

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

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4 **Running Title: Meta-analysis of maternal distress following twins**

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

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21 **Abstract:**

22 The aim of this systematic review and meta-analysis is to provide new evidence on
23 the effects of assisted reproductive technology (ART) multiple births on maternal
24 mental health. A bibliographic search was undertaken using PubMed, PsycINFO,
25 CINAHL, Science Direct.. The data extraction process was completed using the
26 Cochrane Review Group's recommendations, the review was informed following
27 PRISMA and MOOSE guidelines. Meta-analytic data were analysed using random
28 effects models. Eight papers (data from 2993 mothers) were included. Mothers of
29 ART multiple births were significantly more likely to experience depression
30 (standardised mean difference $d=.198$, 95% CI $.050-.0345$, $z=2.623$, $p = .009$;
31 heterogeneity $I^2=36.47\%$, $p=.146$), and stress (standardised mean difference $d=.177$,
32 95% CI $.049-.305$, $p= .007$; heterogeneity $I^2=.01\%$, $p=.535$) than mothers of ART
33 singletons. No difference in psychosocial distress (combined stress and depression)
34 (standardised mean difference $d=.371$, 95% CI $-.153 - .895$ $p =.165$; $I^2=86.962\%$,
35 $p=.001$) or depression between mothers of ART or naturally conceived (NC) multiple
36 births were found ($d =.152$, 95% CI $-.179 - .483$: $z=.901$: $p=.368$; $I^2 =36.918\%$, p
37 $=.208$). In conclusion, mothers of ART multiple births were significantly more likely to
38 have depression and stress than mothers of ART singletons, but were no different
39 from mothers of NC multiples.

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

45 **Introduction**

46 Multiple pregnancy has been recognised as the greatest health risk to both infant
47 and mother following natural conceptions (NC) and assisted reproductive technology
48 (ART), such as In Vitro Fertilization (IVF) (HFEA, 2009a). In order to lower the risks
49 of multiple births through assisted conception, guidelines, elective single embryo
50 transfer policies (eSET), and consensus statements have been introduced
51 internationally (e.g. HFEA, 2009a, 2009b; One at a Time, 2015; Min et al., 2010;
52 CDC, 2014; ASRM, 2012; ESHRE consensus statement 2002 (Land and Evans,
53 2003). Mandatory adoption of eSET in some countries resulted in significant
54 reductions of multiple births (e.g. Bissonnette et al., 2011) and perinatal mortality
55 (Sullivan et al., 2012)

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

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

78

79 In studies comparing ART twins/multiples with NC twins/multiples, no differences in
80 maternal psychological functioning have generally been found (e.g., Colpin et
81 al.,1999; Vilksa et al., 2009; Tully et al., 2003). Others have reported more
82 psychological distress in mothers of ART twins/multiples than in mothers of NC
83 twins/multiples (Baor et al., 2004; Yokoyama, 2003). These differences may be due
84 to a higher risk of depression and marital decline in ART mothers (Klock, 2004).
85 Research evolving around marital satisfaction among ART mothers of multiples and
86 singletons is conflicting. While some studies report no difference between these two
87 groups (Olivenness et al., 2005), others support the hypothesis that a multiple birth
88 decreases marital satisfaction among ART mothers (Roca de Bes, 2009; 2011).
89 Ellison et al. (2005) reported a similar tendency, although the findings were not
90 statistically significant. However, it seems that some ART multiple mothers tend to
91 cope well with the strain and do not divorce more often than mothers of singletons
92 (Pinborg et al., 2003). Many previous reviews are now over 10 years old (Klock,
93 2004; Bryan, 2002), are narrative reviews (Vilksa and Unkila-Kallio, 2010; McGrath
94 et al., 2010), considered twins/multiples briefly (Hammarberg et al., 2008), focused

