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Emotional health and its impact on assisted reproductive technology outcomes: a systematic review and meta-analysis

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Emotional health and its impact on assisted reproductive technology outcomes: a systematic review and meta-analysis

Abstract

This systematic review and meta-analysis addresses ongoing controversy surrounding the association between pre-treatment anxiety, stress and depression and assisted reproductive technology (ART) outcomes. Medline, Embase and PsycINFO were searched up to November 2019. Eligible studies were observational studies reporting the association between pre-treatment anxiety, stress or depression and ART outcomes in men, women or couples undergoing ART. The association between pre-treatment anxiety, stress and depression and ART outcomes were extracted, and meta-analyses carried out if ≥3 studies assessed the same outcome over the same number of cycles and reported results homogenously. This review reports a potential association between decreased sperm motility with increased male state anxiety, and no significant association between women's pre-treatment emotional health and ART outcomes in terms of live birth, clinical pregnancy, chemical pregnancy, oocyte retrieval, embryos transferred or fertilization. Meta-analyses showed a standardised mean difference (SMD) of -0.08 (95% CI -0.20-0.04, I2 0%, n=6) for clinical pregnancy and anxiety/stress and -0.08 (95% CI -0.21-0.04, I2 0%, n=3) for clinical pregnancy and depression, and a SMD of -0.01 (95% CI -0.29-0.27, I2= 53%, n=5) for chemical pregnancy and anxiety/stress and 0.08 (95% CI -0.51-0.67 I2= 83%, n=3) for chemical pregnancy and depression.

Keywords: infertility; assisted reproductive technology; mental health; anxiety; depression

Introduction

Infertility is defined as lack of clinical pregnancy after 1 year of regular sexual intercourse (Zegers-Hochschild et al., 2009). Medical assistance for infertility is often in the form of assisted reproductive technology (ART), such as in vitro fertilization (IVF). Despite significant research, the direction of causality between emotional health and ART outcomes remains unclear; meta-analyses reporting a small, significant negative effect of anxiety, stress and depression on pregnancy rates (Matthiesen et al., 2011; Purewal et al., 2017) are balanced by those reporting no significant effect (Boivin et al., 2011; Nicoloro-SantaBarbara et al., 2018). Potential mechanisms for psychological stress-mediated disruption of fertility include glucocorticoid-mediated inhibition of gonadotropin-releasing hormone and reduced uterine receptivity (Palomba et al., 2018). Poor emotional health is also linked to unhealthy lifestyle choices (Strine et al., 2005) and psychotropic medication use. While it appears selective serotonin reuptake inhibitors do not reduce pregnancy chances in women, there is evidence of associated reduced sperm quality in men (Sylvester et al., 2019). Poor emotional health may also increase the likelihood of discontinuing treatment (Gameiro et al., 2012). Due to the importance of ART success for patients, this association must be investigated. Therefore, this systematic review aims to assess the impact of men, women and couple's pre-treatment emotional health on ART outcomes.

Materials and Methods

This review was prospectively registered on PROSPERO (CRD42020158395).

Defining Anxiety, Stress and Depression

Depression is defined as a symptom complex including low mood, activity and energy (*The ICD-10*, 1992). State anxiety is defined as transient psychological and physiological reactions to adverse events, and trait anxiety as individual differences in tendency to experience state anxiety (Martens, 1971). Stress is defined as feeling in danger due to a perceived threat in the environment (Martens, 1971). Emotional health will be used as a term to encompass these factors.

Eligibility Criteria

Original data on men, women or couples in ART treatment were included. ART was defined as extracorporeal handling of gametes or embryos to induce pregnancy. This includes IVF, intracytoplasmic sperm injection, zygote intrafallopian transfer and gamete intrafallopian transfer but excludes intrauterine insemination. Procedures involving donor materials were excluded to avoid confounding due to the mental state of the donor. Studies must have measured pre-treatment emotional health through validated psychometric scales. Pre-treatment measurement avoided confounding stress from hormonal treatment or feedback on progress. Studies must have reported primary or secondary outcomes (see data items). Clinical pregnancy was defined as ultrasound-confirmed pregnancy, and chemical pregnancy as pregnancy detected through human chorionic gonadotropin measurement. Interventional studies were excluded to avoid confounding effects of treatments. Reviews, animal studies and non-English language papers were excluded.

Information sources and search

Medline, Embase and PsycINFO were searched up to November 2019. See Table 1 for search strategy. Grey literature was searched through inclusion of conference abstracts and clinicaltrials.gov, with authors of relevant trials contacted. A reference search of previous reviews (Boivin et al., 2011; Matthiesen et al., 2011; Nicoloro-SantaBarbara et al., 2018; Purewal et al., 2017) was undertaken. If studies presented incomplete data, missing data was requested.

Study selection

The first author screened titles and abstracts, with subsequent screening of full text articles against eligibility criteria. The second author checked decisions with discrepancies resolved by a third reviewer.

