1 August 2024).

14. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, 71. [CrossRef] [PubMed]
15. Munn, Z.; Stern, C.; Aromataris, E.; Lockwood, C.; Jordan, Z. What kind of systematic review should I conduct? A proposed typology and guidance for systematic reviewers in the medical and health sciences. *BMC Med. Res. Methodol.* **2018**, *18*, 5. [CrossRef]
16. Rethlefsen, M.L.; Kirtley, S.; Waffenschmidt, S.; Ayala, A.P.; Moher, D.; Page, M.J.; Koffel, J.B. PRISMA-S Group. PRISMA-S: An extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. *Syst. Rev.* **2021**, *10*, 39. [CrossRef]
17. Kiyak, S.; Kocoglu-Tanyer, D. Effectiveness of progressive muscle relaxation and laughter therapy on mental health and treatment outcomes in women undergoing in vitro fertilization: A randomized controlled trial. *Res. Nurs. Health* **2021**, *44*, 945–956. [CrossRef]
18. Friedler, S.; Glasser, S.; Levitan, G.; Hadar, D.; Sasi, B.E.; Lerner-Geva, L. Patients' Evaluation of Intervention by a Medical Clown Visit or by Viewing a Humorous Film Following In Vitro Fertilization and Embryo Transfer. *J. Evid. Based Complement. Altern. Med.* **2017**, *22*, 47–53. [CrossRef]
19. Friedler, S.; Glasser, S.; Azani, L.; Freedman, L.S.; Raziel, A.; Strassburger, D.; Ron-El, R.; Lerner-Geva, L. The effect of medical clowning on pregnancy rates after in vitro fertilization and embryo transfer. *Fertil. Steril.* **2011**, *95*, 2127–2130. [CrossRef]
20. Abd-ElGawad, M.; Abdelsattar, N.K.; Kamel, M.A.; Sabri, Y.A.; Fathy, E.M.; El-Moez, N.A.; Abdellatif, Y.S.; Metwally, A.A. The effect of music intervention in decreasing pain and anxiety during outpatient hysteroscopy procedure: A systematic review and meta-analysis of randomized control trials. *BMC Women's Health* **2023**, *23*, 360. [CrossRef] [PubMed]
21. Ashour, A.S.A.; Abd-ElGawad, M.; Yohanna, M.; El-Nagar, M.; Fadl, A.N.; Goda, G.M.; Ouerdane, Y.; Saad, H.; Fouad, M.; El-Nassery, N.; et al. Is music intervention effective in reducing anxiety and pain during breast biopsy procedure? A systematic review and meta-analysis of randomized controlled trials. *Support. Care Cancer* **2022**, *30*, 10379–10389. [CrossRef]
22. Abdelhakim, A.M.; Samy, A.; Abbas, A.M. Effect of music in reducing patient anxiety during colposcopy: A systematic review and meta-analysis of randomized controlled trials. *J. Gynecol. Obstet. Hum. Reprod.* **2019**, *48*, 855–861. [CrossRef] [PubMed]
23. Marston, C.; Renedo, A.; Nyaaba, G.N.; Machiyama, K.; Tapsoba, P.; Cleland, J. Improving the Measurement of Fertility Regulation Practices: Findings from Qualitative Research in Ghana. *Int. Perspect. Sex. Reprod. Health* **2017**, *43*, 111–119. [CrossRef] [PubMed]
24. Zhou, Y.; Sun, Z.; Song, J. Research progress on the impact of anxiety and depression on embryo transfer outcomes of in vitro fertilization. *J. Zhejiang Univ. Med. Sci.* **2023**, *52*, 61–67. [CrossRef] [PubMed]
25. Mahmoud, M.Y.; Labib, K.; Sileem, S.A.; Mustafa, F.A.; Hamed, W.M.; Abd Elhamid, A.; Saleh, D.M.; Alanwar, A.; Riad, A.A.; Abdelhakim, A.M.; et al. The impact of music therapy on anxiety and pregnancy rate among infertile women undergoing assisted reproductive technologies: A systematic review and meta-analysis. *J. Psychosom. Obstet. Gynaecol.* **2022**, *43*, 205–213. [CrossRef]
26. Hullender Rubin, L.E.; Smith, C.A.; Schnyer, R.N.; Tahir, P.; Pasch, L.A. Effect of acupuncture on IVF-related anxiety: A systematic review and meta-analysis. *Reprod. Biomed. Online* **2022**, *45*, 69–80. [CrossRef]
27. Wang, X.; Wang, Y.; Wei, S.; He, B.; Cao, Y.; Zhang, N.; Li, M. An Overview of Systematic Reviews of Acupuncture for Infertile Women Undergoing in vitro Fertilization and Embryo Transfer. *Front. Public Health* **2021**, *9*, 651811. [CrossRef] [PubMed]
28. Yang, H.; Hu, W.H.; Xu, G.X.; Yin, Z.H.; Yu, S.Y.; Liu, J.J.; Xiao, Z.Y.; Zheng, X.Y.; Yang, J.; Liang, F.R. Transcutaneous electrical acupoint stimulation for pregnancy outcomes in women undergoing in vitro fertilization-embryo transfer: A systematic review and meta-analysis. *Front. Public Health* **2022**, *10*, 892973. [CrossRef]
29. Rendón-Macías, M.E.; Zarco-Villavicencio, I.S.; Villasís-Keever, M.A. Métodos estadísticos para el análisis del tamaño del efecto. *Rev. Alerg. Méx.* **2021**, *68*, 128–136. [CrossRef]
30. Zhu, Y.; Wang, R.; Tang, X.; Li, Q.; Xu, G.; Zhang, A. The effect of music, massage, yoga and exercise on antenatal depression: A meta-analysis. *J. Affect. Disord.* **2021**, *292*, 592–602. [CrossRef]
31. Coutiño-Escamilla, L.; Piña-Pozas, M.; Tobías Garces, A.; Gamboa-Loira, B.; López-Carrillo, L. Non-pharmacological therapies for depressive symptoms in breast cancer patients: Systematic review and meta-analysis of randomized clinical trials. *Breast* **2019**, *44*, 135–143. [CrossRef]
32. Tyler, B.; Walford, H.; Tamblyn, J.; Keay, S.D.; Mavrelos, D.; Yasmin, E.; Al Wattar, B.H. Interventions to optimize embryo transfer in women undergoing assisted conception: A comprehensive systematic review and meta-analyses. *Hum. Reprod. Update* **2022**, *28*, 480–500. [CrossRef] [PubMed]
33. Agüero-Millan, B.; Abajas-Bustillo, R.; Ortego-Maté, C. Efficacy of nonpharmacologic interventions in preoperative anxiety: A systematic review of systematic reviews. *J. Clin. Nurs.* **2023**, *32*, 6229–6242. [CrossRef] [PubMed]
34. Yue, X.; Jiang, F.; Lu, S.; Hiranandani, N. To Be or Not to Be Humorous? Cross-Cultural Perspectives on Humor. *Front. Psychol.* **2016**, *7*, 1495. [CrossRef] [PubMed]