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

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

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

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

111 **Materials and Methods**

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

114 **Search strategy**

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

119 augmented with hand searches of articles cited in reference lists and from relevant
120 review papers (e.g. Ross et al., 2010). Most of the databases included the following
121 keywords: ("postpartum" OR "postnatal" OR "pregnan*" OR "perinatal" OR
122 "childbirth" OR "obstetr*" OR "labour" OR "puerperal" OR "parturition" OR "parity"
123 OR "maternal") AND ("multiple births" OR "twins" OR "triplets") AND ("psychological
124 stress" OR "depressive disorder" OR "anxiety" OR "anxiety disorder" OR "adjustment
125 disorder" OR "emotions" OR "psychosomatic medicine" OR "psychological adaption"
126 OR "distress" OR "depression" OR "stress" OR "stressors" OR "mental health" OR
127 "mental illness" OR "mood disorder" OR "baby blues" OR "postpartum depression")
128 AND ("IVF" OR "intracytoplasmic" OR "intracytoplasmic sperm injection" OR "in vitro
129 fertilization" OR "ICSI" OR "assisted reproduct*" OR "ovulation induction" OR
130 "embryo implantation" OR "artificial insemination" OR "sperm injections" OR
131 "infertility" OR "fertility treatment").

132

133 **Study selection**

134 Studies were included if they:

- 135 • compared depression, anxiety or stress of ART twins/multiple birth mothers
136 versus ART singleton birth mothers;
- 137 • compared depression, anxiety or stress of ART twins/multiple birth mothers
138 versus NC twins/multiple birth mothers.

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

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

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

157

158 **Data screening and extraction**

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

166

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

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

183

184 **Quality Assessment**

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

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

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

197 • Comparability: Points were awarded if: 1) the study controlled for confounding
198 variables, such as age, previous maternal mental health, parity and first cycle;
199 2) the study controlled for any other additional factors.

200 • Outcome: Points were awarded if: 1) there was adequate follow up of cohorts
201 (if they had completed a follow up or participants lost to follow up were $\leq 20\%$
202 and unlikely to introduce bias).

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

205

206 **Data analyses**

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

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

226

227 **Results**

228 **Search Results**

229 The screening process is summarised in the PRISMA flow chart (Figure 1). Titles of
230 1346 records were screened out of which 111 were duplicates. A total of 1235 titles
231 were reviewed. Of these, 1075 did not meet the inclusion criteria. Therefore, 160
232 abstracts were reviewed, which led to the selection of 80 full text articles. Of these,
233 37 papers included irrelevant comparison groups (e.g. Baor et al., 2012; Boivin et al.,
234 2009, etc.), 2 papers were reviews (e.g. Spillman, 1987), 3 studies were qualitative
235 (Ellison et al., 2003; Garel et al., 1992; Garel et al., 1997), one paper had incomplete
236 data for analysis and another one was not in English (Monset-Couchard et al., 1998).
237 No assessment of appropriate psychological variable was found in 7 papers (e.g.
238 Gameiro et al., 2011; Hammarberg et al., 2008 etc.). Other papers were excluded for
239 irrelevant data collection time points (Lewis et al., 2011; Fisher et al., 2013 etc.), use
240 of only singleton groups or data reported as adjusted scores or mothers and fathers
241 data not separated. The studies specifically on fathers we identified used combined
242 data sets and did not separate data for mothers and fathers. For example, Baor et al.,
243 (2004) used a mixed group (75 parents of twins: 38 ART and 37 SC) with no gender

244 difference in terms of parenting stress. Colpin et al. (1999) included a mixed group of
245 103 families of twins. Cook et al., (1998) presented data on 26 families of twins and
246 Golombok et al. (2007) used 28 IVF families with triplets and 30 IVF families of
247 singletons in their paper. Where gender differences in parental postpartum mental
248 health are reported, too few control for parent gender and multiplicity separately
249 (Vilkska et al, 2009) to be included in the meta-analysis. In case of multiple reporting,
250 papers using the highest sample size were included. For example, Olivennes (2005)
251 was selected over Freeman et al. (2007) and Golombok et al. (2007). Sheard's (2007)
252 paper was selected over Glazebrook et al. (2004). Finally, 8 papers met the inclusion
253 criteria for the meta-analysis. Authors of original papers were contacted via e-mail by
254 OA for additional data. When necessary, discussions took place to clarify the type of
255 the data needed in our study. Three authors (C. Sheard, M. Roca-de Bes and S.
256 Vilkska) provided supplementary data to be included in the meta-analysis.