Data collection and data items

Data extracted included study and population data (see Tables 2 and 3). Measures of association between emotional health and ART outcomes were extracted, such as odds ratios (ORs), risk ratios (RRs) and mean validated questionnaire scores of pregnant and nonpregnant groups. Primary outcomes were live birth, clinical pregnancy and chemical pregnancy, and secondary outcomes were oocytes harvested, embryos transferred, fertilization and sperm parameters.

Synthesis of results and summary measures

Data were combined in a meta-analysis if ≥3 studies reported the same exposure and outcome in a homogenous manner over the same number of cycles. Anxiety and stress were combined due to their similarity (Martens, 1971). Where state and trait anxiety were both reported, state anxiety was preferentially used. Meta-analyses were conducted using a random effects model

for generic inverse data to produce a standardised mean difference (SMD). The SMD is a measure of the mean difference between validated questionnaire scores of pregnant and non-pregnant groups. A random effects analysis was used due to substantial heterogeneity. Heterogeneity was assessed using I^2. Where I^2 was <60%, a control analysis with a fixed effects model was conducted, but no results differed significantly. Sensitivity analysis was performed if variation in Agency for Healthcare Research and Quality (AHRQ) standards was present. 'Poor' quality studies were excluded, and the meta-analysis repeated. Funnel plots were drawn to detect publication bias.

Risk of bias in individual studies

The Newcastle Ottawa Scale for Cohort Studies was used to assess quality, with adapted criteria for cross-sectional studies. Scores were converted to AHRQ standards of poor, fair and good (Table 4).

[Table 1 near here]

Results

Study selection

The literature search identified 4376 studies and reference searching identified 18 studies. Following duplicate removal, 3424 studies remained, with 290 remaining following title and abstract screening. The narrative and quantitative syntheses included 29 and 11 papers respectively (Figure 1).

[Figure 1 near here]

Study characteristics

In total there were 5750 patients (4961 women and 789 men). See Table 2 for study characteristics and Table 3 for sample characteristics.

Study results

Clinical pregnancy

Of the 12 studies (n=2538) considering stress/anxiety and clinical pregnancy, 8 found no significant association (Anderheim et al., 2005; Cesta et al., 2018; Maroufizadeh et al., 2019; Miller et al., 2019; Thiering et al., 1993; Turner et al., 2013; Visser et al., 1994), including the largest study(Lintsen et al., 2009). All studies were female-only. Eugster et al.(2004) found a trend towards significance only for state anxiety (p=0.06). In contrast, Sanders & Bruce(1999) found lower trait anxiety was associated with increased pregnancy chances. Sohrabvand et al.(2008) found mean undefined anxiety scores to be associated with pregnancy rate. Klonoff-Cohen et al.(2001) found acute positive affect, as a measure of state anxiety, to have a RR of 0.95 for no clinical pregnancy, with a confidence interval of 0.9-1.01(p=0.08). In our meta-analysis (Figure 2), 6 studies produced a SMD of -0.08 (95% CI -0.20-0.04, I^2 0%). Sensitivity analysis did not significantly change results and the funnel plot

did not implicate publication bias.

[Figure 2 near here]

Fewer studies (8, n=1894) considered depression and clinical pregnancy, and 5 found no significant difference (Anderheim et al., 2005; Klonoff-Cohen et al., 2001; Maroufizadeh et al., 2019; Visser et al., 1994), again including the largest study (Lintsen et al., 2009). All subjects were female. Sohrabvand et al.(2008) found significantly reduced pregnancy chances with increased depression scores. Thiering et al.(1993) reported that depressed women were less likely to achieve pregnancy over the first 5 cycles. However, Sanders and Bruce(1999) found higher depression scores to be significantly associated with pregnancy. Our meta-analysis (Figure 3) of 3 studies produced a SMD of -0.08 (95% CI -0.21-0.04, I^2 0%). Study quality was consistent, precluding sensitivity analysis, and funnel plotting showed no indication of bias.

[Figure 3 near here]

Chemical pregnancy

In total, 7 studies (n=1347) assessed stress/anxiety and chemical pregnancy. Most only considered women, but Merari et al.(2002) included men and Cooper et al.(2007) assessed couples independently and together. Of the studies which measured women's stress/anxiety and pregnancy, 4 found no significant association (An et al., 2013; Boivin & Takefman, 1995; Cooper et al., 2007; Merari et al., 2002). Smeenk et al. (2001) and Verhaak et al. (2001) found state anxiety only to be associated with likelihood of pregnancy. Kalaitzaki et al.(2020) found a non-significant difference in mean stress scores between pregnant and non-pregnant subjects yet found a significant effect on logistic regression (OR 0.73 95% CI 0.59-0.91). Both studies considering the male partner alone found no significant association(Cooper et al., 2007; Merari et al., 2002). When Cooper et al.(2007) analysed

couples, the pregnant group experienced significantly more stress, but only for sexual concerns. The meta-analysis of 5 female-only studies produced a SMD of -0.01 (95% CI -0.29-0.27, I^2= 53%) (Figure 4). Quality was consistent between studies and the funnel plot did not suggest publication bias.

