Maternal psychosocial consequences of twins and multiple births following assisted and natural conception: A meta-analysis

Running Title: Meta-analysis of maternal distress following twins

Olga van den Akker[1*]Gianina-Ioana Postavaru[2], Satvinder Purewal[3]

[1]Department of Psychology, School of Science & Technology, Middlesex University, Hendon, London, NW44BT, UK.

[2]Centre for Sustainable Working Life, Birkbeck, University of London, Malet Street, Bloomsbury, London, WC1E 7HX, UK.

[3]Institute of Psychology, Faculty of Education, Health and Wellbeing, University of Wolverhampton, Wolverhampton, WV1 1AD, UK.

*Correspondence address. E-mail: O.vandenakker@mdx.ac.uk

Key words: Meta-analysis, multiple births, psychological, depression, distress.

Abstract:

The aim of this systematic review and meta-analysis is to provide new evidence on the effects of assisted reproductive technology (ART) multiple births on maternal mental health**.** A bibliographic search was undertaken using PubMed, PsycINFO, CINAHL, Science Direct.. The data extraction process was completed using the Cochrane Review Group's recommendations, the review was informed following PRISMA and MOOSE guidelines. Meta-analytic data were analysed using random effects models. Eight papers (data from 2993 mothers) were included. Mothers of ART multiple births were significantly more likely to experience depression (standardised mean difference d=.198, 95% CI .050-.0345, z=2.623, p = .009; heterogeneity I^2=36.47%, p=.146), and stress (standardised mean difference d=.177, 95% CI .049-.305, p= .007; heterogeneity I^2=.01%, p=.535) than mothers of ART singletons. No difference in psychosocial distress (combined stress and depression) (standardised mean difference d=.371, 95% CI -.153 - .895 p =.165; I^2=86.962%, p=.001) or depression between mothers of ART or naturally conceived (NC) multiple births were found (d =.152, 95% CI -.179 - .483: z=.901: p=.368; I^2 =36.918%, p =.208). In conclusion, mothers of ART multiple births were significantly more likely to have depression and stress than mothers of ART singletons, but were no different from mothers of NC multiples.

Key words: ART/ assisted reproductive technology / psychological distress / meta-analysis

Introduction

Multiple pregnancy has been recognised as the greatest health risk to both infant and mother following natural conceptions (NC) and assisted reproductive technology (ART), such as In Vitro Fertilization (IVF) (HFEA, 2009a). In order to lower the risks of multiple births through assisted conception, guidelines, elective single embryo transfer policies (eSET), and consensus statements have been introduced internationally (e.g. HFEA, 2009a, 2009b; One at a Time, 2015; Min et al., 2010; CDC, 2014; ASRM, 2012; ESHRE consensus statement 2002 (Land and Evans, 2003). Mandatory adoption of eSET in some countries resulted in significant reductions of multiple births (e.g. Bissonnette et al., 2011) and perinatal mortality (Sullivan et al., 2012)

Much research on multiple births has emphasised maternal and infant mortality and medical morbidity, particularly in ART multiples (Ezugwu and Van der Burg, 2015). Less research has focused on maternal stress during pregnancy and psychosocial morbidity following (particularly prematurely delivered) multiple pregnancies. According to the fetal programming hypothesis (Egliston et al., 2007), maternal stress during pregnancy can alter the development of the fetus, especially of the brain. Post partum, multiple births can lead to maternal isolation, depression and, in extreme cases, child abuse (Ombelet et al., 2005). Furthermore, evidence also suggests that ART multiple births are associated with greater psychological problems compared with ART singleton births (e.g., Olivenness et al., 2005; Ellison et al., 2005; Vilska et al., 2009), but there are exceptions (Sydsjo et al., 2008). The evidence linking increased risks for depression in mothers of twins is generally well supported for ART multiples (Vilska and Unkila-Kallio, 2010) and NC multiples (Ross

et al., 2011). Ross et al.'s (2011) systematic review reported that mothers of twins/multiples were likely to be at a higher risk for symptoms of postpartum depression. However, the authors did not clearly differentiate between the two possible control/comparison groups (mothers who conceived twins or multiples naturally and mothers who conceived ART singletons). Most of the available literature examined maternal psychological functioning after ART multiples, and there were insufficient data to perform meta-analysis on paternal psychological functioning after ART multiples (Vilska et al, 2009).

In studies comparing ART twins/multiples with NC twins/multiples, no differences in maternal psychological functioning have generally been found (e.g., Colpin et al.,1999; Vilska et al., 2009; Tully et al., 2003). Others have reported more psychological distress in mothers of ART twins/multiples than in mothers of NC twins/multiples (Baor et al., 2004; Yokoyama, 2003). These differences may be due to a higher risk of depression and marital decline in ART mothers (Klock, 2004). Research evolving around marital satisfaction among ART mothers of multiples and singletons is conflicting. While some studies report no difference between these two groups (Olivenness et al., 2005), others support the hypothesis that a multiple birth decreases marital satisfaction among ART mothers (Roca de Bes, 2009; 2011). Ellison et al. (2005) reported a similar tendency, although the findings were not statistically significant. However, it seems that some ART multiple mothers tend to cope well with the strain and do not divorce more often than mothers of singletons (Pinborg et al., 2003). Many previous reviews are now over 10 years old (Klock, 2004; Bryan, 2002), are narrative reviews (Vilska and Unkila-Kallio, 2010; McGrath et al., 2010), considered twins/multiples briefly (Hammarberg et al., 2008), focused

solely on depression as the outcome variable (Ross et al., 2011) and did not control for multiplicity (Gressier et al., 2015). There is a need for other psychological consequences of postnatal emotional adjustment to be examined to gain a better understanding of the complex and multifactorial nature of the postnatal psychological state of women who conceive using ART and have multiple births.

Therefore, the aim of this study is to reconcile the previous research literature on the psychological consequences of twins/multiple births after ART. Given the clinical implications of ART multiple births, this meta-analytic and review process extrapolates the research evidence by comparing depression, anxiety and stress of ART twins/multiples mothers versus NC twins/multiples mothers and ART twins/multiples mothers versus ART singleton mothers. Following the theoretical background, the meta-analysis was based on the following hypotheses:

(1) Mothers of ART twins/multiples will report more psychological problems (depression, anxiety and stress) than mothers of ART singletons.

(2) NC twins/multiples mothers will report fewer psychological problems than ART twins/multiples mothers.

Materials and Methods

Searches were carried out by all three investigators, who all had previous experience of systematic reviewing and meta-analytic techniques.

Search strategy

This systematic review and meta-analysis was organised and structured according to the PRISMA and MOOSE guidelines (Stroup et al., 2000). A bibliographic search for publications was undertaken using PubMed, PsycINFO, CINAHL and Science Direct. Dates of publication ranged from 1976 to September 2014. The search was

augmented with hand searches of articles cited in reference lists and from relevant review papers (e.g. Ross et al., 2010). Most of the databases included the following keywords: ("postpartum" OR "postnatal" OR "pregnan*" OR "perinatal" OR "childbirth" OR "obstetr*" OR "labour" OR "puerperal" OR "parturition" OR "parity" OR "maternal") AND ("multiple births" OR "twins" OR "triplets") 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 "stressors" OR "mental health" OR "mental illness" OR "mood disorder" OR "baby blues" OR “postpartum depression”) AND (“IVF” OR “intracytoplasmic” OR "intracytoplasmic sperm injection" OR "in vitro fertilization" OR “ICSI” OR "assisted reproduct*" OR "ovulation induction" OR "embryo implantation" OR "artificial insemination" OR "sperm injections" OR "infertility" OR "fertility treatment").