257

258 INSERT FIGURE 1 ABOUT HERE

259

260 **ART multiple births versus ART singleton births**

261 **Study characteristics**

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

269 et al., 2011). Time of measurement varied across studies. Sheard et al. (2007)
270 measured depression at six weeks postpartum. Roca de Bes et al. (2009; 2011)
271 collected data at six months to four years postpartum. Ellison et al. (2005) examined
272 depression and stress at one to four years postpartum. Olivennes et al. (2005)
273 provided data for the time between two and five years postpartum while Vilska et al.
274 (2009) collected data at two months and 1 year post-partum (mean 14 months
275 postpartum). Finally, for all, but one of the studies, the quality was high (ranged
276 between 3 and 5 points).

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

280 **Measures:** Data were obtained from self-administered questionnaires assessing
281 depression and stress, such as: CES-D (Ellison et al., 2005; Roca de Bes, 2009;
282 2011), PSI (Olivennes, 2005), Cohen Perceived Stress (Roca de Bes, 2009; 2011),
283 EDS (Olivennes, 2005; Sheard et al., 2007) and GHQ-36 (Vilska et al., 2009).

284 **Participants' characteristics:** Comparisons by multiplicity indicated that there were
285 no statistically significant differences between mothers of ART singletons and
286 mothers of ART multiples in maternal education, pretax household income levels,
287 ethnicity (Ellison et al., 2005), maternal age (Ellison et al., 2005; Sheard et al., 2007;
288 Roca de Bes, 2011), marital status (Roca de Bes, 2011) or regarding children
289 without siblings (Roca de Bes, 2011). However, in some studies, singleton mothers
290 were older than multiple mothers and reported higher levels of employment
291 (Olivennes et al., 2005). For the majority of the respondents (72% in Ellison et al.,
292 2005; 86% in Sheard et al., 2007) this was their first full term pregnancy. Similarly,
293 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 (Vilksa 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

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

328 **Depression meta-analysis:**

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

337

338 **INSERT FIGURE 2 ABOUT HERE**

339

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

344 year postpartum to those taken over 1 year ($Q = 4.664$, $df = 1$, $p = .031$). The effect
345 size for depression at ≤ 1 year was stronger ($d = .389$; $k = 2$: 95% CI .180-.599: z
346 $= 3.640$, $p < .00$; with low levels of heterogeneity $I^2 < .01\%$, $p = .564$) than for
347 depression assessed at > 1 year ($d = .122$, $k = 4$: 95% CI .000-.244, $z = 1.959$, $p = .050$;
348 with low levels of heterogeneity $I^2 < .01\%$, $p = .411$). However, both effect sizes
349 remained significant. As the number of studies was small (two studies with ≤ 1 year
350 depression data), these data must be treated with some caution. Furthermore, meta-
351 regression indicated no evidence for the effect of study quality of results.

352 **Stress meta-analysis:**

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

359

360

INSERT FIGURE 3 ABOUT HERE

361

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

368

369 **ART multiple births versus NC multiple births**

370 **Study characteristics**

371 Three studies were included in the ART multiple births versus NC multiple births
372 meta-analysis (see Table 2). One study measured stress (Boar and Soskolne, 2010),
373 while the other two depression (Yokoyama et al., 2003; Vilska et al., 2009). To test
374 the second hypothesis and given the small number of studies in this comparison,
375 stress and depression scores were collated into a general 'distress score'. This
376 decision was justified with the neurocognitive hypothesis stating that depression and
377 anxiety are involved in the dysregulation of the stress-induced hypothalamus –
378 pituitary–adrenocortical axis (HPA) (Reul and Holsboer, 2002; Sandi and Richter-
379 Levin, 2009). Depression scores were also analysed independently. Data from 1261
380 mothers were included in the distress meta-analysis. Response rates for Baor and
381 Soskolne (2010) and Vilska et al.'s (2009) studies were good. Baor and Soskolne
382 (2010) assessed stress at six months postpartum, while Vilska et al. (2009) and
383 Yokoyama et al. (2003) examined depression at two months and three years
384 postpartum respectively. Study quality for Baor and Soskolne (2010) and Vilska et al.
385 (2009) was good. Yokoyama et al.'s (2003) study had a satisfactory quality (score 3).
386 Since anxiety was measured only in one study, (see Vilska et al., 2009 in Table 2), it
387 was not included in the analysis.

