REVIEW

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

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Abstract  The aim of this meta-analysis is to provide new evidence on the effects on maternal health of multiple births due to assisted reproductive technology (ART). A bibliographic search was undertaken using PubMed, PsycINFO, CINAHL and Science Direct. Data extraction was completed using Cochrane Review recommendations, and the review was performed following PRISMA and MOOSE guidelines. Meta-analytic data were analysed using random effects models. Eight papers (2993 mothers) were included. Mothers of ART multiple births were significantly more likely to experience depression (standardized mean difference [SMD] $d = 0.198$, 95% CI $0.050 - 0.345$, $z = 2.623$, $P = 0.009$; heterogeneity $I^2 = 36.47\%$), and stress (SMD $d = 0.177$, 95% CI $0.049 - 0.305$, $P = 0.007$; heterogeneity $I^2 = 0.01\%$) than mothers of ART singletons. No difference in psychosocial distress (combined stress and depression) (SMD $d = 0.371$, 95% CI $-0.153 - 0.895$; $I^2 = 86.962\%$, $P = 0.001$) or depression ($d = 0.152$, 95% CI $-0.179 - 0.483$; $z = 0.901$; $I^2 = 36.918\%$) were found between mothers of ART and naturally conceived multiple births. 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 naturally conceived multiples.

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Introduction

Multiple pregnancy has been recognized as the greatest health risk to both infant and mother following natural conceptions and assisted reproductive technology, such as 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. ASRM, 2012; CDC, 2014; ESHRE consensus statement 2002 (Land and Evers, 2003); HFEA, 2009a, 2009b; Min et al., 2010; One at a Time, 2010). 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 emphasized maternal and infant mortality and medical morbidity, particularly in assisted reproductive technology 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 (Egлистon 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 assisted reproductive technology multiple births are associated with greater psychological problems compared with assisted reproductive technology singleton births (e.g., Ellison et al., 2005; Olivennes et al., 2005; Vilska et al., 2009), but there are exceptions (Sydsjö et al., 2008). The evidence linking increased risks for depression in mothers of twins is generally well supported for assisted reproductive technology multiples (Vilska and Unkila-Kallio, 2010) and natural conception 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 post-partum 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 singletons via assisted reproductive technology). Most of the available literature examined maternal psychological functioning after assisted reproductive technology multiples, and there were insufficient data to perform meta-analysis on paternal psychological functioning after assisted reproductive technology multiples (Vilska et al., 2009).

In studies comparing assisted reproductive technology twins/multiples with natural conception twins/multiples, no differences in maternal psychological functioning have generally been found (e.g. Colpin et al., 1999; Tully et al., 2003; Vilska et al., 2009). Others have reported more psychological distress in mothers of assisted reproductive technology twins/multiples than in mothers of natural conception twins/multiples (Baor et al., 2004; Yokoyama, 2003). These differences may be due to a higher risk of depression and marital decline in assisted reproductive technology mothers (Klock, 2004). Research revolving around marital satisfaction among assisted reproductive technology mothers of multiples and singletons is conflicting. While some studies report no difference between these two groups (Olivennes et al., 2005), others support the hypothesis that a multiple birth decreases marital satisfaction among assisted reproductive technology mothers (Roca de Bes et al., 2009, 2011). Ellison et al. (2005) reported a similar tendency, although the findings were not statistically significant. However, it seems that some assisted reproductive technology 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 (Bryan, 2002; Klock, 2004), are narrative reviews (McGrath et al., 2010; Vilska and Unkila-Kallio, 2010), considered twins/multiples briefly (Hammargerg 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 post-natal emotional adjustment to be examined in order to gain a better understanding of the complex and multifactorial nature of the post-natal psychological state of women who conceive using assisted reproductive technology 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 assisted reproductive technology. Given the clinical implications of assisted reproductive technology multiple births, this meta-analytic and review process extrapolates the research evidence by comparing depression, anxiety and stress of assisted reproductive technology twins/multiples mothers versus natural conception twins/multiples mothers and assisted reproductive technology twins/multiples mothers versus assisted reproductive technology singleton mothers. Following the theoretical background, the meta-analysis was based on the following hypotheses: (i) mothers of assisted reproductive technology twins/multiples will report more psychological problems (depression, anxiety and stress) than mothers of assisted reproductive technology singletons; (ii) natural conception twins/multiples mothers will report fewer psychological problems than assisted reproductive technology mothers of twins/multiples.