Study selection

Studies were included if they:

- compared depression, anxiety or stress of ART twins/multiple birth mothers versus ART singleton birth mothers;
- compared depression, anxiety or stress of ART twins/multiple birth mothers versus NC twins/multiple birth mothers.

Studies encompassing validated measures of depression, anxiety or stress, such as State-Trait Anxiety Inventory (Spielberger and Gorsuch, 1983), and Cohen’s Perceived Stress Scale (Cohen et al., 1983) and reporting continuous or categorical data (either self-report or observer rated) were included. Psychological distress was measured postpartum with no initial restriction for time. However, time was used in

the sensitivity data analysis. We were interested in any depression, not just post-natal depression, defined as onset within 5 (DSM IV) or 6 weeks post-delivery (ICD-10) to any point in the first year (Pearlstein et al, 2009). Papers presenting original data (e.g. journal articles and conference abstracts) were included.

Studies were excluded if they were qualitative, case studies, reviews, reanalyses of data presented elsewhere, did not report standardised measurements, did not include a suitable comparison group and were not published in English. Another exclusion criterion was the impossibility to calculate effect sizes for variables. Where necessary, authors were contacted for additional information regarding their data. To avoid multiple publication bias (Higgins and Green, 2011) only the paper that reported the highest number of participants was included, if authors used the same data in different studies (selection of paper from multiple reports is noted in Tables 1 and 2).

Data screening and extraction

GP and OvdA independently screened all titles. GP, OvdA and SP independently screened all abstracts and full-text papers retrieved from the searches using PRISMA guidelines (Moher et al., 2009). The selection of studies was informed by the inclusion/exclusion criteria. All authors independently extracted and cross checked the data from each included study. Any disagreement relating to study selection and data extraction was fully resolved by authors through discussion to achieve total consensus.

Psychological data (stress, anxiety and depression) were extracted and analysed separately. In case of insufficient number of studies, data were combined to create a

psychological ‘distress' score. Due to small sample sizes in studies of mothers of triplets, data were combined into 'multiples' score if studies reported psychological scores from twins and triplets separately. Therefore, two comparison groups were used (ART multiples versus ART singletons and ART multiples versus NC multiples). Additionally, available data on publication date, treatment location, *sociodemographic* (average age, average number of married mothers, average relationship length, average socio-economic status, median level of education, ethnicity -percentage of white mothers- and average number of women reporting religiosity), *medical* (average parity, average first or multiple cycles, average duration of infertility, use of donor sperm or oocytes -any versus none-, average duration of pregnancy, type of delivery -natural or C-section- and average percentage of medical complications for child(ren)) and *psychosocial* characteristics of mothers (average previous maternal mental health, average reported quality of marital relationship and reported social support) were extracted.

Quality Assessment

The quality criteria checklist included the recommendations of the Cochrane Collaboration (Deeks, 2009) and the Newcastle-Ottawa quality assessment scale (Wells et al., 2010). Each study was initially independently assessed (SP and OvdA). Then the results were collated and discussed. Full consensus was reached with regard to the full-text papers included in the meta-analysis.

- Selection: Points were awarded if: 1) the sample was *representative* (more than 80% eligibility to participate or participation rate or sample size higher than 300, according to Biovin et al., 2011) or *somewhat representative* of the ART population (more than 60% of eligible patients were invited and accepted

to participate); 2) the selection of the control cohort was drawn from the same community as the main treatment cohort; 3) the study demonstrated that 'distress' (depression, state anxiety or stress) was not present at start of study.

- Comparability: Points were awarded if: 1) the study controlled for confounding variables, such as age, previous maternal mental health, parity and first cycle; 2) the study controlled for any other additional factors.
- Outcome: Points were awarded if: 1) there was adequate follow up of cohorts (if they had completed a follow up or participants lost to follow up were <=20% and unlikely to introduce bias).

A study was considered good quality if it scored higher than four points. The maximum a study would achieve was six points.

Data analyses

Data were analysed by SP and GP using the Comprehensive Meta-Analysis software program (Borenstein et al., 2005). Stress, anxiety or depression scores (e.g. events –presence of depression-, means) were converted into standardised mean differences and used to compare ART twins/multiple birth mothers with mothers of NC twins/multiples; and mothers of ART twins/multiples with mothers of ART singletons. A weighted effect size was calculated for all studies by using a random effects model. Timing of psychological assessment and quality ratings were used in the sensitivity analyses to examine whether effects were robust under different methodological assumptions. That is, we examined the effects of study quality and timing of psychological measurement on effect size results. A small number of studies and heterogeneity in study effect sizes (I^2 statistic) would prevent an analysis of the moderator effects. However, in case of heterogeneity, moderator analysis

could have been performed if more than 10 studies provided data on the putative moderating variables (Deeks et al., 2009). Since insufficient studies provided relevant data on variables for inclusion in moderator analysis, this could not be run. Finally, publication bias was tested by using Duval and Tweedie's trim and fill method to impute studies where evidence of asymmetry was present (Duval and Tweedie, 2000). The significance of these effects was examined by using Egger's t-test (Egger et al., 1997).

Results

Search Results

The screening process is summarised in the PRISMA flow chart (Figure 1). Titles of 1346 records were screened out of which 111 were duplicates. A total of 1235 titles were reviewed. Of these, 1075 did not meet the inclusion criteria. Therefore, 160 abstracts were reviewed, which led to the selection of 80 full text articles. Of these, 37 papers included irrelevant comparison groups (e.g. Baor et al., 2012; Boivin et al., 2009, etc.), 2 papers were reviews (e.g. Spillman, 1987), 3 studies were qualitative (Ellison et al., 2003; Garel et al., 1992; Garel et al., 1997), one paper had incomplete data for analysis and another one was not in English (Monset-Couchard et al., 1998). No assessment of appropriate psychological variable was found in 7 papers (e.g. Gameiro et al., 2011; Hammarberg et al., 2008 etc.). Other papers were excluded for irrelevant data collection time points (Lewis et al., 2011; Fisher et al., 2013 etc.), use of only singleton groups or data reported as adjusted scores or mothers and fathers data not separated. The studies specifically on fathers we identified used combined data sets and did not separate data for mothers and fathers. For example, Baor et al., (2004) used a mixed group (75 parents of twins: 38 ART and 37 SC) with no gender

difference in terms of parenting stress. Colpin et al. (1999) included a mixed group of 103 families of twins. Cook et al., (1998) presented data on 26 families of twins and Golombok et al. (2007) used 28 IVF families with triplets and 30 IVF families of singletons in their paper. Where gender differences in parental postpartum mental health are reported, too few control for parent gender and multiplicity separately (Vilska et al, 2009) to be included in the meta-analysis. In case of multiple reporting, papers using the highest sample size were included. For example, Olivennes (2005) was selected over Freeman et al. (2007) and Golombok et al. (2007). Sheard's (2007) paper was selected over Glazebrook et al. (2004). Finally, 8 papers met the inclusion criteria for the meta-analysis. Authors of original papers were contacted via e-mail by OA for additional data. When necessary, discussions took place to clarify the type of the data needed in our study. Three authors (C. Sheard, M. Roca-de Bes and S. Vilska) provided supplementary data to be included in the meta-analysis.

