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Review

Depression and state anxiety scores during assisted reproductive treatment are associated with outcome: a meta-analysis

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KEY MESSAGE

Depression and state anxiety during ART treatment are associated with poor ART outcome, but there is no evidence that changes in anxiety and depression scores from baseline to during ART treatment are associated with ART outcomes. Depression and state anxiety during ART may have a stronger effect on ART outcomes than baseline depression/anxiety.

A B S T R A C T

This meta-analysis investigated whether state anxiety and depression scores during assisted reproductive technology (ART) treatment and changes in state anxiety and depression scores between baseline and during ART treatment are associated with treatment outcome. PubMed, PsycInfo, Embase, ScienceDirect, Web of Science and Scopus were searched and meta-analytic data analysed using random effects models to estimate standardized mean differences. Eleven studies (2202 patients) were included. Women who achieved pregnancy had significantly lower depression scores during treatment than women who did not become pregnant (−0.302; 95% CI: −0.551 to −0.054, $z = -2.387$, $P = 0.017$; $I^2 = 77.142\%$, $P = 0.001$). State anxiety scores were also lower in women who became pregnant (−0.335; 95% CI: −0.582 to −0.087, $z = -2.649$, $P = 0.008$; $I^2 = 81.339\%$, $P = 0.001$). However, changes in state anxiety ($d = -0.056$; 95% CI: −0.195 to 0.082, $z = -0.794$; $I^2 = 0.00\%$) and depression scores ($d = -0.106$; 95% CI: −0.296 to 0.085, $z = -1.088$; $I^2 = 0.00\%$) from baseline to treatment were not associated with ART outcome. Clinics should aim to promote better psychosocial care to help patients manage the psychological and physical demands of ART treatment, giving realistic expectations.

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Introduction

Infertility is experienced by nearly one in six couples and many of these go on to seek assisted reproductive technology (ART) treatment to help them conceive (Farquhar et al., 2015). However, it is estimated that only a quarter of women will get pregnant after a single ART cycle in the UK (Kushnir et al., 2017), so most couples will experience negative pregnancy results and repeat treatment. A recent meta-analysis found that rates of depression and anxiety increased after ART treatment failure, but depression decreased after successful treatment (Milazzo *et al.*, 2016). Another recent meta-analysis also found no increased risk of depressive symptoms in women after they conceived using fertility treatment compared with those with spontaneous pregnancies (Gressier et al., 2015).

However, common psychological reactions during ART include stress, anxiety and depression (Eugster and Vingerhoets, 1999). Many women experience ART treatments as stressful, with stress and state anxiety levels increasing during oocyte retrieval and pregnancy test stages (An et al., 2013; Boivin and Takefman, 1995). Turner et al. (2013) found that women with higher stress and anxiety levels on the day prior to oocyte retrieval had a lower chance of obtaining positive pregnancy results. It is perhaps not surprising that some women drop out of treatment due to a variety of psychological and physical burdens (Gameiro et al., 2012).

Moreover, meta-analyses have found small but significant associations between baseline (before ART treatment has started) depression, state and trait anxiety scores and reduced pregnancy chances with ART (Matthiesen et al., 2011; Purewal et al., 2017a). However, Boivin et al. (2011) found no impact of baseline psychological distress (combined depression and anxiety scores) on ART treatment success. To date, no meta-analysis has investigated whether depression and anxiety scores during ART treatment and changes in levels of anxiety or depression from baseline (pretreatment) to treatment are associated with ART outcomes, despite studies (e.g. An et al., 2013; Boivin and Takefman, 1995) reporting increases in anxiety and depression rates over the course of treatment. The aims of this meta-analysis were therefore to (i) investigate the impact of state anxiety and depression scores during ART treatment on ART treatment outcome and (ii) investigate whether changes in levels of state anxiety and depression from baseline to during treatment predict ART treatment outcome.

Materials and methods

This meta-analysis is part of a larger project that also investigated whether baseline psychological distress is associated with ART outcome (Purewal et al., 2017a) and whether investigated lifestyle (smoking and alcohol use) and body mass index (BMI) are predictors of ART outcome (Purewal et al., 2017b).

The systematic review and meta-analysis was performed following PRISMA and MOOSE guidelines (Stroup et al., 2000).

Eligibility criteria

Eligible studies were considered if they reported as follows.

(i) Prospective studies that reported maternal depression and state anxiety scores during ART treatment (e.g. during oocyte retrieval or the day of embryo transfer) and ART outcomes, ideally with baseline measures (before treatment has started) of depression and state anxiety scores. Studies that reported depression and state anxiety scores after embryo transfer were excluded. Trait anxiety scores were excluded because the effects of treatment stage on state anxiety scores was of interest, not stable trait scores.

(ii) Studies were included if they used a standardized psychological measure (e.g. Beck's Depression Inventory [BDI] and the State-Trait Anxiety Inventory-State scale [STAI]) reporting continuous or categorical (cut-off score) data.

(iii) Studies were included if they reported only original data, reported live birth rates or pregnancy outcome data and ART treatments were included (e.g. IVF, intracytoplasmic sperm injection [ICSI], ZIFT). Other exclusion criteria were if it was not possible to calculate unadjusted effect sizes for predictor variables (e.g. predictor data grouped by outcome, only adjusted data reported, percentages without numbers reported) and therefore meta-analysis of unadjusted effect sizes could not be achieved.

Information sources and search

Six bibliographic databases were searched: PubMed, PsycInfo, Embase, ScienceDirect, Web of Science and Scopus. In PubMed, the following keywords in keywords and abstracts were used: ('Pregnancy'[Mesh] OR 'Pregnancy' OR 'pregnant' OR 'live birth' OR 'birth rate') and ('IVF' OR 'intracytoplasmic' OR 'intracytoplasmic sperm injection' OR '*in vitro* fertilization' OR 'ICSI' OR 'assisted reproductive technology' OR '*in vitro* fertilization') and ('psychological stress' OR 'depressive disorder' OR 'anxiety' OR 'anxiety disorder' OR 'adjustment disorder' OR 'emotions' OR 'psychosomatic medicine' OR 'psychological adaption' OR 'distress' OR 'depression' OR 'stress' OR 'occupation stress' OR 'stressful life events' OR 'major life events' OR 'stressors'). The searches were limited to the period from 1 January 1979 to November 2016 and humans. Hand searches of references cited in relevant papers were also conducted.

Study selection, data collection process and data items

Using PRISMA guidelines (Moher *et al.*, 2009) all authors independently screened titles, abstracts and full-text reports and disagreements were resolved by discussion between all authors. Data were extracted and independent (depression and state anxiety scores at baseline and during ART treatment) and dependent variables (live birth or pregnancy) and sample sizes were recorded. When two or more dependent variables were reported (e.g. serum pregnancy, clinical pregnancy and live birth), the data considered 'gold standard' (Maheshwari et al., 2008) were recorded (in this case, live birth; however, no study reported live birth data, so clinical pregnancy rates were used). Other data were also extracted, such as patient characteristics (e.g. average female age, whether they were first-time ART users or had previously used ART, number of oocytes retrieved, percentage with primary infertility); treatment characteristics (e.g. treatment location, ICSI use [all/some versus none used ICSI]), average number of embryos transferred, single or multiple cycles recorded, pregnancy verification (pregnancy test versus ultrasound scan) and study characteristics (e.g. publication date, design of study).