[Figure 4 near here]

Fewer studies (5, n=1049) considered depression and chemical pregnancy. All 5 included women, while only 1 considered men. Merari et al.(2002) found male partners in non-pregnant couples to have significantly increased depression scores compared to pregnant couples but found no significant association between female depression and chemical pregnancy. Similarly, the two largest studies (An et al., 2013; Smeenk et al., 2001) found no significant difference. Kalaitzaki et al.(2020) found no significant difference between negative emotion scores of pregnant and non-pregnant women, but reported increased pregnancy chances with higher scores on logistic regression (OR 1.67, 95% CI 1.16–2.39). However, Verhaak et al.(2001) reported significantly higher depression scores in non-pregnant women. When Smeenk et al.(2001) used composite scores of anxiety and depression, it was significant on regression analysis (-0.17, p=0.01). A total of 3 female only studies were included in the meta-analysis, which found a SMD of 0.08 (95% CI -0.51-0.67 I^2= 83%) (Figure 5). Consistent quality of studies precluded sensitivity analysis and a funnel plot did not suggest bias.

[Figure 5 near here]

Studies that failed to define pregnancy (Nouri et al., 2014; Tamhankar et al., 2013) were not included in this synthesis.

Live birth

Of the 7 studies (n=1205) considering anxiety/stress and live birth, 7, 2 and 1 assessed

women, men and couples respectively. Of those considering women, 3 found no association (de Klerk et al., 2008; Pasch et al., 2012; Pottinger et al., 2016). Pasch et al.(2012) combined live births and ongoing pregnancy at the end of the study period as an outcome measure. An et al.(2013) did not report associations between baseline stress and live birth. However, Klonoff-Cohen et al.(2001) reported a RR of 1.25 (1.01-1.54) for female anxiety and no live birth, but a RR of 0.5 (0.28-0.89) for concern about infertility and no live birth. Nouri et al.(2014) reported that 18% vs 31% of couples with increased vs decreased male stress respectively achieved live birth, with no measures of significance. Cooper et al.(2007) found couples who achieved live birth had significantly higher global stress scores and did report significant associations for men and women separately but only in specific areas, such as need for parenthood. Insufficient homogeneity of data reporting prevented meta-analysis.

Fewer studies (4, n=906) considered depression and live birth, and An et al. (2013) did not report association with baseline depression. The 3 female-only remaining studies found no association (de Klerk et al., 2008; Klonoff-Cohen et al., 2001; Pasch et al., 2012). However, negative affect as a measure of depression and anxiety was associated with significantly reduced chances of live birth(de Klerk et al., 2008).

Sperm parameters

In total 4 studies (n=330) looked at anxiety/stress and sperm parameters, and 1 considered depression. Bártolo et al.(2016) considered state anxiety, trait anxiety and depression in first time and repeat ART patients. Concentration, motility and morphology were measured, and the only significant association was increased state anxiety and decreased slow progressive motility in first time ART patients. Similarly, Clarke et al.(1999) found significant negative correlations between state anxiety and concentration and motility, and no significant association with lateral head displacement. Vellani et al.(2013) found significant negative

regression coefficients between state and trait anxiety and concentration, motility, DNA fragmentation and volume. The only non-significant correlation was state anxiety and volume. Nouri et al.(2014) reported no difference between volume, concentration and motility in stressed and non-stressed groups.

Oocyte aspiration, embryo transfer and fertilization

Of 4 studies (n=1361) considering oocyte aspiration (Cesta et al., 2018; Donarelli et al., 2016; Klonoff-Cohen et al., 2001; Smeenk et al., 2001), 3 only considered women, and 1 assessed men, women and couples. The only significant correlation reported was the smallest study(Klonoff-Cohen et al., 2001) reporting significant correlations between chronic negative affect as a measure of trait anxiety and number of oocytes retrieved. Definitions of success varied, from yes/no undergoing oocyte aspiration to different successful follicle size. Only 3 female-only studies (n=927) considered embryo transfer (Cesta et al., 2018; Klonoff-Cohen et al., 2001; Smeenk et al., 2001), again with varying definitions of success. Only Klonoff-Cohen et al. (2001) found a significant correlation between chronic negative affect and number of embryos transferred. Of 2 studies(Harlow et al., 1996; Klonoff-Cohen et al., 2001) (n=246) considering fertilization, both found no significant difference.

Risk of bias

Newcastle-Ottawa scores ranged from 4-9. Most studies (n= 26) were assigned a 'Good' AHRQ standard, and 3 a 'Poor' standard. See Table 4 for detailed scoring.