388

389 **INSERT TABLE 2 ABOUT HERE**

390

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

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

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

404 **Stress and Depression meta-analysis:**

405 The findings for the combined 'distress score' for 1261 mothers did not support the
406 second hypothesis of the meta-analysis. They indicated that mothers who conceived
407 multiples through ART did not score differently on psychological distress compared
408 with mothers who conceived multiples naturally (standardised mean difference
409 $d=.371$, 95% CI $-.153 - .895$: $z=1.387$: $p =.165$; with significant heterogeneity
410 $I^2=86.962\%$, $p=.001$). When only depression data were used ($n=1075$ mothers), the
411 results were also non-significant, with non-significant heterogeneity (standardised
412 mean difference $d =.152$, 95% CI $-.179 - .483$: $z=.901$: $p =.368$; $I^2 =36.918\%$, $p =.208$)
413 (see Figures 4 and 5 for forest plots).

414

415

INSERT FIGURES 4 AND 5 HERE

416

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

421

422 **Discussion**

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

435

436 **Strengths and Weaknesses**

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

442 exceeded 1000 each. This allowed for acceptable comparisons to be made. Given
443 the scarce number of studies and the lack of heterogeneity, moderator effect
444 analysis could not be run (Deeks et al., 2009). As a history of previous depression is
445 one of the highest risk factors for postnatal depression (Sutcliffe and Derom, 2006;
446 Fisher and Stocky, 2003), such an analysis would have allowed the examination of
447 the effects of baseline depression on depression in the postpartum. Most studies did
448 not include baseline measurements of psychological distress, therefore, baseline
449 measurement was not included as an essential criterion for study selection. Although
450 reliable and valid measures of psychological constructs were used, a distinction
451 should be made between these in terms of their theoretical grounds, as a
452 combination of generic and specific scales were included. For example, parenting
453 stress as measured by the PSI (Olivennes, 2005) is substantively and theoretically
454 distinct from generalized stress as measured by the Cohen Perceived Stress (Roca
455 de Bes, 2009; 2011), and thus these two should not be confounded. In addition, a
456 distinction should be made between depression measured by generic scales such as
457 the General Health Questionnaire (GHQ-36 in Vilska et al., 2009) or the
458 Epidemiological Studies Depression Scale (Ellison et al., 2005; Roca de Bes, 2009;
459 2011) and by the Edinburgh postnatal depression scale (EPDS) (Olivennes, 2005;
460 Sheard et al., 2007). However, as previous studies indicate, there is normally a high
461 degree of overlap between general depression scales and postnatal depression
462 scales (e.g. EPDS) (Gaynes et al., 2005). De Beurs (2004), for example, used items
463 on the Brief Symptom Inventory, while in other studies GHQ anxiety and depression
464 (Goldberg, 1972) were combined with state and trait anxiety (Spielberger et al, 1970;
465 Rondo et al., 2003). Validated measures of depression, anxiety and emotional

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

468

469 Our methodological strategy to combine stress and depression into a 'distress score'
470 was supported by the tripartite model of anxiety and depression (Clark and Watson,
471 1991) and neurocognitive theories that suggest that similar pathways are involved in
472 the three constructs (Reul and Holsboer, 2002). Accordingly, general distress,
473 physiological hyperarousal (specific anxiety) and anhedonia (specific depression) are
474 components of the diagnosis of mixed anxiety-depression. Increased concentrations
475 of corticotropin-releasing hormone (CRH) in the cerebrospinal fluid have been
476 reported in both anxiety and depression (Boyer, 2000). CRH plays a central role in
477 the regulation of the hypothalamic-pituitary-adrenal (HPA)-axis, i.e., the final
478 common pathway in the stress response (Swaab et al., 2005). A similar design was
479 used in a previous meta-analysis that combined anxiety and depression, the author
480 arguing that these are "reliably related to stress induced activation of the
481 hypothalamic-pituitary-adrenal axis" (Boivin et al. 2011). However, as these
482 components can be differentiated on the basis of their specific factors, we
483 recommend some caution in terms of the implications of our findings.