Summary measures and synthesis of results

The meta-analyses were performed on Comprehensive Meta-Analysis V2 (Borenstein et al., 2005) using weighted effect sizes with a random effects model. The extracted data (e.g. state anxiety and depression mean scores, standard deviations and sample sizes for pregnant and not pregnant groups at two time points; Time 1 [baseline] and Time 2 [during ART treatment]) were inputted. These data were converted into standardized mean differences and used to compare women who became pregnant and women who did not. Outliers were identified as studies with residuals greater than 1.96 and they were removed from the analysis as recommended.

Heterogeneity

The I^2 statistics were used to quantify heterogeneity, with 50–90% representing potentially substantial heterogeneity (Deeks et al., 2009). As recommended in this study, the intention was to conduct moderator analyses to investigate significant heterogeneity if there were 10 studies or more that provided data on potential moderators (e.g. average female age, duration of subfertility, FSH and number of oocytes; see Van Loendersloot et al., 2010). However, apart from mean maternal age for state anxiety during ART (where there were 10 studies per confounder variable), there were insufficient numbers of studies to analyse moderators, hence these analyses could not be performed.

Risk of bias

To assess the quality of studies, the Newcastle-Ottawa Scale (NOS) (Wells et al., 2009) was used. SP and OvdA independently assessed the quality of each selected study and cross-checked with each other to reach 100% consensus. The scale awarded a maximum of nine stars to each study: four stars for the adequate selection of cases and controls, two stars for comparability of cases and controls, and three stars for the adequate ascertainment of the exposure in both the case and control groups. High quality was defined as scoring at least seven stars; medium quality as scoring five or six stars and low quality as four stars or less.

Risk of bias analyses were conducted to examine whether effects were robust under different methodological assumptions. These included when ultrasound was used to diagnose pregnancy and not pregnancy test; when only first-time ART user's data was included; when results from a single cycle were used (not multiple cycles); when only IVF treatments were used; when only psychological data was collected before or during the oocyte retrieval period and not after; when only high-quality studies were included; and when studies were recent (studies published from 2010 onwards were considered recent).

Publication bias

Publication bias was tested for by examining funnel plots for evidence of asymmetry. Asymmetric funnel plots can occur because of biased publication strategies, e.g. if small, imprecise studies are only published if they support a particular hypothesis, but are not published if they do not support the hypothesis (Sterne and Egger, 2001). Duval and Tweedie's trim and fill method (Duval and Tweedie, 2000) was used, which imputes studies where evidence of asymmetry is present and tested for the significance of these effects using Egger's t-test.

Results

Study selection

The screening process is summarized in the study PRISMA flow chart (**Figure 1**). A total of 11 studies (An et al., 2011; Gourounti et al., 2011; Gürhan et al., 2009; Hashemi et al., 2012; Karlidere et al., 2008; Li et al., 2011; Lintsen et al., 2009; Saravelos et al., 2016; Taguchi et al., 2015; Turner et al., 2013; Zaig et al., 2012) were included in the meta-analysis.

Study characteristics

An overview of the study characteristics is presented in **Table 1**. Data from 2202 patients were included in the meta-analyses. Most studies collected psychological data before or during the oocyte retrieval period (An et al., 2011; Gourounti et al., 2011; Gürhan et al., 2009; Hashemi et al., 2012; Li et al., 2011; Lintsen et al., 2009; Saravelos et al., 2016; Turner et al., 2013; Zaig et al., 2012) with only the Karlidere et al. (2008) and Taguchi et al. (2015) studies collecting data on the day before and on the day of embryo transfer, respectively.

Risk of bias within studies

The quality of the studies was high or medium with none scoring a 'low' score (four or less stars). All studies used pregnancy diagnosis, with pregnancy ultrasound scan used to verify pregnancy in most cases (An et al., 2011; Gourounti et al., 2011; Karlidere et al., 2008; Li et al., 2011; Lintsen et al., 2009; Saravelos et al., 2016; Turner et al., 2013; Zaig et al., 2012). Most studies were published after 2010 (An et al., 2011; Gourounti et al., 2011; Hashemi et al., 2012; Li et al., 2011; Saravelos et al., 2016; Taguchi et al., 2015; Turner et al., 2013; Zaig et al., 2012) and used the STAI to measure state anxiety (An et al., 2011; Gourounti et al., 2011; Gürhan et al., 2009; Hashemi et al., 2012; Karlidere et al., 2008; Lintsen et al., 2009; Saravelos et al., 2016; Turner et al., 2013; Zaig et al., 2012), with half of the depression studies using BDI (An et al., 2011; Gürhan et al., 2009; Karlidere et al., 2008; Saravelos et al., 2016). The most common ART procedure was IVF (Gürhan et al., 2009; Li et al., 2011; Taguchi et al., 2015; Turner et al., 2013; Zaig et al., 2012) or IVF/ICSI (An et al., 2011; Gourounti et al., 2011; Hashemi et al., 2012; Karlidere et al., 2008; Lintsen et al., 2009; Saravelos et al., 2016).

Only five studies reported baseline data (An et al., 2011; Gürhan et al., 2009; Li et al., 2011; Lintsen et al., 2009; Turner et al., 2013). All baseline data are reported in **Table 1**. Only two studies (An et al., 2011; Lintsen et al., 2009) reported statistical comparisons between patient's anxiety baseline (time 1) scores and anxiety during ART treatment (time 2) by pregnancy outcome and both studies found no significant anxiety score gains from baseline to during ART treatment. **Table 1** also includes the main summary of each study's results. Each study's calculated standardized means differences between pregnant and not pregnant women for depression and state anxiety scores and changes in depression and state anxiety scores from baseline to during treatment are presented in forest plots (**Figures 2 to 5**).

Synthesis of results

Depression during ART

Results of individual studies and synthesis of results: depression was measured in eight studies (An et al., 2011; Gourounti et al., 2011;