[Tables 2, 3 and 4 near here]

Discussion

Summary of results

Overall, we report no significant association between state anxiety, trait anxiety, stress or depression and chemical or clinical pregnancy, and studies reporting significant associations found positive and negative associations. Few studies considered live birth, sperm parameters, oocyte aspiration, embryo transfer or fertilization, and these were heterogeneous and found no clear relationship. Of studies measuring sperm parameters, 3 found associations between state anxiety and motility (Bártolo et al., 2016; Clarke et al., 1999; Vellani et al., 2013), and 2 found associations between state anxiety and concentration (Clarke et al., 1999; Vellani et al., 2013).

Limitations

While studies were mostly of satisfactory quality, there was large variation in manner and timing of assessment of exposure and outcome (Table 2). Often measures of exposure were reported for specific concerns, where differences in stress type were unlikely to affect biological response e.g. concern about missing work vs procedures. The sample populations were also heterogeneous, with some studies excluding repeat ART patients and others not. Unsuccessful treatments have been shown to affect emotional health (Harata et al., 2012) and repeated exposure to a stressor leads to reduced biological response (Grissom & Bhatnagar, 2009), so subjective experience and biological response likely vary between these patients. Habituation of stress response may occur less in cases of mental illness (Grissom & Bhatnagar, 2009), further complicating this relationship. Many studies did not consider mental health diagnoses in design or analysis. Cause and type of infertility varied and not all studies controlled for confounders such as lifestyle factors or psychotropic medication. As the

studies were observational and did not adequately control for confounders, no conclusions about causality can be made. In addition to data weaknesses, the combining of stress and anxiety into one variable may introduce confounding through lack of consideration of coping strategies.

Future research needs

Our review highlights future research needs: increased consensus on eligible patients and appropriate measures of exposure are required for more robust data, and composite scores of anxiety and depression may prove useful to measure overall psychological difficulty. However, assessing the effect of psychological interventions on ART outcomes may be more patient centred. It is paramount to consider the association between men's and couples' emotional health on outcomes, due to a paucity of research in these areas.

Conclusions

We report a potential association between male state anxiety and sperm motility and no evidence of an association between female emotional health and ART outcomes. However, this does not indicate causation due to the observational design of studies and potential confounding. Further research is needed into the association between of male and couple's emotional health on ART outcomes due to paucity of data.

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Disclosure of interest

The authors report no conflict of interest.

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Figure Captions

Figure 1. PRISMA flow chart for article selection.

Figure 2. Forest plot of comparison of anxiety/stress scores and clinical pregnancy chances.

Figure 3. Forest plot of comparison of depression scores and clinical pregnancy chances.

Figure 4. Forest plot of comparison of anxiety/stress scores and chemical pregnancy chances.

Figure 5. Forest plot of comparison of depression scores and chemical pregnancy chances.

Biographical Notes

Peaston G

Ms Peaston is a medical student at Hull York Medical School, currently undertaking an iBSc at Kings College London in Anatomy, Developmental and Human Biology. She has a wide range of interests and has held positions on multiple societies at Hull York Medical School, such as Secretary of Hull Surgical Society and Events Organiser for the Obstetrics and Gynaecology Society.

Subramanian V

Dr Subramanian is a clinical research fellow at King's Fertility and is currently undertaking an MD with King's College London exploring mental health in patients attending assisted conception treatment. He is a South London trainee in Obstetrics and Gynaecology and has taken time out of programme to pursue this fellowship. He has a clinical and academic interest in reproductive medicine as well as medical education.

Brunckhorst O

Dr Brunckhorst is a current PhD Fellow in Urology at King's College London, currently taking time out of training as a South London Urology Trainee. His interests in academic urology and surgery include mental wellbeing and quality of life in men's health including malignant and benign pathology, surgical education and curriculum development, simulation-based training, non-technical skills in operating theatres and surgical innovation.

Sarris I

Dr Sarris is a Consultant in Reproductive Medicine, and the Director of King's Fertility in London. He is also a member of the British Fertility Society's Executive Committee and

Training Subcommittee. Dr Sarris completed specialty training at several London teaching hospitals, moved to Newcastle for subspecialty training in reproductive medicine and surgery, and returned to London to take up a consultant position.

Ahmed K

Mr Ahmed is a Consultant Urological Surgeon at King's College Hospital, London and a Senior Lecturer at King's College London. Having completed his specialist urology training in London, he undertook clinical fellowship training at the University College London Hospital in andrology, men's reconstructive surgery, and male factor infertility management. He is a specialist in management of male factor infertility, andrology and genito-urinary conditions.

	Population	Exposure	Outcome
	Assisted reproduction technology	Psychological stress	Live birth Semen analysis
Synonyms	ART		Pregnancy rate
Broader terms		Stress Distress	Pregnancy IVF outcome Sperm
Narrower terms	In vitro fertilisation IVF Intracytoplasmic sperm injection ICSI	Depressive disorder Depression Anxiety Anxiety disorder	Sperm motility Sperm count Sperm morphology Oocyte retrieval Implantation rate
Related terms		Low mood Major life events Adjustment disorder	
Alternative spellings and variants	Assisted reproductive techn*		

Table 1. Search box of terms in PEO format for literature search.