INSERT FIGURE 1 ABOUT HERE

ART multiple births versus ART singleton births

Study characteristics

Six studies were included in the ART multiple births versus ART singleton births meta-analysis (Table 1). Of these, four studies measured stress and six measured depression. The first hypothesis was partially tested as there were insufficient data to compare the levels of anxiety reported by mothers of ART multiples and mothers of ART singletons. Data from 1732 mothers were included in this meta-analysis. Response rates for questionnaires and retention for follow-up studies were satisfactory with only one study reporting a response rate below 50% (Roca de Bes

et al., 2011). Time of measurement varied across studies. Sheard et al. (2007) measured depression at six weeks postpartum. Roca de Bes et al. (2009; 2011) collected data at six months to four years postpartum. Ellison et al. (2005) examined depression and stress at one to four years postpartum. Olivennes et al. (2005) provided data for the time between two and five years postpartum while Vilska et al. (2009) collected data at two months and 1 year post-partum (mean 14 months postpartum). Finally, for all, but one of the studies, the quality was high (ranged between 3 and 5 points).

Sites: Studies were conducted in United States (Ellison et al., 2005) and Europe (France: Olivennes et al., 2005; Spain: Roca de Bes et al., 2009; 2011; United Kingdom: Sheard et al., 2007; Finland: Vilska et al., 2009).

Measures: Data were obtained from self-administered questionnaires assessing depression and stress, such as: CES-D (Ellison et al., 2005; Roca de Bes, 2009; 2011), PSI (Olivennes, 2005), Cohen Perceived Stress (Roca de Bes, 2009; 2011), EDS (Olivennes, 2005; Sheard et al., 2007) and GHQ-36 (Vilska et al., 2009).

Participants' characteristics: Comparisons by multiplicity indicated that there were no statistically significant differences between mothers of ART singletons and mothers of ART multiples in maternal education, pretax household income levels, ethnicity (Ellison et al., 2005), maternal age (Ellison et al., 2005; Sheard et al., 2007; Roca de Bes, 2011), marital status (Roca de Bes, 2011) or regarding children without siblings (Roca de Bes, 2011). However, in some studies, singleton mothers were older than multiple mothers and reported higher levels of employment (Olivennes et al., 2005). For the majority of the respondents (72% in Ellison et al., 2005; 86% in Sheard et al., 2007) this was their first full term pregnancy. Similarly, the majority of mothers of ART singletons (90.2%) and ART multiples (76.7%)

294 included in the study of Roca de Bes et al., (2009) were primiparous (85.7% of 37
295 mothers of twins and 40% of 9 mothers of triplets).

296 INSERT TABLE 1 ABOUT HERE

297

298 While scoring above 12 on the EPDS cannot be seen as indicating that a mother is
299 experiencing post-natal depression, this tool is useful to detect those mothers that
300 experience clinically significant psychological symptoms. In Roca de Bes's (2009)
301 study, although perceived stress and depression were higher in the mothers of ART
302 multiples the difference was not statistically significant. A trend towards significance
303 was also identified for ART multiple birth mothers on the EPDS with 15.6% scoring
304 above 12 compared with 5.9% of the mothers of ART singletons in Sheard et al.'s
305 (2007) study. This trend was associated with a difficult infant (Sheard et al., 2007), a
306 multiple birth (Ellison et al., 2005; Sheard et al., 2007) and child-related stressors
307 (Vilska et al., 2009). In line with this, mothers of ART multiple births reported feeling
308 significantly more socially marked and devalued by their treatment decision than
309 their ART singleton counterparts (Ellison et al., 2005; Roca de Bes, 2009; 2011).
310 Although some studies included in this meta-analysis revealed that there was no
311 difference between mothers of ART multiples and mothers of ART singletons in
312 terms of assistance received from family members (Olivennes et al., 2005), families
313 with ART multiples found it more difficult to cover basic needs (Roca de Bes, 2009;
314 2011). In addition, a significantly higher proportion of mothers of ART twins than
315 mothers of ART singletons found parenting difficult (Olivennes et al., 2005; Ellison et
316 al., 2005; Roca de Bes, 2009). Similarly, there was a significant difference between
317 mothers of ART twins and mothers of ART singletons in the amount of pleasure they
318 obtained from their child, with fewer mothers of twins than mothers of singletons

reporting feelings of great pleasure (Olivennes et al., 2005). Child-related stressors referred to child development and health problems in these studies. ART multiple birth children had greater health and developmental problems than their ART singleton counterparts in two studies (Olivennes etal., 2005; Roca de Bes, 2011), but the difference was non-significant in two other studies (Ellison et al., 2005; Roca de Bes, 2009). In Olivennes et al.' study (2005), 10.7% of ART twins and 7.3% of ART singletons obtained scores above cut-off; these scores were in line with the expected value of 10% for the general population and were not significantly different from each other.

Depression meta-analysis:

Six studies reported data on depression in 1732 mothers in the post-natal period (Ellison et al., 2005; Olivennes et al., 2005; Roca de Bes et al., 2009; Roca de Bes et al., 2011; Sheard et al., 2007 and Vilska et al., 2009). Data supported the prediction that mothers who conceived multiples through ART were significantly more likely to experience depression than mothers who conceived singletons through ART (standardised mean difference d =.198, 95% CI .050-.0345, z =2.623, p = .009, with moderate levels of non-significant heterogeneity I^2 =36.467%, p =.146). See Figure 2 for a forest plot.

INSERT FIGURE 2 ABOUT HERE

No publication bias was revealed. Egger's regression intercepts were non-significant, the funnel plot was symmetrical (Figure 2) and Duval and Tweedie's trim-and-fill analyses indicated that no additional studies were needed. Sensitivity analysis showed a significant difference between the effect size of results taken at or before 1

year postpartum to those taken over 1 year (Q = 4.664, df =1, p =.031). The effect size for depression at =<1 year was stronger (d =.389; k =2: 95% CI .180-.599: z =3.640, p <.00; with low levels of heterogeneity I^2<.01%, p =.564) than for depression assessed at >1 year (d =.122, k =4: 95% CI .000-.244, z =1.959, p =.050; with low levels of heterogeneity I^2<.01%, p=.411). However, both effect sizes remained significant. As the number of studies was small (two studies with =1<year depression data), these data must be treated with some caution. Furthermore, meta-regression indicated no evidence for the effect of study quality of results.

Stress meta-analysis:

Four studies reported data on stress in 1199 mothers (Ellison et al., 2005; Olivennes et al., 2005; Roca de Bes et al., 2009 and Roca de Bes et al., 2011). Data supported the prediction that mothers who conceived multiples through ART were significantly more likely to experience stress than mothers who conceived singletons through ART (standardised mean difference d =.177, 95% CI .049-.305, p = .007; heterogeneity I^2 =.01%, p =.535). See Figure 3 for a forest plot.