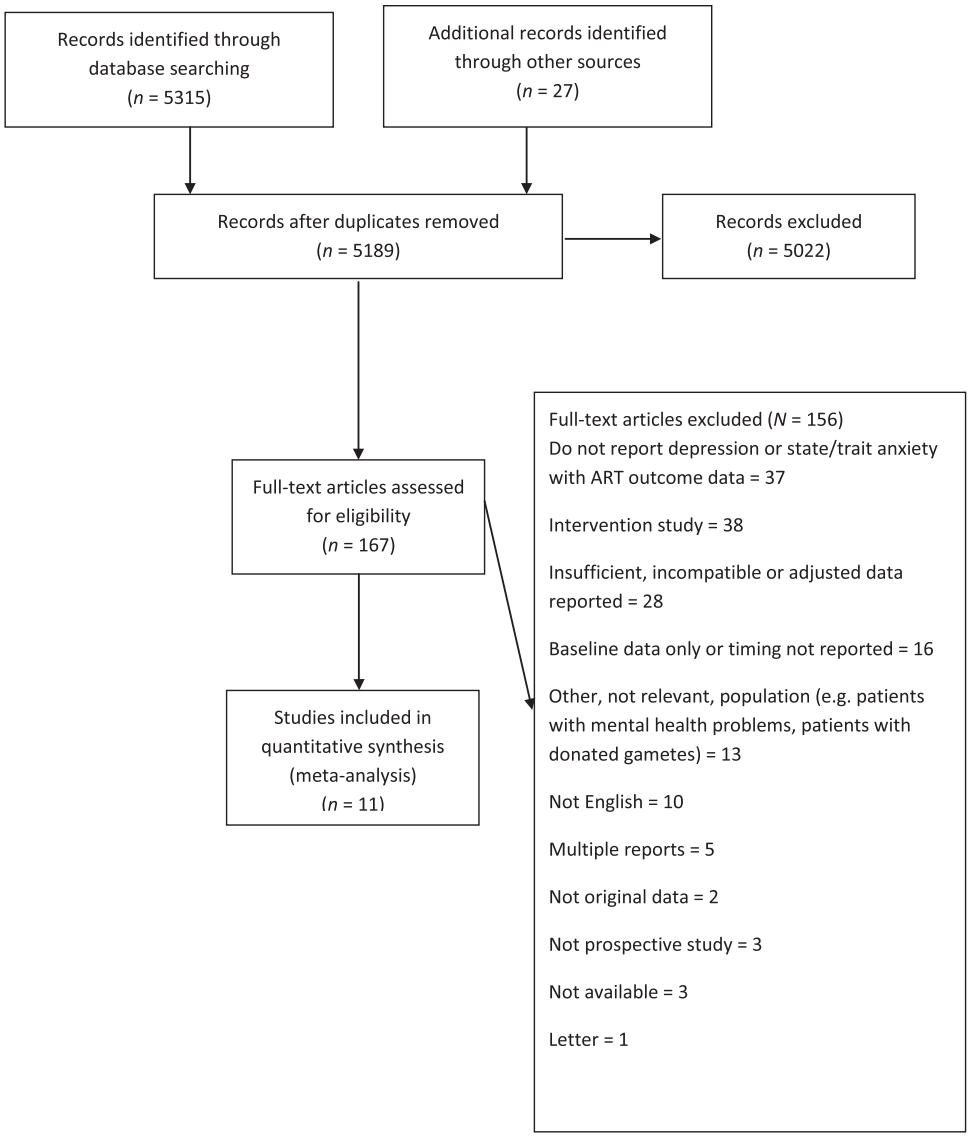


Figure 1 – Flow diagram of studies included in the meta-analysis.

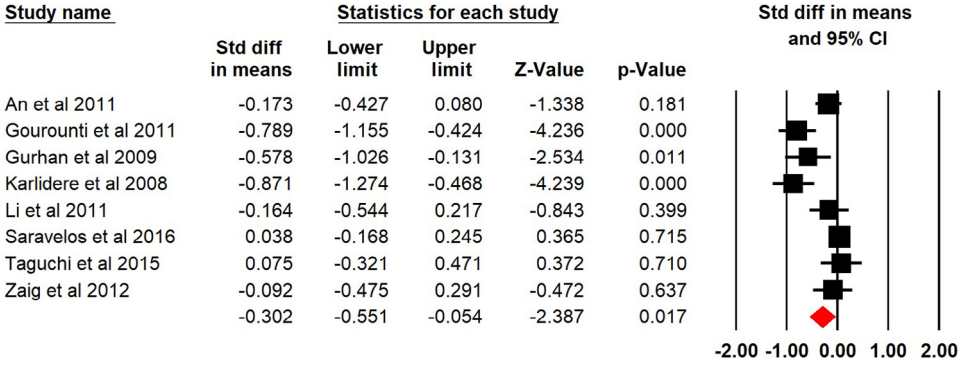


Figure 2 – Forest plot of depression scores during assisted reproductive technology (ART) shown as standardized mean differences between pregnant and not pregnant women (d = –0.302; 95% CI: –0.551 to –0.054, z = –2.387, P = 0.017; I^2 = 77.142%, P = 0.001).

Table 1 – Study characteristics.

Authors and country	Psychological variable and measurement	Time of assessment and period of enrolment	Method of pregnancy diagnosis	Study design and sample size	Treatment	Main findings	Newcastle-Ottawa quality score
An et al. (2011), China	State Anxiety – *STAI* Depression – *BDI*	Baseline and day of oocyte retrieval Period of enrolment 2009–2010	Ultrasound scan	Prospective, cohort study *N* = 264 All first-time ART users	IVF, ICSI Data from single treatment cycle	**At baseline** **Depression (NS)** Pregnant (*n* = 92, 1.5 ± 1.3) Not pregnant (*n* = 172, 1.6 ± 1.5) **State anxiety (NS)** Pregnant (*n* = 92, 36.1 ± 8.8) Not pregnant (*n* = 172, 37.6 ± 10.0) **At day of oocyte retrieval** **Depression (NS)** Pregnant (*n* = 92, 1.6 ± 1.6) Not pregnant (*n* = 172, 1.9 ± 18) **State anxiety (NS)** Pregnant (*n* = 92, 38.7 ± 6.7) Not pregnant (*n* = 172, 39.7 ± 7.4)	Selection**** Comparability** Outcome***
Gourounti et al. (2011), Greece	State Anxiety – *STAI* Depression – *Centre for Epidemiological Studies Depression Scale (CES-D)*	Before oocyte retrieval Period of enrolment November 2008 and July 2009	Ultrasound scan	Prospective, cohort study *N* = 160 Mix of first and multiple time ART users	IVF, ICSI Data from single treatment cycle	**Before oocyte retrieval** **Depression (*P* < 0.001)** Pregnant (*n* = 41, 7.9 ± 6.9) Not pregnant (*n* = 119, 15.0 ± 9.6) **State anxiety (*P* < 0.001)** Pregnant (*n* = 41, 33.7 ± 7.3) Not pregnant (*n* = 119, 43.5 ± 9.7)	Selection**** Comparability** Outcome***
Gürhan et al. (2009), Turkey	Depression – *BDI* State Anxiety – *STAI*	Baseline and day of oocyte retrieval Period of enrolment September 2004 and July 2005	HCG test	Prospective, cohort study *N* = 80 All first-time ART users	IVF First cycle of treatment Data from single treatment cycle	**At baseline** **Depression (*P* < 0.05)** Positive test (*n* = 39, 10.1 ± 5.2) Negative test (*n* = 41, 12.7 ± 6.2) **State anxiety (NS)** Positive test (*n* = 39, 45.0 ± 4.6) Negative test (*n* = 41, 47.6 ± 7.8) **At day of oocyte retrieval** **Depression (*P* = 0.01)** Positive test (*n* = 39, 15.2 ± 5.7) Negative test (*n* = 41, 19 ± 7.3) **State anxiety (*P* = 0.01)** Positive test (*n* = 39, 51.7 ± 5.1) Negative test (*n* = 41, 55.0 ± 5.5)	Selection**** Comparability Outcome**
Hashemi et al. (2012), Iran	State anxiety – *STAI*	Before oocyte retrieval Period of enrolment not reported	HCG test	Prospective, cohort study *N* = 180 Mix of first and multiple time ART users	IVF, ICSI, ZIFT Data from single treatment cycle	**Before oocyte retrieval** **State anxiety (NS)** Positive test (*n* = 19, 46.32 ± 10.8) Negative test (*n* = 161, 47.45 ± 10.6)	Selection*** Comparability** Outcome**
Karlidere et al. (2008), Turkey	Depression – *BDI* State Anxiety – *STAI*	Day before embryo transfer Period of enrolment June 2001 to July 2003	Ultrasound scan	Prospective, cohort study *N* = 104 All first-time ART users.	IVF, ICSI Data from single treatment cycle	**Day before embryo transfer** **Depression (*P* = 0.001)** Pregnant (*n* = 49, 6.21 ± 4.34) Not pregnant (*n* = 55, 10.55 ± 5.49) **State anxiety (*P* = 0.001)** Pregnant (*n* = 49, 33.21 ± 7.91) Not pregnant (*n* = 55, 40.14 ± 8.37)	Selection**** Comparability** Outcome***