	Study design	Data collection period	Treatment	Follow up period (cycles)	Exposure	Measure of exposure	Timing of measurement	Outcome measure	Composition of unsuccessful group
An et al. (2013)	Prospective cohort	Jan 2009-March 2010	IVF/ICSI	12 month follow up	Anxiety (state)	STAI		Chemical pregnancy, live birth	underwent embryo transfer
					Depression	BDI			
Anderheim et al. (2005)	Prospective cohort	March 1999-June 2002	IVF/ICSI	1	Anxiety (state)	PGWB (anxiety)	1 month before treatment	Clinical pregnancy	underwent embryo transfer
					Depression	PGWB (depression)			
Bartolo et al. (2016)	Cross sectional		ART (undefined)	1	Anxiety (state and trait)	STAI		Sperm concentration, morphology, slow progressive motility, rapid progessive motility, total motility	N/A
					Depression	BDI-II			
					Stress (fertility-specific)	FPI			
Boivin & Takefman	Prospective		IVF/ICSI	1	Anxiety (state and	STAI		Chemical pregnancy	underwent embryo

(1995)	cohort				trait)				transfer
					Stress (fertility-specific)	The Infertility Questionnaire			
Cesta et al. (2018)	Prospective cohort	Sept 2011-Dec 2014	IVF/ICSI	1	Stress (fertility-specific)	COMPI-FPSS		Oocyte aspiration, embryo transfer, clinical pregnancy	underwent embryo transfer
					Stress (general)	PSS			
Clarke et al. (1999)	Prospective cohort		IVF/ICSI	1	Anxiety (state)	STAI	4-6 weeks before treatment	Sperm concentration, motile sperm concentration, total motile spermatozoa, lateral head displacement	N/A
Cooper et al. (2007)	Prospective cohort	May 2002-April 2005	IVF/ICSI	1	Stress (fertility-specific)	FPI		Chemical pregnancy, live birth	entered IVF cycle
de Klerk et al. (2008)	Prospective cohort	Feb 2002-Feb 2004	IVF/ICSI	1	Anxiety (state)	HADS (anxiety)		Live birth	entered IVF cycle
					Depression	HADS (depression)			
Donarelli et al. (2016)	Prospective cohort	March 2009-	ART (undefined)	1	Anxiety (state)	STAI	Maximum 21 days before	Number of follicles ≥ 16 mm in diameter	underwent oocyte

		Dec 2012					treatment start		aspiration
					Stress (fertility-specific)	FPI			
Eugster et al. (2004)	Prospective cohort		IVF/ICSI	1	Anxiety (state and trait)	STAI	On waiting list/ 1st gynaecology visit	Clinical pregnancy	entered IVF cycle
Harlow et al. (1996)	Prospective cohort		IVF	1	Anxiety (state and trait)	STAI		Fertilization	entered IVF cycle
Kalaitzaki et al. (2019)	Prospective cohort	January–June 2015	IVF	1	Stress (general)	PSS		Chemical pregnancy	entered IVF cycle
					Depression	SPANE (negative emotions)			
Klonoff-Cohen et al. (2001)	Prospective cohort	July 1993-June 1998	IVF/GIFT/ZIFT	1	Depression	POMS (elated-depression)	Initial clinic visit	Oocytes aspirated, fertilization, embryos transferred, clinical pregnancy, live births	entered IVF cycle
					Anxiety (state and trait)	POMS (anxiety), PANAS (negative affect)			

					Stress (general)	PSS			
					Stress (fertility-specific)	Infertility Reaction scale (concern about infertility)			
Lintsen et al. (2009)	Prospective cohort	2002-2004	IVF/ICSI	1	Anxiety (state)	STAI	Maximum 2 months before start of treatment	Clinical pregnancy	underwent oocyte aspiration
					Depression	BDI-PC			
Maroufizadeh et al. (2019)	Prospective cohort	Feb-March 2017	IVF	1	Anxiety (state)	HADS (anxiety)		Clinical pregnancy	entered IVF cycle
					Depression	HADS (depression)			
					Stress (general)	PSS			
Merari et al. (2002)	Prospective cohort		IVF	1	Anxiety (state and trait)	STAI	10-15 days before start of treatment	Chemical pregnancy	underwent embryo transfer
					Depression	DACL			
Miller et al.	Prospective	Jan 2017-	IVF	1	Anxiety	STAI	At least 1 month before	Clinical pregnancy	entered IVF