INSERT FIGURE 3 ABOUT HERE

No publication bias was found. Egger's regression intercepts were non-significant, the funnel plot was symmetrical (Figure 3) and Duval and Tweedie's trim-and-fill analyses indicated that additional studies were not needed. As none of these studies provided data before 1 year postpartum, sensitivity analysis on time of assessment was not performed. Further, meta-regression indicated no evidence for the effect of study quality of results.

ART multiple births versus NC multiple births

Study characteristics

Three studies were included in the ART multiple births versus NC multiple births meta-analysis (see Table 2). One study measured stress (Boar and Soskolne, 2010), while the other two depression (Yokoyama et al., 2003; Vilska et al., 2009). To test the second hypothesis and given the small number of studies in this comparison, stress and depression scores were collated into a general 'distress score'. This decision was justified with the neurocognitive hypothesis stating that depression and anxiety are involved in the dysregulation of the stress-induced hypothalamus – pituitary–adrenocortical axis (HPA) (Reul and Holsboer, 2002; Sandi and Richter-Levin, 2009). Depression scores were also analysed independently. Data from 1261 mothers were included in the distress meta-analysis. Response rates for Baor and Soskolne (2010) and Vilska et al.'s (2009) studies were good. Boar and Soskolne (2010) assessed stress at six months postpartum, while Vilska et al. (2009) and Yokoyama et al. (2003) examined depression at two months and three years postpartum respectively. Study quality for Boar and Soskolne (2010) and Vilska et al. (2009) was good. Yokoyama et al.'s (2003) study had a satisfactory quality (score 3). Since anxiety was measured only in one study, (see Vilska et al., 2009 in Table 2), it was not included in the analysis.

INSERT TABLE 2 ABOUT HERE

Sites and Measures: Data were collected in Europe (Finland: Vilska et al., 2009) and Asia (Japan: Yokoyama, 2003; Israel: Baor et al., 2010) through self-

administered measures assessing depression and stress, such as: SF PSI (Baor et al., 2010), GHQ-36 (Vilska et al., 2009) and DSM IV (Yokoyama, 2003).

Participants' characteristics: ART multiple birth mothers were older than NC mothers of multiples (Yokoyama, 2003). The pattern of psychological distress (combined anxiety and depression) was associated in these studies with child-related stressors (Yokoyama, 2003; Vilska et al., 2009; Baor et al., 2010) and employment status (Baor et al., 2010). ART mothers were more delighted when informed of a multiple pregnancy than mothers of NC multiples (Yokoyama, 2003). Additionally, in Yokoyama's study (2003), ART mothers reported lower levels of anxiety about nursing the infants and economic concerns after delivery than mothers of NC.

Stress and Depression meta-analysis:

The findings for the combined 'distress score' for 1261 mothers did not support the second hypothesis of the meta-analysis. They indicated that mothers who conceived multiples through ART did not score differently on psychological distress compared with mothers who conceived multiples naturally (standardised mean difference d=.371, 95% CI -.153 - .895: z=1.387: p =.165; with significant heterogeneity I^2=86.962%, p=.001). When only depression data were used (n=1075 mothers), the results were also non-significant, with non-significant heterogeneity (standardised mean difference d =.152, 95% CI -.179 - .483: z=.901: p =.368; I^2 =36.918%, p =.208) (see Figures 4 and 5 for forest plots).

INSERT FIGURES 4 AND 5 HERE

No publication bias was found for both depression and distress studies. Egger's regression intercepts were non-significant, the funnel plots were symmetrical (Figures 4 and 5) and Duval and Tweedie's trim-and-fill analyses indicated no need for additional studies.

Discussion

The aim of this meta-analysis was to reconcile the previous research literature on the psychological consequences of twins/multiple births after ART. Eight studies were included to examine depression, anxiety and stress of mothers of ART twins/multiples versus mothers of NC twins/multiples and mothers of ART twins/multiples versus mothers of ART singletons. Two hypotheses informed the analytic process. The first hypothesis was partially tested, as there were not enough data on anxiety for mothers of ART multiples and mothers of ART singletons to run the analysis. However, results supported the predictions for depression and stress scores. To test the second hypothesis we adopted the methodological strategy to combine scores on stress and depression in the data analysis with ART multiples and NC multiples, given the limited number of studies. Results did not support the second prediction.

Strengths and Weaknesses

Despite its contribution to knowledge, this meta-analysis has some limitations. Although the overall number of studies was small, the sample sizes were generally good. The number of participants in two (mothers of ART singletons versus mothers of ART multiples - depression and stress analysis; ART multiple births versus NC multiple births - depression and combined stress analysis) of the four datasets

exceeded 1000 each. This allowed for acceptable comparisons to be made. Given the scarce number of studies and the lack of heterogeneity, moderator effect analysis could not be run (Deeks et al., 2009). As a history of previous depression is one of the highest risk factors for postnatal depression (Sutcliffe and Derom, 2006; Fisher and Stocky, 2003), such an analysis would have allowed the examination of the effects of baseline depression on depression in the postpartum. Most studies did not include baseline measurements of psychological distress, therefore, baseline measurement was not included as an essential criterion for study selection. Although reliable and valid measures of psychological constructs were used, a distinction should be made between these in terms of their theoretical grounds, as a combination of generic and specific scales were included. For example, parenting stress as measured by the PSI (Olivennes, 2005) is substantively and theoretically distinct from generalized stress as measured by the Cohen Perceived Stress (Roca de Bes, 2009; 2011), and thus these two should not be confounded. In addition, a distinction should be made between depression measured by generic scales such as the General Health Questionnaire (GHQ-36 in Vilska et al., 2009) or the Epidemiological Studies Depression Scale (Ellison et al., 2005; Roca de Bes, 2009; 2011) and by the Edinburgh postnatal depression scale (EPDS) (Olivennes, 2005; Sheard et al., 2007). However, as previous studies indicate, there is normally a high degree of overlap between general depression scales and postnatal depression scales (e.g. EPDS) (Gaynes et al., 2005). De Beurs (2004), for example, used items on the Brief Symptom Inventory, while in other studies GHQ anxiety and depression (Goldberg, 1972) were combined with state and trait anxiety (Spielberger et al, 1970; Rondo et al., 2003). Validated measures of depression, anxiety and emotional

(psychological) subscales from QoL questionnaires (Veltman-Verhulst, 2012) were used in combination too.

Our methodological strategy to combine stress and depression into a ‘distress score’ was supported by the tripartite model of anxiety and depression (Clark and Watson, 1991) and neurocognitive theories that suggest that similar pathways are involved in the three constructs (Reul and Holsboer, 2002). Accordingly, general distress, physiological hyperarousal (specific anxiety) and anhedonia (specific depression) are components of the diagnosis of mixed anxiety-depression. Increased concentrations of corticotropin-releasing hormone (CRH) in the cerebrospinal fluid have been reported in both anxiety and depression (Boyer, 2000). CRH plays a central role in the regulation of the hypothalamic-pituitary-adrenal (HPA)-axis, i.e., the final common pathway in the stress response (Swaab et al., 2005). A similar design was used in a previous meta-analysis that combined anxiety and depression, the author arguing that these are “reliably related to stress induced activation of the hypothalamic-pituitary-adrenal axis" (Boivin et al. 2011). However, as these components can be differentiated on the basis of their specific factors, we recommend some caution in terms of the implications of our findings.