(*continued on next page*)

Table 1 – (*continued*)

Authors and country	Psychological variable and measurement	Time of assessment and period of enrolment	Method of pregnancy diagnosis	Study design and sample size	Treatment	Main findings	Newcastle-Ottawa quality score
Li et al. (2011), China	State Anxiety – *Zung self-rating anxiety scale (SAS)* Depression – *Zung self-rating depression scale (SDS)*	Day of oocyte retrieval Period of enrolment 2007–2008	Ultrasound scan	Prospective, cohort study *N* = 107 All first-time ART users.	IVF Data from single treatment cycle	**At baseline** **Depression (NS)** Pregnant (*n* = 50, 52.66 ± 12.34) Not pregnant (*n* = 57, 54.06 ± 11.34) **State anxiety (NS)** Pregnant (*n* = 50, 39.66 ± 8.04) **At day of oocyte retrieval** **Depression (NS)** Pregnant (*n* = 50, 55.27 ± 9.18) Not pregnant (*n* = 57, 56.39 ± 10.93) **State anxiety (NS)** Pregnant (*n* = 50, 42.66 ± 7.12) Not pregnant (*n* = 57, 41.96 ± 9.23)	Selection**** Comparability** Outcome***
Lintsen et al. (2009), the Netherlands	State Anxiety – *STAI*	Day before oocyte retrieval Period of enrolment 2002–2004	Ultrasound scan	Prospective, cohort study *N* = 690 (at baseline), of which *n* = 413 had completed questionnaire on day before oocyte retrieval All first-time ART users	IVF, ICSI Data from single treatment cycle	**Baseline** **Depression (NS)** Pregnant (*n* = 196, 1.2 ± 1.8) Not pregnant (*n* = 494, 1.4 ± 2.4) **State anxiety (NS)** Pregnant (*n* = 196, 176 ± 4.7) Not pregnant (*n* = 494, 17.7 ± 5.0) **Day before oocyte retrieval** **State anxiety (NS)** Pregnant (*n* = 122, 18.4 ± 5.8) Not pregnant (*n* = 291, 18.5 ± 5.8)	Selection**** Comparability** Outcome**
Saravelos et al. (2016), Hong Kong	Depression – *BDI* State Anxiety – *STAI*	Day of oocyte retrieval Period of enrolment 2011–2014	Ultrasound scan	Prospective, cohort study *N* = 360 First-time ART users or multiple users not specified	IVF, ICSI Data from multiple treatment cycle	**Day of oocyte retrieval** **Depression (NS)** Pregnant (*n* = 175, 7.8 ± 8.2) Not pregnant (*n* = 185, 7.5 ± 7.4) **State anxiety (NS)** Pregnant (*n* = 175, 55.1 ± 10) Not pregnant (*n* = 185, 54.8 ± 8.6)	Selection**** Comparability** Outcome***
Taguchi et al. (2015), Japan	*Zung self-rating depression scale (SDS)*	Day of embryo transfer Period of enrolment April 2012 to May 2012	HCG test	Prospective, cohort study *N* = 113 First-time ART users or multiple users not specified	IVF Data from single treatment cycle	**Day of embryo transfer** **Depression (NS)** Pregnant (*n* = 36, 37.2 ± 6.3) Not pregnant (*n* = 77, 36.7 ± 6.8)	Selection*** Comparability** Outcome*

(*continued on next page*)

Table 1 – (*continued*)

Authors and country	Psychological variable and measurement	Time of assessment and period of enrolment	Method of pregnancy diagnosis	Study design and sample size	Treatment	Main findings	Newcastle-Ottawa quality score
Turner et al. (2013), USA	State Anxiety – *STAI*	Day before oocyte retrieval Period of enrolment June 2009-September 2009	Ultrasound scan	Prospective, cohort study *N* = 36 included in baseline sample and *n* = 35 included in day before oocyte retrieval sample First- or second-time ART users	IVF Data from single treatment cycle	**Baseline** **State anxiety (NS)** Pregnant (*n* = 15, 37.53 ± 12.33) Not pregnant (*n* = 21, 43.57 ± 14.44) **Day before oocyte retrieval** **State anxiety (*P* = 0.05)** Pregnant (*n* = 15, 34.93 ± 11.18) Not pregnant (*n* = 20, 44.35 ± 13.63)	Selection*** Comparability Outcome**
Zaig et al. (2012), Israel	Depression – *CESD Centre for Epidemiologic Studies Depression scale* State Anxiety – *STAI*	At ovulation induction Period of enrolment January 2006 to December 2007	Ultrasound scan	Prospective, cohort study *N* = 108 First- or second-time ART users	IVF Data from single treatment cycle	**At ovulation induction** **Depression (NS)** Pregnant (*n* = 45, 34.06 ± 9.4) Not pregnant (*n* = 63, 34.93 ± 9.47 **State anxiety (NS)** Pregnant (*n* = 45, 42.42 ± 11.4) Not pregnant (*n* = 63, 44.07 ± 11.79).	Selection**** Comparability Outcome***

The sample size refers to data that is extracted from the papers and used in the meta-analysis.
BDI = Beck's Depression Inventory; ICSI = intracytoplasmic sperm injection; NS = non-significant differences between women who were pregnant and women who were not pregnant; *P* = value; STAI = State-Trait Anxiety Inventory-State scale.

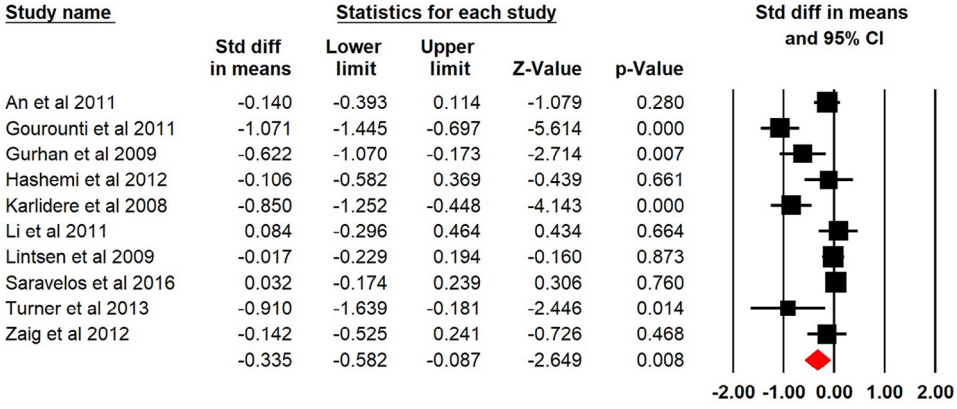


Figure 3 – Forest plot of state anxiety scores during ART shown as standardized mean differences between pregnant and not pregnant women (*d* = –0.335; 95% CI: –0.582 to –0.087: *z* = –2.649, *P* = 0.008; I^2 = 81.339%, *P* = 0.001).