(2019)	cohort	Feb 2018			(undefined)		treatment		cycle
Nouri et al. (2014)	Prospective cohort	March 2008-June 2012	IVF	1	Stress (fertility-specific)	FPI		Sperm motility, concentration and volume, pregnancy (undefined), live birth	N/A
Pasch et al. (2012)	Prospective cohort	2000-2004	IVF	1	Anxiety (state)	STAI	Around 2 months before treatment	Ongoing clinical pregnancy or live birth by end of study	entered IVF cycle
					Depression	CES-D			
Pottinger et al. (2016)	Retrospective cross sectional	2003-2012	IVF	Multiple	Stress (general)	Holmes and Rahe stress inventory		Live birth	underwent embryo transfer
Sanders et al. (1999)	Prospective cohort	Feb 1990-Feb 1993	IVF/GIFT	Median2, Maximum 12	Anxiety (state and trait)	STAI	1-3 months before treatment	Clinical pregnancy	entered IVF cycle
					Depression	POMS (elated-depressed)			
Smeenk et al. (2001)	Prospective cohort	Jan 1999-March 2000	IVF/ICSI	1	Anxiety (state and trait)	STAI	Around 3 weeks before treatment	Number of follicles ≥ 9 mm, number of embryos, chemical pregnancy	underwent embryo transfer
					Depression	BDI			
Sohrabvand et al. (2008)	Prospective cohort	Jan 2006-Jan 2007	ICSI	1	Anxiety (undefined)	Iranian Cattle Anxiety		Clinical pregnancy	entered IVF cycle

					Depression	BDI			
Tamhankar et al. (2013)	Prospective cohort	June 2011-Dec 2012	IVF	1	Stress (fertility-specific)	EHIQ		Pregnancy (undefined)	entered IVF cycle
Thiering et al. (1993)	Prospective cohort		IVF	Followed for 12 months	Anxiety (state and trait)	STAI	Maximum 1 month before treatment start	Clinical pregnancy	entered an IVF cycle
					Depression	CES-D			
Turner et al. (2013)	Prospective cohort	June 2009-Sep 2009	IVF	1	Anxiety (state and trait)	STAI		Clinical pregnancy	underwent embryo transfer
					Stress (general)	PSS			
Vellani et al. (2013)	Cross sectional	July 2006-March 2008	IVF	1	Anxiety (state and trait)	STAI		Semen volume, concentration, total count, total motility, DNA fragmentation	N/A
Verhaak et al. (2001)	Prospective cohort	1999	IVF/ICSI	1	Anxiety (state)	STAI	3-12 days before treatment cycle	Chemical pregnancy	underwent embryo transfer
					Depression	BDI, BDI-PC, POMS (elated-depressed)			

Visser et al. (1994)	Prospective cohort	May 1986-Jan 1989	IVF	Multiple	Anxiety (state) Depression	STAI Hopkins-Symptom-Checklist (depression)	Clinical pregnancy	underwent embryo transfer

Table 2. Table of study characteristics. N/A= not applicable. Cells were left empty when data was not reported. STAI= Spielberger state-trait anxiety inventory, PGWB= Psychological general wellbeing index, HADS= Hospital anxiety and depression scale, POMS= Profile of Mood States, BDI= Beck Depression Inventory, CES-D= Center for Epidemiological Studies depression scales, DACL= Depression adjective checklist, PANAS= Positive and negative affect scale, SPANE= scale of positive and negative experience, PSS= Perceived stress scale, FPI= Fertility problem inventory, EHIQ= Emotional Health in Infertility Questionnaire, COMPI-FPSS= Copenhagen multi-centre psychosocial infertility research program fertility problem stress scale.

	Country	Sample size	M/ F/ C	Mean age of patients	Mean duration of infertility	Previous ART use	Number successful	Number unsuccessful
An et al. (2013)	China	264	F	P=33.1 (4.10) NP=33.4 (3.90)	P=6.80 (3.30) NP= 7.00 (3.50)		92	172
Anderheim et al. (2005)	Sweden	166	F	32.1	P=4.70 (2.60) NP=4.20 (2.10)	Yes- 6%	58	81
Bartolo et al. (2016)	Portugal	112	M	1st time= 34.1(4.10) Repeat= 36.4(4.10)	1st time=4.70(2.80) Repeat=6.20(2.80)	Yes- 50%	N/A	N/A
Boivin & Takefman (1995)	Canada	40	F	NP= 33.52(4.30) P=33.1(2.90)	NP= 4.04(2.3) P=4.82(1.8)	No	17	23
Cesta et al. (2018)	Sweden	485	F	33.8 (4.14)	2.60 (1.84)		129	356
Clarke et al. (1999)	USA	40	M			No	N/A	N/A
Cooper et al. (2007)	USA	129 C	M, F and C	P(F)= 34.0(1.00) NP(F)= 35.0(1.00) P(M)=35.0(1.00) NP(M)=36.0(1.00)			69	60
de Klerk et al. (2008)	The Netherlands	289	F	32.8 (3.10)	3.60 (1.90)		73	216
Donarelli et al. (2016)	Italy	217 C	M, F and C	F=33.1(4.73) M=36.1 (5.17)	3.77 (2.64)	No		
Eugster et al. (2004)	The Netherlands	43	F	33.2(3.50)	3.88(2.63)	Yes- 100%	15	28