Our results indicate that depression and stress are more likely to occur after ART multiple births compared with ART singleton births, but the mechanism underpinning this process is unclear, given the constrains imposed by the available data upon this meta-analysis. This review provides convincing evidence that more research is necessary to tease out factors that may influence psychosocial consequences of ART and multiplicity, including previous mental health problems. No publication

biases were found for any of the meta-analyses of the psychological components included in the study.

Generalization of the findings

Since previous research has shown that ART treatment itself can be stressful (Eugster and Vingerhoets, 1999; Williams et al., 2007), we carried out further meta-analyses comparing mothers of NC multiples with ART multiples in an attempt to tease out the effect of multiples from the effects of ART. Only three studies (Baor et al., 2010; Vilska et al., 2009; Yokoyama et al., 2003) could be used in the comparison. The results show that there might be something particularly stressful about having multiple births, regardless of mode of conception. It is possible that there are specific effects of premature births, more common in multiple births, although we could not find sufficient data to support this. Premature multiple birth infants are often diagnosed with health problems such as respiratory and neuro-developmental difficulties or disabilities and require extended and frequent hospitalization (Blickstein, 2002; 2003). Other factors such as difficulty establishing breastfeeding, and physical recovery (Fisher and Stocky 2003) in parents of multiples may also be responsible. Our meta-analysis showed no effect of mode of conception on depression and distress scores. These findings support Klock's review (2004) on the psychological adjustment to twins after infertility, indicating that mothers of multiples are likely to be more vulnerable to depression. Contrary to Ross et al's (2011) systematic review and Gressier et al.'s (2015) meta-analysis, other authors have reported that ART is stressful (Eugster and Vingerhoets, 1999; Williams et al., 2007). Increased risks of premature and low birth weight babies in ART twins compared with NC twins, after accounting for confounders, have been

reported in a previous meta-analysis of 12 studies (McDonald et al., 2010), and this needs further study. However, this meta-analysis focused on ART versus NC twin perinatal outcomes.

Alternative explanations for the results

We cannot conclude that ART multiple births lead to stress and depression (Ross et al, 2011). However, different potential explanations for higher psychological problems in ART multiple birth mothers have been provided previously. It has been suggested that infant temperament may combine with other vulnerability factors to increase the risk of depression (Cutrona and Troutman, 1986; Murray et al., 1996). It is also possible that ART multiple birth mothers are more distressed or more vulnerable to distress during pregnancy (e.g. age, having multiple embryos implanted and more difficult pregnancies or not being able to afford multiple rounds of IVF, according to van Balen et al., 1996) and in the postpartum (Roca de Bes et al., 2009; Sutcliffe and Derom, 2006; Fisher and Stocky, 2003). In addition, maternal prenatal distress is associated with low birth weight and prematurity (Rondo et al., 2003), although ART treatment itself has been reported to lead to little or no increased risk for post-partum depression (Ross et al., 2011; Gressier et al., 2015). Therefore, ART multiple birth mothers may not be completely comparable with the mothers of ART singleton cohorts.

Finally, the studies included were mainly performed in Europe (France: Olivennes et al., 2005; Spain: Roca de Bes et al., 2009; 2011; United Kingdom: Sheard et al., 2007; Finland: Vilska et al., 2009), with three studies from different countries/continents (US - Ellison et al., 2005; Japan - Yokoyama, 2003; and Israel -

Baor et al., 2010). The amount of state support offered to women during and after pregnancy has an impact on maternal and child health and mental health outcomes and different countries have different policies on maternal and child health support (International Labour Organization 2014). For example, the UK offers comprehensive maternity protection, with 365 maternity leave days, whereas the US only offers 84 maternity days and Japan with 98 days (International Labour Organization 2014). Unfortunately, with the limited number of studies, it is difficult to comment on whether differing national policies on maternal and child health (and childcare) has an impact on maternal psychological functioning after multiples. However, more research is needed worldwide to investigate this and possibly develop an international framework to support multiple families better.

Implications of the results

We strongly recommend that the clinical implications of ART specific multiple births should be explored further because: a) post-natal distress is likely to co-exist with previous pregnancy distress (Scottish Intercollegiate Guidelines Network, 2002); b) the consequences of distress in pregnancy are known to affect fetal growth (Henrichs et al., 2009); c) prematurity and low birth weight are important determinants of neonatal mortality (Shinwell et al., 2015) and neonatal, infant and childhood morbidity (de Kleine et al., 2007); d) the incidence of prematurity in mothers with comorbid anxiety and depression is greater than in non-depressed mothers (Field et al., 2010); and e) the consequences of maternal depression and distress in the first years following delivery affect mothers' interaction with their babies, which in turn is known to alter their cognitive, social and emotional development (Murray et al., 1999). Taken together, these effects are complex and

566 likely to pose considerable and serious public health concerns (Black and
567 Bhattacharya, 2010).
568
569 **Guidelines for future research**
570 One of the aims of this meta-analysis was to compare levels of depression in ART
571 and NC multiple births mothers. There was a dearth of research into men's
572 psychological health and insufficient paternal data within multiple/ singleton; ART /
573 NC groups. Given the scarce identified evidence that was available even in women,
574 it can be concluded that the psychological consequences of multiple births
575 specifically and ART generally are understudied (van den Akker, 2013). Vilska et al.
576 (2009) reported 1<=year depression data and found no difference between mothers
577 of ART multiples and mothers of NC multiples, while Yokoyama (2003) found a
578 greater level of depression in ART multiple births mothers than NC multiple births
579 mothers >1 year postpartum. Our findings suggest the need of more research on the
580 psychological consequences of multiple births and assisted reproduction to allow
581 more comprehensive meta-analyses involving moderating variables. Such an effort
582 would contribute to the explanation and clinical implications of the associations found
583 in our meta-analysis in terms of depression and stress in ART multiple births
584 mothers compared with ART singleton births mothers and NC multiple births
585 mothers. Personality characteristics, such as neuroticism and specific coping
586 strategies, for example, have recently been identified as positively associated with
587 ART distress (Rockliff et al., 2014). The same systematic review indicated that
588 positive emotional states were rarely reported (Rockliff et al., 2014). The relative
589 contributions of distress in pregnancy (which could not be included in our meta-
590 analysis) and the different etiological factors (biological or psychological) to describe

mechanisms for distress and depression in the first years' post-partum remain elusive. However, extrapolating differences within populations is important, thus allowing for effectively targeted treatment (Dennis et al., 2005). It can be still argued that psychological research is lagging behind ART practice.