Table 2 – Sensitivity analyses.

	d [95% CI OR]	Heterogeneity (I^2)
Depression during ART treatment		
Pregnancy diagnosed with ultrasound scan only (k = 6)	−0.323 [−0.617 to −0.029], *z* = −2.152, *P* = 0.03	80.784%, *P* = 0.001
First ART (k = 5)	−0.357 [−0.637 to 0.077], *z* = −2.498, *P* = 0.013	66.010%, *P* = 0.019
Single cycle only (k = 7)	−0.363 [−0.628, −0.097], *z* = −2.678, *P* = 0.007	72.610%, *P* = 0.001
Only IVF (k = 4)	−0.174 [−0.428, 0.080], *z* = −1.342, NS	37.932%, NS
Data collected before or during oocyte retrieval period (k = 6)	−0.268 [−0.519, −0.018] *z* = −2.100, *P* = 0.036	72.556%, *P* = 0.003
High quality (k = 6)	−0.323 [−0.617, −0.029] *z* = −2.152, *P* = 0.031	80.784%, *P* = 0.001
Recent only (k = 6)	−0.175 [−0.408, 0.058], *z* = −1.470, NS	69.277%, *P* = 0.006
State anxiety during ART treatment		
Pregnancy diagnosed with ultrasound scan only (k = 8)	−0.330 [−0.614, −0.046], *z* = −2.279: *P* = 0.023	84.317%, *P* = 0.001
First ART (k = 5)	−0.280 [−0.588, 0.028], *z* = −1.075, NS	475.503%, *P* = 0.001
Single cycle (k = 9)	−0.388 [−0.666, −0.110], *z* = −2.737, *P* = 0.006	80.793%, *P* = 0.001
IVF only (k = 4)	−0.332 [−0.731, 0.068], *z* = −1.625, NS	66.888%, *P* = 0.029
Data collected before or during oocyte retrieval period (k = 9)	−0.273 [−0.515, −0.032], *z* = −2.215, *P* = 0.027	78.766%, *P* = 0.001
High quality (k = 8)	−0.261 [−0.524, −0.003], *z* = −1.941, *P* = 0.052	82.857%, *P* = 0.001
Recent only[a] (k = 7)	−0.280 [−0.587, 0.026], *z* = −1.793, NS	81.130%, *P* = 0.001
Changes in depression from baseline to during ART treatment		
Pregnancy diagnosed with ultrasound scan only (k = 2)	−0. 088 [−0.299, 0.123], *z* = −0.816, NS	<0.001%, NS
First ART (k = 2)	−0. 088 [−0.299, 0.123], *z* = −0.816, NS	<0.001%, NS
Single cycle only (k = 2)	−0. 088 [−0.299, 0.123], *z* = −0.816, NS	<0.001%, NS
Only IVF (k = 2)	−0. 093 [−0.380, 0.195], *z* = −0.633, NS	<0.001%, NS
Data collected before or during oocyte retrieval period (k = 3)	−0.106 [−0.296, 0.085], *z* = −1.088, NS	<0.00%, NS
High quality (k = 2)	−0.088 [−0.299, 0.123], *z* = −1.816, NS	<0.001%, NS
Recent only[a] (k = 2)	−0. 088 [−0.299, 0.123], *z* = −0.816, NS	<0.001%, NS
Changes in state anxiety from baseline to during ART treatment		
Pregnancy diagnosed with ultrasound scan only (k = 4)	−0.048 [−0.194, 0.098], *z* = −0.941, NS	<0.001%, NS
First ART (k = 3)	−0.031 [−0.180, 0.119], *z* = −0.401, NS	<0.001%, NS
Single cycle (k = 4)	−0.048 [−0.194, 0.098], *z* = −0.641, NS	<0.001%, NS
IVF only (k = 3)	−0.130 [−0.396, 0.136], *z* = −0.957, NS	<0.001%, NS
Data collected before or during oocyte retrieval period (k = 5)	−0.056 [−0.195, 0.082], *z* = −0.794, NS	<0.00%, NS
High quality (k = 3)	−0.031 [−0.180, 0.119], *z* = −0.401, NS	<0.001%, NS
Recent only[a] (k = 3)	−0.091 [−0.293, 0.111], *z* = −0.887, NS	<0.001%, NS

[a] Studies published from 2010 onwards.
NS = *P*-value was not significant.

Gürhan et al., 2009; Karlidere et al., 2008; Li et al., 2011; Saravelos et al., 2016; Taguchi et al., 2015; Zaig et al., 2012). Results revealed that women who achieved pregnancy reported lower depression mean scores than women who did not achieve a pregnancy (−0.302; 95% CI: −0.551 to −0.054, *z* = −2.387, *P* = 0.017) with significantly high levels of heterogeneity (I^2 = 77.142%, *P* = 0.001) (see **Figure 2** for forest plots).

Risk of bias

The effects of depression remained consistent in the sensitivity analyses, which considered studies that only used first-time ART patients (An et al., 2011; Gürhan et al., 2009; Karlidere et al., 2008; Li et al., 2011; Lintsen et al., 2009), reported pregnancies diagnosed by ultrasound (An et al., 2011; Gourounti et al., 2011; Karlidere et al., 2008; Li et al., 2011; Saravelos et al., 2016; Zaig et al., 2012), single cycle results only (An et al., 2011; Gourounti et al., 2011; Gürhan et al., 2009; Karlidere et al., 2008; Li et al., 2011; Taguchi et al., 2015; Zaig et al., 2012), data collected before or during oocyte retrieval (An et al., 2011; Gourounti et al., 2011; Gürhan et al., 2009; Li et al., 2011; Saravelos et al., 2016; Zaig et al., 2012) and high-quality studies (An et al., 2011; Gourounti et al., 2011; Karlidere et al., 2008; Li et al., 2011; Saravelos et al., 2016; Zaig et al., 2012) (see **Table 2**). However, the effect became smaller when the analysis was conducted in fewer studies reporting IVF outcome (not ICSI) (Gürhan et al., 2009; Li et al., 2011; Taguchi

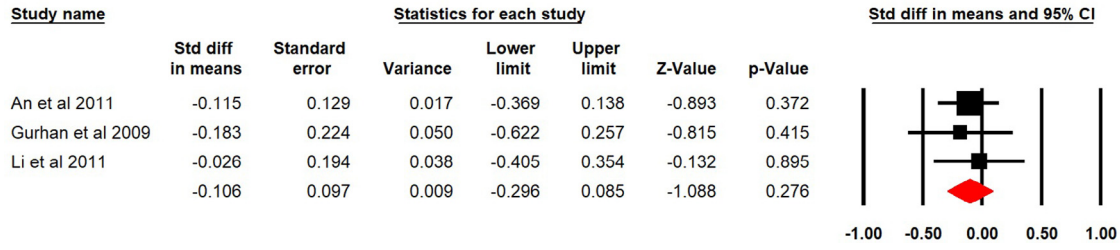
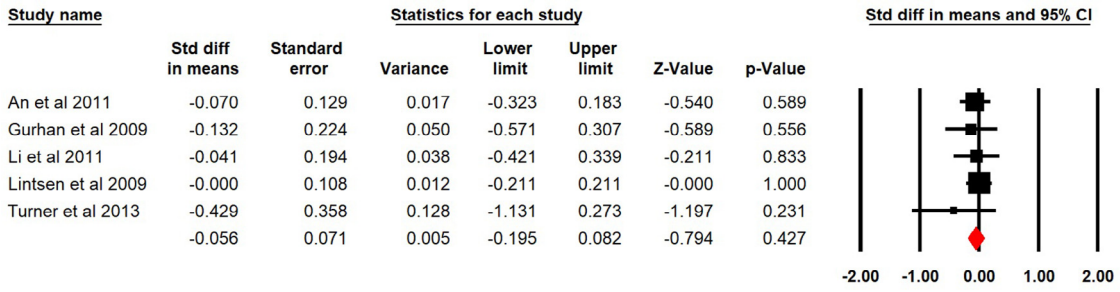


Figure 4 – Forest plot of changes in depression scores from baseline to during ART shown as standardized mean differences between pregnant and not pregnant women (*d* = −0.106; 95% CI: −0.296 to 0.085, *z* = −1.088; I^2 = 0.00%).