Harlow et al. (!996)	UK	95	F					
Kalaitzaki et al. (2019)	Greece	61	F	37.2(4.40)	3.30(2.10)	Yes- 77%	31	30
Klonoff-Cohen et al. (2001)	USA	151	F	36.8(4.31)	4.06(3.02)	Yes- 33%	30	121
Lintsen et al. (2009)	The Netherlands	783	F	33.2(3.70)	3.4(1.90)		252	531
Maroufizadeh et al. (2019)	Iran	142	F	32.1(5.52)	7.04(4.36)		38	104
Merari et al. (2002)	Israel	113 C	M and F	M= 37.1(3.80) F=33.9(5.30)	F(P)=7.6(5.40) F(NP)=6.7(4.40)	Yes- (-)	23	90
Miller et al. (2019)	Israel	72	F	29.5(5.50)	2.35(1.50)	Yes- 33%	23	49
Nouri et al. (2014)	Austria	84	M	33.5(6.10)	≤2	No	28	56
Pasch et al. (2012)	USA	202	F	35.5(4.50)	<1y=16% 1-2y=36.5% >2=47.5%	No	57	145
Pottinger et al. (2016)	Jamaica	215	F	Age 25-31= 90 Age 32-37=166 Age ≥38= 170	1-3y=138 >3y=271	No	48	167
Sanders et al. (1999)	Australia	90	F	32.6(4.40)		Yes- 23%	32	58
Smeenk et al. (2001)	The Netherlands	291	F	33.4(3.70)	3.70(2.00)	No		
Sohrabvand et al. (2008)	Iran	106	F	NP=29.4(5.22) P=30.0(4.77)	NP=7.32(5.02) P=8.26(4.16)		25	81

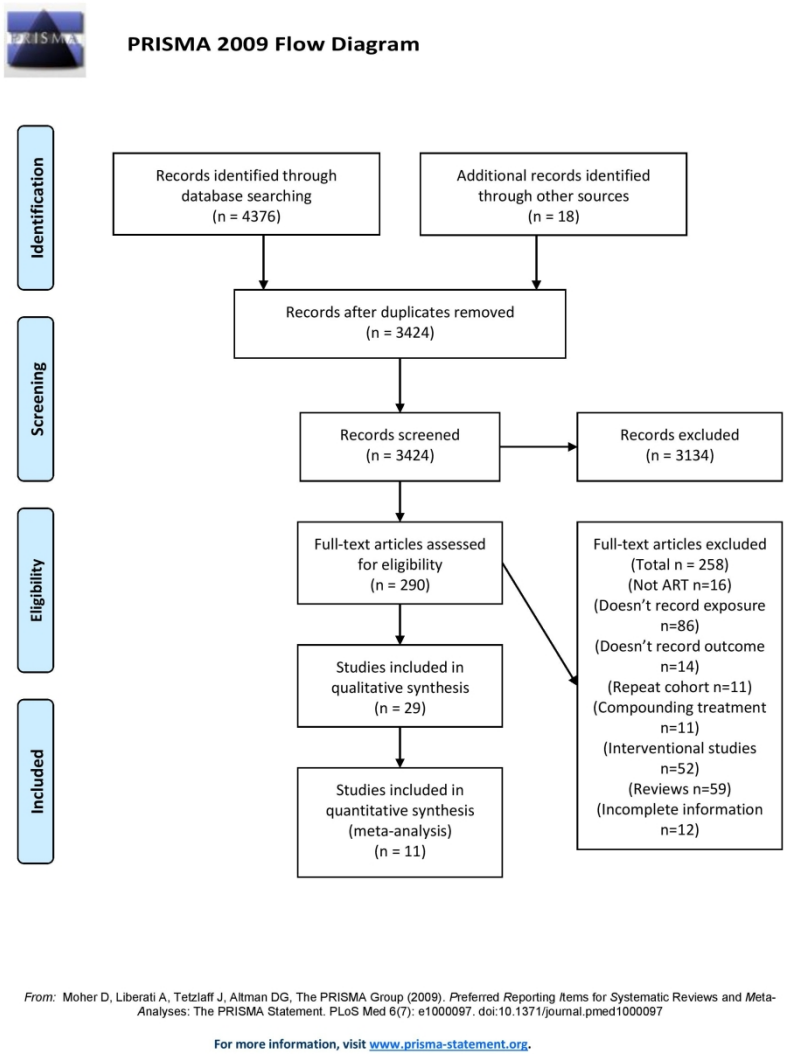
Tamhankar et al. (2013)	UK	300	F				101	199
Thiering et al. (1993)	Australia	330	F	1st time= 33.0(3.90) Repeat=43.0(4.00)		Yes- 66%		
Turner et al. (2013)	USA	44	F	35.3(3.82)		Yes- 34%	15	29
Vellani et al. (2003)	Italy	94	M	38.91(4.54)		No	N/A	N/A
Verhaak et al. (2001)	The Netherlands	207	F	33.4(3.70)	3.7 (2.00)	No	59	148
Visser et al. (1994)	The Netherlands	126	F			No	18	108

Table 3. Sample characteristics of included studies. M= male, F= female, C= couples, P=pregnant, NP=nonpregnant. N/A= not applicable. Cells were left empty when data was not reported. Numbers reported to 3 significant figures.