Conclusion

Mothers of ART multiple births exhibit significantly more stress and depression compared with mothers of ART singleton births. Methodological and clinical features failed to explain the effect size variations. Heterogeneity was small and study quality had no effect. Based on the results of our meta-analysis, and bearing in mind the limitations described, clinicians should be aware of the likelihood of stress and depression in mothers of multiples and women undergoing ART. Such data should be used to deter multiple embryo transfers and encourage eSET, given the clear evidence for the effects in the first 2 years post-partum. Finally, the effects for depression were stronger at <=1 year postpartum than at >1 year postpartum, suggesting that women need more support to cope with multiples following the first year post-delivery. Postnatal depression is more common at 1<= postpartum than after the first year and its occurrence in ART multiple births may be underplayed because of their increased efforts to have a baby and the assumption that they will be happy and able to cope.

Disclosure of funding Source

OvdA (PI) and SP (CI) received a grant from the British Academy: grant number SG132634

Acknowledgements

We are grateful for the useful comments made to the analysis by Dr Sarah Chapman.

Authors' roles

OA and SP conceptualised the review. OvdA, SP and GP searched databases, selected articles and performed the data extraction. SP and GP performed the statistical analysis. OvdA and SP took the lead in writing the review, and all authors approved the final version of the article.

Declaration of interests

The authors have no interests to declare.

References

van den Akker, O.B.A.2013. For your eyes only: Bio-behavioural and psycho-social research priorities. Hum. Fertil. 16(1), 89–93

American Psychiatric Association (ed). 1994.Diagnostic and Statistical Manual of Mental Disorders (DSM IV). American Psychiatric Press. Washington, DC, pp. 720–721.

American Society for Reproductive Medicine ASRM (2012) https://www.asrm.org/uploadedFiles/ASRM_Content/News_and_Publications/Practice_Guidelines/Committee_Opinions/eSET-nonprintable.pdf

Van Balen F., Naaktgeboren, N., Trimbos-Kemper, T.C. 1996. In-vitro fertilization: the experience of treatment, pregnancy and delivery. Hum Reprod.11,95–98.

Baor, L., Bar-David, J., Blickstein. I. 2004. Psychosocial resource depletion of parents of twins after assisted versus spontaneous reproduction. Int J Fertil Womens Med.49(1),13-8.

Baor, L., Soskolne, V. 2010. Mothers of IVF and spontaneously conceived twins: a comparison of prenatal maternal expectations, coping resources and maternal stress. Hum Reprod. 25(6),1490-6.

Baor, L., Soskolne, V. 2012. Mothers of IVF Twins: The Mediating Role of Employment and Social Coping Resources in Maternal Stress. Women & Health. 52(3).

Beck, A. T., Steer, R. A., Brown, G. K. 1996. Manual for the beck depression inventory-II. TX: Psychological Corporation, San Antonio

De Beurs, E. 2004. Brief Symptom Inventory .Handleiding (Manual). Pits Publishers: Leiden.The Netherlands.

Bissonnette, F., Phillips, S.J., Gunby, J., Holzer, H., Mahutte, N., St-Michel, P., et al .2011. Working to eliminate multiple pregnancies: A success story in Québec. Reprod Biomed Online. 23. 500–4.

Black, M., Bhattacharya, S. 2010. Epidemiology of multiple pregnancy and the effect of assisted conception. Sem. in Fetal and Neonat. Med.15. 306-312.

Blickstein, I. (2002). Cerebral palsy in multifoetal pregnancies. Developmental Medicine & Child Neurology, 44, 352-355.

Blickstein, I., & Keith, L. (2003). Outcome of triplets and high-order multiple pregnancies. Current Opinion in Obstetrics & Gynecology, 15, 113-118.

675 Boivin, J., Griffiths, E., Venetis, C. A. 2011. Emotional distress in infertile women and
676 failure of assisted reproductive technologies: meta-analysis of prospective
677 psychosocial studies. BMJ. 342: d223.
678
679 Boivin, J., Rice, F., Hay, D., Harold, G., Lewis, A., van den Bree, M.B., Thapar, A.
680 2009. Associations between maternal older age, family environment and parent and
681 child wellbeing in families using assisted reproductive techniques to conceive. Soc.
682 Sci. Med. 68(11), 1948–1955.
683
684 Borenstein, M., Hedges, L., Higgins, J., Rothstein, H. 2005. Comprehensive meta-
685 analysis version 2, NJ: Biostat, Englewood
686
687 Boyer, P. 2000. Do anxiety and depression have a common pathophysiological
688 mechanism? Acta Psychiat. Scand. 102(406), 24–29,
689
690 Bryan, E. 2002. Educating families, before, during and after a multiple birth**.**
691 SeminNeonatol. 7(3). 241-6.
692
693 Centre for Disease Control CDC. 2014. National Center for Chronic Disease
694 Prevention and Health Promotion, Division of Reproductive Health.
695 http://www.cdc.gov/art/patientResources/transfer.html accessed 25/09/2015.
696

697 Clark, L. A., Watson, D. 1991. Tripartite model of anxiety and depression:
698 psychometric evidence and taxonomic implications. J Abnorm Psychol. 100(3), 316-
699 36

700

701 Cohen, S., Kamarck, T., Mermelstein, R. 1983. A global measure of perceived
702 stress. J. Health Soc. Beh. 385-396.

703

704 Colpin, H., de Munter, A., Nys, K., Vandemeulebroecke, L. 1999. Parenting stress
705 and psychosocial well-being among parents with twins conceived naturally or by
706 reproductive technology. Hum. Reprod. 4 (12):3133-3137.

707

708 Cutrona, C.E., Troutman, B.R. 1986. Social support, infant temperament and
709 parenting self-efficacy: a mediational model of postpartum depression. Child
710 Dev.;57. 1507–1518.

711

712 Deeks, J., Bossut, P., Gatsonis, C. 2009. Cochrane Handbook for Systematic
713 Reviews of Diagnostic Test Accuracy. In (ed). Book Cochrane Handbook for
714 Systematic Reviews of Diagnostic Test Accuracy. The Cochrane Collaboration, City.

715

716 Dennis, C.L. 2005. Psychosocial and psychological interventions for prevention of
717 postnatal depression: systematic review.BMJ.331:15

718

719 Duval, S., Tweedie, R. 2000. Trim and fill: A simple funnel-plot-based method of
720 testing and adjusting for publication bias in meta-analysis. BIOMETRICS.56: 455-
721 463.

Egger, M., Davey, G., Smith,GD., Schneider, M., Minder, C. 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ.315, 629–34

Egliston, K.A., McMahon, C., Austin, M., 2007. Stress in pregnancy and infant HPA axis function: conceptual and methodological issues relating to the use of salivary cortisol as an outcome measure. Psychoneuroendocrinol. 32(1), 1-13.

Ellison, M., A., Janet E Hall, J., E. 2003. Social stigma and compounded losses: quality-of-life issues for multiple-birth families. Fertil. Steril.. 80(2), 405–414

Ellison, M., A., Hotamisligil, S., Lee, H., Rich-Edwards, J., W., Pang, S., C., Hall, J., E. 2005. Psychosocial risks associated with multiple births resulting from assisted reproduction. Fertil Steril. 83(5).1422-8.

ESHRE consensus statement 2002 in Land, J., A., Evers, J., I. 2003. Risks and complications in assisted reproduction techniques: Report of an ESHRE consensus meeting. Hum Reprod. 18, 455–7.