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
An et al 2011	-0.070	0.129	0.017	-0.323	0.183	-0.540	0.589
Gurhan et al 2009	-0.132	0.224	0.050	-0.571	0.307	-0.589	0.556
Li et al 2011	-0.041	0.194	0.038	-0.421	0.339	-0.211	0.833
Lintsen et al 2009	-0.000	0.108	0.012	-0.211	0.211	-0.000	1.000
Turner et al 2013	-0.429	0.358	0.128	-1.131	0.273	-1.197	0.231
	-0.056	0.071	0.005	-0.195	0.082	-0.794	0.427

Figure 5 – Forest plot of changes in state anxiety scores from baseline to during ART shown as standardized mean differences between pregnant and not pregnant women (d = –0.056; 95% CI: –0.195 to 0.082, z = –0.794; I^2 = 0.00%).

et al., 2015; Zaig et al., 2012) and recent studies (An et al., 2011; Gourounti et al., 2011; Li et al., 2011; Saravelos et al., 2016; Taguchi et al., 2015; Zaig et al., 2012).

Publication bias

Data analyses generally indicated low levels of publication bias risk for depression. The trim and fill data analyses revealed only one additional study would be needed to ensure the funnel plot was generally symmetrical and Egger's regression intercept was not significant (t(6) = 1.77).

State anxiety during ART

Results of individual studies and synthesis of results

State anxiety was measured in ten studies (An et al., 2011; Gourounti et al., 2011; Gürhan et al., 2009; Hashemi et al., 2012; Karlidere et al., 2008; Li et al., 2011; Lintsen et al., 2009; Saravelos et al., 2016; Turner et al., 2013; Zaig et al., 2012). Results revealed that women who achieved a pregnancy reported lower state anxiety mean scores than women who did not achieve a pregnancy (–0.335; 95% CI: –0.582 to –0.087; z = –2.649; P = 0.008) with evidence of high levels of significant heterogeneity (I^2 = 81.339%, P = 0.001) (see **Figure 3** for forest plot of results from individual studies and synthesis of results).

Mixed effects meta-regression was performed to test whether mean maternal age moderated the effect of state anxiety on outcome. This revealed no effect of age (slope = –0.06, 95% CI, –0.20 to 0.08). It was not possible to perform moderator analyses on any other variables due to the small numbers of studies (fewer than 10 studies per moderator variable).

Risk of bias analysis

The effect for state anxiety was robust under different methodological conditions, such as studies that diagnosed pregnancy by ultrasound (not pregnancy test) (An et al., 2011; Gourounti et al., 2011; Karlidere et al., 2008; Li et al., 2011; Lintsen et al., 2009; Saravelos et al., 2016; Turner et al., 2013; Zaig et al., 2012), single cycle outcome (An et al., 2011; Gourounti et al., 2011; Gürhan et al., 2009; Hashemi et al., 2012; Karlidere et al., 2008; Li et al., 2011; Lintsen et al., 2009; Turner et al., 2013; Zaig et al., 2012), data collected before or during oocyte retrieval (An et al., 2011; Gourounti et al., 2011; Gürhan et al., 2009; Hashemi et al., 2012; Li et al., 2011; Lintsen et al., 2009; Saravelos et al., 2016; Turner et al., 2013; Zaig et al., 2012) and high-quality studies (An et al., 2011; Gourounti et al., 2011; Hashemi et al., 2012; Karlidere et al., 2008; Li et al., 2011; Lintsen et al., 2009; Saravelos et al., 2016; Zaig et al., 2012). However, the effects became smaller for first-time ART users (An et al., 2011; Gürhan et al., 2009; Karlidere et al., 2008; Li et al., 2011; Lintsen et al., 2009), IVF only (Gürhan et al., 2009; Li et al., 2011; Turner et al., 2013; Zaig et al., 2012), and recent studies only (An et al., 2011; Gourounti et al., 2011; Hashemi et al., 2012; Li et al., 2011; Saravelos et al., 2016; Turner et al., 2013; Zaig et al., 2012) (see **Table 1**).

Publication bias

Some evidence of publication bias was present for state anxiety. The trim and fill data analyses for state anxiety revealed two additional studies were needed to make the funnel plot symmetrical. However, state anxiety's Egger's regression intercept was not significant (t(8) = 2.235).

Changes in depression scores from baseline to during ART treatment

Results of individual studies and synthesis of results: depression was reported at baseline and during ART treatment in three studies (An et al., 2011; Gürhan et al., 2009; Li et al., 2011). Results revealed that changes in reported depression scores from baseline (time 1) to during ART treatment (time 2) were not associated with ART outcome (–0.106; 95% CI, –0.296 to 0.085, z = –1.088) with low and non-significant heterogeneity (I^2 = 0.00%) (see **Figure 4** for forest plots).

Risk of bias analysis

The non-significant effects of depression remained consistent in the sensitivity analyses (see **Table 2**).

Publication bias

There was limited evidence of publication bias, possibly due to the small number of included studies. The trim and fill data analyses for changes in depression revealed no additional studies were needed to make the funnel plot symmetrical. Egger's regression intercept was also not significant (t(1) = 0.38).

Changes in state anxiety scores from baseline to during ART treatment

Results of individual studies and synthesis of results: state anxiety was reported at baseline (time 1) and during ART treatment (time 2)

in five studies (An et al., 2011; Gürhan et al., 2009; Li et al., 2011; Lintsen et al., 2009; Turner et al., 2013). Results revealed that changes in reported state anxiety mean scores from baseline to during ART treatment were not associated with ART outcome (–0.056; 95% CI: –0.195 to 0.082, z = –0.794) with low, non-significant heterogeneity (I^2 < 0.00%) (see **Figure 5** for forest plots).

Risk of bias analysis

The small effect for state anxiety was generally consistent under different methodological conditions (see **Table 2**).

Publication bias

Some evidence of publication bias was present for changes in state anxiety. The trim and fill data analyses for state anxiety revealed two additional studies were needed to make the funnel plot symmetrical. However, the state anxiety's Egger's regression intercept was not significant (t(3) = 3.28).

Discussion

This is the first meta-analysis to investigate the relationship between anxiety and depression experienced during ART and ART outcome. The analysis of the available research has shown that depression and state anxiety scores reported during ART treatment stages (most studies reported before or during the oocyte retrieval stage) are significantly associated with ART treatment outcome. Although the significant effect sizes for depression (–0.302) and state anxiety (–0.335) were small, they were generally consistent under different methodological conditions and there was little evidence of publication bias. However, there was no evidence that changes in depression or state anxiety scores from baseline (time 1) to during ART treatment (time 2) were associated with ART treatment outcome. Heterogeneity was high for depression and state anxiety during ART, suggesting that the effects varied between studies. However, our findings were consistent under different methodological assumptions, although the number of studies included in the latter analyses were small.

Previous meta-analyses have found small associations between baseline depression, state and trait anxiety and stress and reduced pregnancy chances with ART (Matthiesen et al., 2011; Purewal et al., 2017a). However, this study found that baseline depression (d = –0.177) and state anxiety (d = –0.096) demonstrated a weaker effect on ART outcome (Purewal et al., 2017a) than the effect size found reported in this current paper. It therefore appears that depression and state anxiety taken at certain stages of the ART treatment cycle (i.e. before or during – mainly the oocyte retrieval stage) are relevant factors in predicting ART outcome, but there is no evidence that changes in levels of depression or state anxiety from baseline to during treatment is associated with ART outcome. However, the numbers of studies in the baseline versus during ART treatment analyses were relatively small, and more extensive investigations are needed for definitive answers.