	Selection	Comparability	Exposure	Total	AHRQ standard
An et al. (2013)	3	2	2	7	Good
Anderheim et al. (2005)	3	2	1	6	Poor
Bartolo et al. (2016)	3	1	2	6	Good
Boivin & Takefman (1995)	4	2	3	9	Good
Cesta et al. (2018)	3	2	2	7	Good
Clarke et al. (1999)	3	1	2	6	Good
Cooper et al. (2007)	4	2	3	9	Good
de Klerk et al. (2008)	3	2	3	8	Good
Donarelli et al. (2016)	3	2	2	7	Good
Eugster et al. (2004)	3	2	3	8	Good
Harlow et al. (1996)	3	0	2	5	Poor
Kalaitzaki et al. (2019)	3	2	3	8	Good
Klonoff-Cohen et al. (2001)	3	2	2	7	Good
Lintsen et al. (2009)	3	2	3	8	Good
Maroufizadeh et al. (2019)	3	2	2	7	Good
Merari et al. (2002)	3	2	3	8	Good
Miller et al. (2019)	3	2	2	7	Good
Nouri et al. (2014)	3	2	3	8	Good
Pasch et al. (2012)	4	2	2	8	Good
Pottinger et al. (2016)	3	2	3	8	Good
Sanders et al. (1999)	3	1	3	7	Good
Smeenk et al. (2001)	3	2	3	8	Good

Sohrabvand et al. (2008)	4	2	3	9	Good
Tamhankar et al. (2013)	2	0	2	4	Poor
Thiering et al. (1993)	3	1	2	6	Good
Turner et al. (2013)	3	2	3	8	Good
Vellani et al. (2013)	3	1	3	7	Good
Verhaak et al. (2001)	3	2	3	8	Good
Visser et al. (1994)	3	0	3	6	Poor

Table 4. Quality assessment for included studies. Criteria for conversion to AHRQ standards: Good= 3 or 4 stars in selection AND 1 or 2 in comparability AND 2 or 3 in outcome. Fair= 2 stars in selection AND 1 or 2 in comparability AND 2/3 in outcome. Poor= 0 or 1 star in selection OR 0 stars in comparability domain OR 1 star in outcome.



PRISMA flow chart for article selection.

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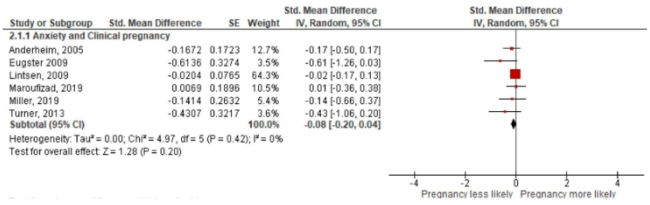
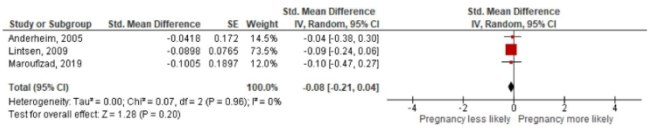


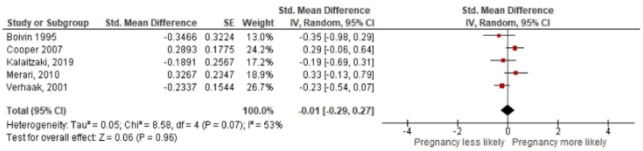
Forest plot of comparison of anxiety/stress scores and clinical pregnancy chances.

210x297mm (300 x 300 DPI)



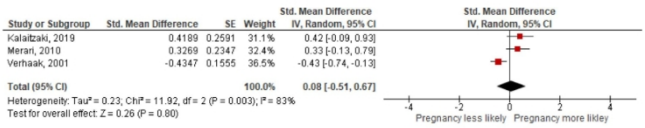
Forest plot of comparison of depression scores and clinical pregnancy chances.

210x297mm (300 x 300 DPI)



Forest plot of comparison of anxiety/stress scores and chemical pregnancy chances.

210x297mm (300 x 300 DPI)



Forest plot of comparison of depression scores and chemical pregnancy chances.

210x297mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table I
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5 & Tables 2 and 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5 & 6

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5 & 6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P7 & Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P11 & Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P7-11 & Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	P7-9 & Figures 2-5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12 & 13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.