Ezugwu, E., C., Van der Burg, S. 2015. Debating Elective Single Embryo Transfer after *in vitro* Fertilization: A Plea for a Context-Sensitive Approach Ann Med Health Sci Res. Jan-Feb; 5(1), 1–7.

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

Field, T., Diego, M., Hernandez-Reif, M., Figueiredo, B., Deeds, O., Ascencio, A., Schanberg, S., Kuhn, C. 2010. Comorbid depression and anxiety effects on pregnancy and neonatal outcome. Infant Beh. Developm.. 33, 23-29.

Fisher, J., Stocky, A. 2003. Maternal Perinatal Mental Health and Multiple Births: Implications for Practice. Twin Res. 6(6), 506-513.

Fisher, J., Hammarberg, K., Wynter, K., McBain, J., Gibson, F., Boivin, J., McMahon., C.2013. Assisted conception, maternal age and breastfeeding: an Australian cohort study. Acta Paediatrica. 102(10), 970–976.

Freeman, T., Golombok, S., Olivennes, F., Ramogida, C., Rust, J. 2007. Psychological assessment of mothers and their assisted reproduction triplets at age 3 years. Reprod. BioMed. Online. 15(3).

Gameiro, S., Nazare, B., Fonseca, A., Moura-Ramos, M., Canavarro, M., C. 2011. Changes in marital congruence and quality of life across the transition to parenthood in couples who conceived spontaneously or with assisted reproductive technologies. Fertil. Steril.. 96(6).

Garel, M., Blondel, B. 1992. Assessment at 1 year of the psychological consequences of having triplets. Hum. Reprod. 7 (5): 729-732.

771 Garel, M., Salobir, C., Blondel, B., 1997. Psychological consequences of having
772 triplets: a 4-year follow-up study. Fertil Steril., 67(6),1162-5.
773
774 Gaynes, B., N., Gavin, N., Meltzer-Brody, S., Lohr, K.,N., Swinson, T., Gartlehner, G,
775 Brody, S., Miller, W.C. 2005. Perinatal Depression: Prevalence, Screening Accuracy,
776 and Screening Outcomes. Summary, Evidence Report/Technology Assessment:
777 Number 119. AHRQ Publication Number 05-E006-1, February. Agency for
778 Healthcare Research and Quality, Rockville
779
780 Glazebrook, C., Charlotte S., Cox, S., Oates, M., Ndukwe, G. 2004. Parenting stress
781 in first-time mothers of twins and triplets conceived after in vitro fertilization. Fertil.
782 Steril. 81(3), 505–511
783
784 Goldberg, D., P. 1972.The Detection of Psychiatric Illness by Questionnaire. Oxford
785 University Press. London
786
787 Golombok, S., Olivennes, F., Ramogida, C., Rust, J., Freeman, T., 2007. Parenting
788 and the psychological development of a representative sample of triplets conceived
789 by assisted reproduction. Hum. Reprod. 22 (11):2896-2902
790
791 Gressier, F., Letranchant, A., Cazas, O., Sutter-Dallay, A.L., Falissard, B., Hardy, P.
792 2015. Post partum depressive symptoms and medically assisted conception: a
793 systematic review and meta-analysis. Hum. Reprod. 30 (11), 2575-2586.
794

795 Hammarberg, K., Fisher, J., R., W., Wynter, K., H. 2008. Psychological and social
796 aspects of pregnancy, childbirth and early parenting after assisted conception: a
797 systematic review. Hum. Reprod. Update.14 (5), 395-414.
798
799 Henrichs, J., Schenk, J.J., Roza, S., van den Berg, M, Schmidt, H.G., Steegers, E.,
800 Hofman, A., Jaddoe, V., Verhukst, F Tieneier, H. 2009. Maternal psychological
801 distress and fetal growth trajectories: the generation R study. Psychol. Med. 40, 633-
802 643.
803
804 Higgins, J.P.T., Green, S. 2011.Cochrane Handbook for Systematic Reviews of
805 Interventions. Accessed at http://handbook.cochrane.org/
806
807 HFEA. 2009a. Multiple births – Background and Statistics. At
808 http://www.hfea.gov.uk/docs/200727_risks_multiple_births_background_and_statisti
809 cs.pdf
810
811 HFEA. 2009b. Authority Paper on Multiple Births. At
812 http://www.hfea.gov.uk/docs/2009-12-09_Authority_papers-527_Multiple_Births.pdf
813
814 International Classification of Diseases (ICD10) (2015).CM Diagnosis Code F53.
815
816 International Labour Organization (2014) http://www.ilo.org/global/publications/ilo-
817 bookstore/order-online/books/WCMS_242615/lang--en/index.htm
818
819 De Kleine, M., den Ouden, A., Kollee, L., Ilsen, A van Wassenaear, A., Brand,R.,

820 Verloove-Vanhorick, S.P. 2007. Lower mortality but higher neonatal morbidity over a
821 decade in very preterm infants. Paediatric Perinatal Epidemiol. 21(1). : 15-25.
822
823 Klock, S., C. 2004. Psychological adjustment to twins after infertility. Best Pract Res
824 Clin Obstet Gynaecol. 18, 645-656.
825
826 Land, J., A., Evers, J., I. 2003. Risks and complications in assisted reproduction
827 techniques: Report of an ESHRE consensus meeting. Hum Reprod. 18, 455–7.
828
829 Lewis, G., Rice, F., Harold, G., T., Collishaw, S., Thapar, A. 2011. Investigating
830 Environmental Links Between Parent Depression and Child Depressive/Anxiety
831 Symptoms Using an Assisted Conception Design. J. Am. Academy of Child &
832 Adolesc. Psychiat. 5(5), 451–459.
833
834 McDonald, S., D., Han, Z., Mulla, S., Ohlsson, A., Beyene, J., Murphy, K., E. 2010.
835 Preterm birth and low birth weight among in vitro fertilization twins: a systematic
836 review and meta-analyses. Eur J Obstet Gynecol Reprod Biol.148, 105–113.
837
838 McGrath, J. M., Samra, H. A., Zukowsky, K., Baker, B. 2010. Parenting after infertility:
839 issues for families and infants. MCN: The Am. J. of Maternal/Child Nurs.*35*(3), 156-
840 164.
841
842 Min, J.,K., Hughes, E., Young, D., Gysler, M., Hemmings, R., Cheung, A.,P.,
843 Goodrow, G.,J., Senikas, V., Wong, B.,C., Sierra, S., Carranza-Mamane, B., Case,
844 A., Dwyer, C., Graham, J., Havelock, J., Lee, F., Liu, K., Vause, T. 2010. Joint

Society of Obstetricians and Gynaecologists of Canada-Canadian Fertility and Andrology Society Clinical Practice Guidelines Committee.Elective single embryo transfer following in vitro fertilization..J Obstet Gynaecol Can. 32(4), 363-77.

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

Monset-Couchard, M.,de Bethmann, O. , Relier, J., P.1998. Mid- and long-term outcome of 77 triplets and their families. Journal de Gynecologie, Obstetrique et Biologie de la Reproduction 27(4),430-437

Murray, L., Fiori-Cowley, A., Hooper, R., Cooper, P., J. 1996. The impact of postnatal depression and associated adversity on early mother infant interactions and later infant outcome. Child Dev. 67, 2512-26.