These findings are interesting and help to frame future investigations. High levels of heterogeneity were obtained for the effect of depression and state anxiety scores during ART, but it was not possible to fully investigate the source of heterogeneity because there were insufficient numbers of studies to test for moderator effects (such as BMI, number of oocytes retrieved, poor responders, etc.) (Deeks et al., 2009). However, it was possible to investigate the moderating effect of age on state anxiety and ART outcome and no impact was found, but the sample size was small (k = 10). These results are interesting and highlight that there are many potential explanations for the associations between depression and state anxiety during ART procedures and ART outcome that could lead to variability across studies. Increases in anxiety or depression scores may be associated with other variables that are linked to negative outcome. Future research needs to examine whether women with poor prognosis (e.g. older women, women with high BMI, smoking, previous unsuccessful IVF experiences, knowledge of negative test results or of poor responses, medical comorbidities) experience a greater association between state anxiety and depression and ART outcomes than women with better prognosis (see Van Loendersloot et al., 2010). Some of these relationships are complex and interrelated. For example, depression and anxiety are often comorbid with obesity and binge eating (Luppino et al., 2010; Nicholls et al., 2016). Obesity has also been found to negatively impact ART outcomes (Purewal et al., 2017b; Rittenberg et al., 2011; Metwally et al., 2007).

Alternatively, there is some suggestion, largely from animal studies, that anxiety and depression may be linked to changes in immune system function associated with miscarriage (for review, see Qu et al., 2017). It is possible that these factors vary across study populations or have different effects across different IVF treatment protocols, contributing to heterogeneity. Moreover, the association between depression and anxiety scores during ART treatment and outcome could arise because women who respond poorly to the stimulation cycle may experience higher levels of anxiety or depression over the knowledge of poor test results. For example, the number of oocytes retrieved predicts IVF outcomes (Smeenk et al., 2000; Stolwijk et al., 1996) and a higher number of oocytes is associated with lower state anxiety and depression scores (Gourounti et al., 2011). Boivin and Takeman (1995) also reported that greater stress during ART treatment was significantly correlated with lower numbers of oocytes retrieved and embryos transferred. More research is necessary to tease out these relationships and understand the underlying mechanisms (Purewal et al., 2017a, 2017b). Future research should adopt a more holistic approach that investigates how psychological variables interconnect with physiological factors. However, given the ethical issues that would need to be confronted to explore some of these factors (e.g. manipulating whether patients should be blind to their baseline results and to how they are responding to the treatment), it may remain difficult to fully map the factors underpinning these associations.

Whether anxiety and depression during ART are markers for other factors linked to poorer outcomes, or contributors to poorer outcomes, a conservative response to our findings might be to provide tailored psychosocial care for patients during different ART stages to help them manage the psychological and physical toil of undergoing certain aspects of treatment (i.e. receiving news of poor response). This is likely to have a positive influence, as a number of studies have examined the effect of psychological interventions on ART outcomes with generally positive results. For example, Hämmerli et al.'s (2009) meta-analysis found psychological interventions were effective at improving ART pregnancy rates but did not reduce depression or anxiety. Chow et al. (2016) recently found evidence that psychosocial interventions improved psychological and pregnancy outcome in their critical review. Frederiksen et al. (2015) performed a meta-analysis on 39 studies and found significant effects of psychosocial interventions on ART clinical pregnancy and that reductions

in anxiety were associated with improvement in pregnancy rates. These findings indicate that attempts to manage and reduce psychological distress during ART can be successful in improving pregnancy outcome. Recent research has further highlighted the importance of psychosocial adjustment in women who went through treatment successfully (Toscano and Montgomery, 2009) and unsuccessfully (Gameiro and Finnigan, 2017). The psychological treatment and support needs of infertile patients who fail to fulfil their goal of parenthood has been previously described (Boivin et al., 2005). A recent systematic review and meta-analysis of the longer-term mental health of infertile patients who failed to become parents emphasizes the need for appropriately tailored psychosocial support for those individuals who eventually relinquish their parenthood goals (Gameiro and Finnigan, 2017).

The small number of studies included in this review is a limitation, particularly in the data analyses examining changes in levels of state anxiety and depression and its association with ART outcome. So, it is not possible to say with authority yet whether changes in levels of anxiety or depression are associated with ART outcome. Further, only a small number of studies included first-time ART patients (n = 5), with all the others including a mix of first-time ART patients and patients who have had previous unsuccessful treatment. This is a shortcoming because rates of depression and anxiety are known to increase after ART treatment failure (Milazzo *et al.*, 2016).

In conclusion, depression and state anxiety during ART treatment are associated with poor ART outcome, but there is no evidence that changes in the levels of anxiety and depression from baseline to during ART treatment are associated with ART outcome. However, the numbers of studies were small and more detailed empirical research is necessary to make a more definitive review. These findings help to frame future research questions and investigations and could help target psychological support during different stages of treatment. However, more detailed empirical research is necessary, to measure women's psychological functioning during the course of treatment and its association with ART outcome.

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REFERENCES

An, Y., Wang, Z., Ji, H., Zhang, Y., Wu, K., 2011. Pituitary-adrenal and sympathetic nervous system responses to psychiatric disorders in women undergoing *in vitro* fertilization treatment. Fertil. Steril. 6, 404–408.

An, Y., Sun, Z., Li, L., Zhang, Y., Ji, H., 2013. Relationship between psychological stress and reproductive outcome in women undergoing *in vitro* fertilization treatment: psychological and neurohormonal assessment. J. Assist. Reprod. Genet. 30, 35–41.

Boivin, J., Takefman, J.E., 1995. Stress level across stages of *in vitro* fertilization in subsequently pregnant and nonpregnant women. Fertil. Steril. 64, 802–810.

Boivin, J., Takefman, J., Braverman, A., 2005. Giving Bad News:'It's Time to Stop'. Assisted Reproduction in the Complicated Patient. Taylor and Francis, London, pp. 233–240.

Boivin, J., Griffiths, E., Venetis, C.A., 2011. Emotional distress in infertile women and failure of assisted reproductive technologies: meta-analysis of prospective psychosocial studies. BMJ 342, d223.

Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2005. Comprehensive meta-analysis version 2. Englewood, NJ. Biostat 104.

Chow, K.M., Cheung, M.C., I., Cheung, K., 2016. Psychosocial interventions for infertile couples: a critical review. J. Clin. Nurs. 15, 2101–2113.

Deeks, J., Bossuyt, P., Gatsonis, C., 2009. Cochrane handbook for systematic reviews of diagnostic test accuracy version 1.0. 0. Cochrane Collaboration.

Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455–463.

Eugster, A., Vingerhoets, A.J., 1999. Psychological aspects of *in vitro* fertilization: a review. Soc. Sci. Med. 48, 575–589.

Farquhar, C., Rishworth, J.R., Brown, J., Nelen, W.L., Marjoribanks, J., 2015. Assisted reproductive technology: an overview of Cochrane Reviews. The Cochrane Library.

Frederiksen, Y., Farver-Vestergaard, I., Skovgård, N.G., Ingerslev, H.J., Zachariae, R., 2015. Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: a systematic review and meta-analysis. BMJ Open 5, e006592.