484

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

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

493

494 **Generalization of the findings**

495 Since previous research has shown that ART treatment itself can be stressful
496 (Eugster and Vingerhoets, 1999; Williams et al., 2007), we carried out further meta-
497 analyses comparing mothers of NC multiples with ART multiples in an attempt to
498 tease out the effect of multiples from the effects of ART. Only three studies (Baor et
499 al., 2010; Vilska et al., 2009; Yokoyama et al., 2003) could be used in the
500 comparison. The results show that there might be something particularly stressful
501 about having multiple births, regardless of mode of conception. It is possible that
502 there are specific effects of premature births, more common in multiple births,
503 although we could not find sufficient data to support this. Premature multiple birth
504 infants are often diagnosed with health problems such as respiratory and neuro-
505 developmental difficulties or disabilities and require extended and frequent
506 hospitalization (Blickstein, 2002; 2003). Other factors such as difficulty establishing
507 breastfeeding, and physical recovery ([Fisher and Stocky 2003](#)) in parents of
508 multiples may also be responsible. Our meta-analysis showed no effect of mode of
509 conception on depression and distress scores. These findings support Klock's review
510 (2004) on the psychological adjustment to twins after infertility, indicating that
511 mothers of multiples are likely to be more vulnerable to depression. Contrary to Ross
512 et al's (2011) systematic review and Gressier et al.'s (2015) meta-analysis, other
513 authors have reported that ART is stressful (Eugster and Vingerhoets, 1999;
514 Williams et al., 2007). Increased risks of premature and low birth weight babies in
515 ART twins compared with NC twins, after accounting for confounders, have been

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

519

520 **Alternative explanations for the results**

521 We cannot conclude that ART multiple births lead to stress and depression (Ross et
522 al., 2011). However, different potential explanations for higher psychological
523 problems in ART multiple birth mothers have been provided previously. It has been
524 suggested that infant temperament may combine with other vulnerability factors to
525 increase the risk of depression (Cutrona and Troutman, 1986; Murray et al., 1996). It
526 is also possible that ART multiple birth mothers are more distressed or more
527 vulnerable to distress during pregnancy (e.g. age, having multiple embryos
528 implanted and more difficult pregnancies or not being able to afford multiple rounds
529 of IVF, according to van Balen et al., 1996) and in the postpartum (Roca de Bes et
530 al., 2009; Sutcliffe and Derom, 2006; Fisher and Stocky, 2003). In addition, maternal
531 prenatal distress is associated with low birth weight and prematurity (Rondo et al.,
532 2003), although ART treatment itself has been reported to lead to little or no
533 increased risk for post-partum depression (Ross et al., 2011; Gressier et al., 2015).
534 Therefore, ART multiple birth mothers may not be completely comparable with the
535 mothers of ART singleton cohorts.

536

537 Finally, the studies included were mainly performed in Europe (France: Olivennes et
538 al., 2005; Spain: Roca de Bes et al., 2009; 2011; United Kingdom: Sheard et al.,
539 2007; Finland: Vilska et al., 2009), with three studies from different
540 countries/continents (US - Ellison et al., 2005; Japan - Yokoyama, 2003; and Israel -

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

552

553 **Implications of the results**

554 We strongly recommend that the clinical implications of ART specific multiple births
555 should be explored further because: a) post-natal distress is likely to co-exist with
556 previous pregnancy distress (Scottish Intercollegiate Guidelines Network, 2002); b)
557 the consequences of distress in pregnancy are known to affect fetal growth
558 (Henrichs et al., 2009); c) prematurity and low birth weight are important
559 determinants of neonatal mortality (Shinwell et al., 2015) and neonatal, infant and
560 childhood morbidity (de Kleine et al., 2007); d) the incidence of prematurity in
561 mothers with comorbid anxiety and depression is greater than in non-depressed
562 mothers (Field et al., 2010); and e) the consequences of maternal depression and
563 distress in the first years following delivery affect mothers' interaction with their
564 babies, which in turn is known to alter their cognitive, social and emotional
565 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

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

595

596 **Conclusion**

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

611

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618

619 **Authors' roles**

620 OA and SP conceptualised the review. OvdA, SP and GP searched databases,

621 selected articles and performed the data extraction. SP and GP performed the

622 statistical analysis. OvdA and SP took the lead in writing the review, and all authors

623 approved the final version of the article.

624

625 **Declaration of interests**

626 The authors have no interests to declare.

627

628

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