Murray, L., Sinclair, D., Cooper, P., Dunournau, P., Turner, P. 1999. The socioemotional development of 5-year-old children of postnatally depressed mothers. J. Child Psychol. Psychiat. 40 (8), 1259-1271.

Olivennes, F., Golombok, S,.Ramogida, C., Rust, J. 2005. Follow-Up Team, Behavioral and cognitive development as well as family functioning of twins conceived by assisted reproduction: findings from a large population study, Fertil. Steril.. 84(3)725-733.

870 Ombelet, W., De Sutter, P., Van der Elst, J., Martens, G. 2005. Multiple gestation
871 and infertility treatment: registration, reflection and reaction—the Belgian project.
872 Hum. Reprod. Update. 11(1), 3-14.
873
874 One at a Time. 2010. The UK professionally-led site aimed at reducing the risks of
875 multiple pregnancies from fertility treatment http://www.oneatatime.org.uk/211.htm
876 accessed 25/09/2015
877
878 Pearlstein, T., Howard, M., Salisbury, A., Zlotnick, C. 2009. Postpartum depression.
879 Am J Obstet Gynecol. 200,357–364.
880
881 Pinborg, A., Loft, A., Schmidt, L., Andersen, A., N. 2003. Morbidity in a Danish
882 national cohort of 472 IVF/ICSI twins, 1132 non-IVF/ICSI twins and 634 IVF/ICSI
883 singletons: health-related and social implications for the children and their families.
884 Hum Reprod. Jun.18(6),1234-43.
885
886 Reul, J. M., Holsboer, F. 2002. Corticotropin-releasing factor receptors 1 and 2 in
887 anxiety and depression. Current Opinion in Pharmacol. *2*(1), 23-33.
888
889 Roca de Bes, M., Gutierrez Maldonado, J., Gris Martínez, J., M. 2009. Psychosocial
890 risks associated with multiple births resulting from assisted reproduction: a Spanish
891 sample. Fertil Steril. Sep. 92(3)1059-66.
892
893 Roca de Bes, M., Gutierrez-Maldonado, J., Gris-Martinez, J. M. 2011. Comparative
894 study of the psychosocial risks associated with families with multiple births resulting

from assisted reproductive technology (ART) and without ART. Fertil. Steril..96(1)170-174.

Rockliff, H.E., Lightman, S., Rhidian, E., Buchanan, H., Gordon, U., Vedhara, K. 2014. A systematic review of psychosocial factors associated with emotional adjustment in vitro fertilization patients Hum. Reprod. Update 20(4) 594-613.

Rondo, O., Fereeira R., F., Nogueira, F., Ribeiro, M., Lobert, H., Artes, R. 2003. Maternal psychological stress and distress as predictors of low birth weight, prematurity and intrauterine growth retardation. European J. Clin. Nutrition. 57, 266-72.

Ross,L.,E., McQueen, K., Vigod, S., Dennis, C.,L. 2011. Risk for postpartum depression associated with assisted reproductive technologies and multiple births: a systematic review. Hum Reprod Update.17. 96-106.

Sandi, C., Richter-Levin, G. 2009. From high anxiety trait to depression: a neurocognitive hypothesis. Trends in Neurosci. 32(6), 312-320.

Scottish Intercollegiate Guidelines Network. 2002.Postnatal depression and Puerperal psychosis. A national clinical guideline. Royal College of Physicians. Edinburgh.

Sheard, C., Cox, S., Oates, M., Ndukwe, G., Glazenbrook, C. 2007. Impact of a multiple, IVF birth on post-partum mental health: a composite analysis. Hum Reprod. 22, 2058-2065.

Spielberger, CD, Gorush, R.,I.,.Lushene, R.,E. 1970. STAI Manual for the State-Trait Anxiety Inventory. CA: Consulting Psychologist Press. Palo Alto.

Spillman J., R.1987. Emotional aspects of experiencing a multiple birth. Midwife Health Visit Community Nurse. 23(2), 54-8.

Shinwell, E., Blickstein, I., Lusky, A., Reichman, B. 2015. Excess risk of mortality in very low birth weight triplets: a national, population based study. Archives of Diseases in Childhood.Fetal Neonatal Ed. 88:F36-F40.

Spielberger, C., D., Gorsuch, R., L. 1983. State-Trait Anxiety Inventory for Adults: Manual and Sample: Manual, Instrument and Scoring Guide. CA: Consulting Psychologists Press. Palo Alto

Sullivan, E., A., Wang, Y., A., Hayward, I., Chambers, GM., Illingworth, P., McBain, J., Norman, R., J. 2012. Single embryo transfer reduces the risk of perinatal mortality, a population study. Hum Reprod. 27:3609–15.

Sutcliffe, A., G., Derom, C. 2006. Follow-up of twins: health, behaviour, speech, language outcomes and implications for parents. Early Hum Dev.82, 379–386.

Swaab, D., F, Bao, A., M, , Lucassen, P., J. 2005. The stress system in the human brain in depression and neurodegeneration. Ageing Res Rev.4(2), 141-94.

Sydsjö, G., Wadsby, M., Sydsjö, A., Selling, K., E. 2008. Relationship and parenthood in IVF couples with twin and singleton pregnancies compared with spontaneous singleton primiparous couples--a prospective 5-year follow-up study. Fertil Steril. Mar. 89(3), 578-85.

Tully, L., A., Moffitt, T.,B., Caspi, A. 2003. Maternal adjustment, parenting and child behaviour in families of school-aged twins conceived after IVF and ovulation induction. J Child Psychol Psychiatry. Mar.44(3),316-25.

Veltman-Verhulst, S., M., Boivin, J., Eijkemans, M., Fauser, B. 2012. Emotional distress is a common risk in women with polycystic ovary syndrome: a systematic review and meta-analysis of 28 studies, Hum. Reprod. Update. 18(6), 638–651.

Vilska, S., Unkila-Kallio, L., Punamäki, R., L., Poikkeus, P., Repokari, L., Sinkkonen, J., Tiitinen, A., Tulppala, M. 2009. Mental health of mothers and fathers of twins conceived via assisted reproduction treatment: a 1-year prospective study. Hum Reprod. Feb. 24(2), 367-77.

Vilska, S.,Unkila-Kallio, L. 2010. Mental health of parents of twins conceived via assisted reproductive technology. Current Opinion in Obstet. Gynecol. *22*(3), 220-226.

968 Wells, G., A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M.,Tugwell, P.
969 2010. The Newcastle-Ottawa scale (NOS) for assessing the quality of
970 nonrandomized studies in meta-analysis. The Ottawa Health Research Institute.
971
972 Williams, K., E., Marsh, W.,K., Rasgon, N., L. 2007. Mood disorders and fertility in
973 women: acritical review of the literature and implications for future research. Hum
974 Reprod Update.13, 607–616.
975
976 Yokoyama, Y. 2003. Comparison of child-rearing problems between mothers with
977 multiple children who conceived after infertility treatment and mothers with multiple
978 children who conceived spontaneously. Twin Res. 6, 89-96.