Gameiro, S., Finnigan, A., 2017. Long-term adjustment to unmet parenthood goals following ART: a systematic review and meta-analysis. Hum. Reprod. Update 23, 322–337.

Gameiro, S., Boivin, J., Peronace, L., Verhaak, C.M., 2012. Why do patients discontinue fertility treatment? A systematic review of reasons and predictors of discontinuation in fertility treatment. Hum. Reprod. Update 18, 652–669.

Gourounti, K., Anagnostopoulos, F., Vaslamatzis, G., 2011. The relation of psychological stress to pregnancy outcome among women undergoing in-vitro fertilization and intracytoplasmic sperm injection. Women Health 51, 321–339.

Gressier, F., Letranchant, A., Cazas, O., Sutter-Dallay, A.L., Falissard, B., Hardy, P., 2015. Post-partum depressive symptoms and medically assisted conception: a systematic review and meta-analysis. Hum. Reprod. 30, 2575–2586.

Gürhan, N., Atici, D., Akyüz, A., Kisa, S., 2009. Association of depression and anxiety with oocyte and sperm numbers and pregnancy outcomes during *in vitro* fertilization treatment. Psychol. Rep. 104, 796–806.

Hämmerli, K., Znoj, H., Barth, J., 2009. The efficacy of psychological interventions for infertile patients: a meta-analysis examining mental health and pregnancy rate. Hum. Reprod. Update 15, 279–295.

Hashemi, S., Simbar, M., Ramezani-Tehrani, F., Shams, J., Majd, H.A., 2012. Anxiety and success of *in vitro* fertilization. Eur. J. Obstet. Gynecol. Reprod. Biol. 164, 60–64.

Karlidere, T., Bozkurt, A., Ozmenler, K.N., Ozsahin, A., Kucuk, T., Yetkin, S., 2008. The influence of emotional distress on the outcome of in-vitro fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI) treatment among infertile Turkish women. Isr. J. Psychiatry Relat. Sci. 45, 55.

Kushnir, V.A., Barad, D.H., Albertini, D.F., Darmon, S.K., Gleicher, N., 2017. Systematic review of worldwide trends in assisted reproductive technology 2004–2013. Reprod. Biol. Endocrinol. 15, 6.

Li, X.H., Ma, Y.G., Geng, L.H., Qin, L., Hu, H., Li, S.W., 2011. Baseline psychological stress and ovarian norepinephrine levels negatively affect the outcome of *in vitro* fertilization. Gynecol. Endocrinol. 27, 139–143.

Lintsen, A.M.E., Verhaak, C.M., Eijkemans, M.J.C., Smeenk, J.M.J., Braat, D.D.M., 2009. Anxiety and depression have no influence on the cancellation and pregnancy rates of a first IVF or ICSI treatment. Hum. Reprod. 24, 1092–1098.

Luppino, F.S., de Wit, L.M., Bouvy, P.F., Stijnen, T., Cuijpers, P., Penninx, B.W., Zitman, F.G., 2010. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch. Gen. Psychiatry 1, 220–229.

Maheshwari, A., Bhattacharya, S., Johnson, N.P., 2008. Predicting fertility. Hum. Fertil. (Camb.) 11, 109–117.

Matthiesen, S.M.S., Frederiksen, Y., Ingerslev, H.J., Zachariae, R., 2011. Stress, distress and outcome of assisted reproductive technology (ART): a meta-analysis. Hum. Reprod. 26, 2763–2776.

Metwally, M., Li, T.C., Ledger, W.L., 2007. The impact of obesity on female reproductive function. Obes. Rev. 8, 515–523.

Milazzo, A., Mnatzaganian, G., Elshaug, A.G., Hemphill, S.A., Hiller, J.E., Astute Health Study Group, 2016. Depression and anxiety outcomes associated with failed assisted reproductive technologies: a systematic review and meta-analysis. PLoS ONE 11, e0165805.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., PRISMA Group, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ b2535.

Nicholls, W., Devonport, T.J., Blake, M., 2016. The association between emotions and eating behaviour in an obese population with binge eating disorder. Obes. Rev. 17, 30–42.

Purewal, S., Chapman, S., van den Akker, O.A.B., 2017a. A systematic review and meta-analysis of psychological predictors of successful assisted reproductive technologies. BMC Res. Notes 10, 711.

Purewal, S., Chapman, S., van den Akker, O.A.B., 2017b. A systematic review and meta-analysis of lifestyle and body mass index predictors of successful assisted reproductive technologies. J. Psychosom. Obstet. Gynaecol. 1–17.

Qu, F., Wu, Y., Zhu, Y.H., Barry, J., Ding, T., Baio, G., Muscat, R., Todd, B.K., Wang, F.F., Hardiman, P.J., 2017. The association between psychological stress and miscarriage: a systematic review and meta-analysis. Sci. Rep. 7.

Rittenberg, V., Seshadri, S., Sunkara, S.K., Sobaleva, S., Oteng-Ntim, E., El-Toukhy, T., 2011. Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. Reprod. Biomed. Online 23, 421–439.

Saravelos, S.H., Wong, A.W., Kong, G.W., Huang, J., Klitzman, R., Li, T.C., 2016. Pain during embryo transfer is independently associated with clinical pregnancy in fresh/frozen assisted reproductive technology cycles. J. Obstet. Gynaecol. Res. 42, 684–693.

Smeenk, J.M.J., Stolwijk, A.M., Kremer, J.A.M., Braat, D.D.M., 2000. External validation of the Templeton model for predicting success after IVF. Hum. Reprod. 15, 1065–1068.

Sterne, J.A., Egger, M., 2001. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J. Clin. Epidemiol. 54, 1046–1055.

Stolwijk, A.M., Zielhuis, G.A., Hamilton, C.J.C.M., Straatman, H.M.P.M., Hollanders, J.M.G., Goverde, H.J., Van Dop, P.A., Verbeek, A.L.M., 1996. Pregnancy: prognostic models for the probability of achieving an ongoing pregnancy after in-vitro fertilization and the importance of testing their predictive value. Hum. Reprod. 11, 2298–2303.

Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., Thacker, S.B., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 283, 2008–2012.

Taguchi, S., Hayashi, T., Tada, Y., Kitaya, K., Funabiki, M., Iwaki, Y., Karita, M., Nakamura, Y., 2015. Do combined psychological stress examinations predict pregnancy outcome in an assisted reproductive technology program? Clin. Exp. Obstet. Gynecol. 42, 309–310.

Toscano, S.E., Montgomery, R.M., 2009. The lived experience of women pregnant (including preconception) post *in vitro* fertilization through the lens of virtual communities. Health Care Women Int. 30, 1014–1036.

Turner, K., Reynolds-May, M.F., Zitek, E.M., Tisdale, R.L., Carlisle, A.B., Westphal, L.M., 2013. Stress and anxiety scores in first and repeat IVF cycles: a pilot study. PLoS ONE 8, e63743.

Van Loendersloot, L.L., Van Wely, M., Limpens, J., Bossuyt, P.M.M., Repping, S., Van Der Veen, F., 2010. Predictive factors in *in vitro* fertilization (IVF): a systematic review and meta-analysis. Hum. Reprod. Update 16, 577–589.

Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P., 2009. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. (Accessed 19 October 2009).

Zaig, I., Azem, F., Schreiber, S., Gottlieb-Litvin, Y., Meiboom, H., Bloch, M., 2012. Women's psychological profile and psychiatric diagnoses and the outcome of *in vitro* fertilization: is there an association? Arch. Womens Ment. Health 15, 353–359.