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 organized 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., 2011). Most of the databases included the following keywords: (“postpartum” OR “postnatal” OR “pregnancy” OR “perinatal” OR “childbirth” OR “obstetric” 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 reproduction” OR “ovulation induction” OR “embryo implantation” OR “artificial insemination” OR “sperm injections” OR “infertility” OR “fertility treatment”).

Study selection

Studies were included if they: (i) compared depression, anxiety or stress of assisted reproductive technology twins/multiple birth mothers versus assisted reproductive technology singleton birth mothers; or (ii) compared depression, anxiety or stress of assisted reproductive technology twins/multiple birth mothers versus natural conception 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 post-partum with no initial restriction for time. However, time was used in the sensitivity data analysis. The study was 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, re-analyses of data presented elsewhere, did not report standardized 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. Owing 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 (assisted reproductive technology multiples versus assisted reproductive technology singletons and assisted reproductive technology multiples versus natural conception multiples). Additionally, available data on publication date, treatment location, sociodemographic (average age, average number of married mothers, average relationship length, average socioeconomic 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 spermatozoa or oocytes – any versus none, average duration of pregnancy, type of delivery – natural or Caesarean 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 et al., 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: (i) the sample was representative (more than 80% eligibility to participate or participation rate or sample size higher than 300, according to Boivin et al., 2011) or somewhat representative of the assisted reproductive technology population (more than 60% of eligible patients were invited and accepted to participate); (ii) the selection of the control cohort was drawn from the same community as the main treatment cohort; and (iii) the study demonstrated that “distress” (depression, state anxiety or stress) was not present at start of study.

Comparability

Points were awarded if: (i) the study controlled for confounding variables, such as age, previous maternal mental health, parity and first cycle; and (ii) the study controlled for any other additional factors.

Outcome

Points were awarded if 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 four points or more. The maximum a study could 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 standardized mean differences and used to compare assisted reproductive technology twins/multiple birth mothers with mothers of natural conception twins/multiples; and mothers of assisted reproductive technology twins/multiples with mothers of assisted reproductive technology 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 (I² 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). A P-value < 0.05 was considered statistically significant.

Results

Search results

The screening process is summarized in the PRISMA flow chart (Figure 1). Titles of 1346 records were screened, out of which 111 were duplicates. In total, 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, two papers were reviews, there were qualitative studies, three studies were multiple reports, one paper had incomplete data for analysis and another one was not in English. No assessment...
of appropriate psychological variable was found in seven papers. Other papers \((n = 6)\) were excluded for irrelevant data collection time points, use of only singleton groups \((n = 4)\), or data reported as adjusted scores or mothers’ and fathers; data not separated \((n = 8)\). The studies indentified specifically on fathers 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 via assisted reproductive technology and 37 spontaneously conceived) 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 Golumbok et al. (2007) used 28 IVF families with triplets and 30 IVF families of singletons in their paper. Where gender differences in parental post-partum 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 et al. (2005) was selected over Freeman et al. (2007) and Golumbok et al. (2007). Sheard et al.’s (2007) paper was selected over Glazebrook et al. (2004). Finally, eight papers \((Baor and Soskolne, 2010; Ellison et al., 2005; Olivennes et al., 2005; Roca de Bes et al., 2009, 2011; Sheard et al., 2007; Vilska et al., 2009, Yokoyama, 2003)\) 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 this study. Three authors \((\text{C Sheard, M Roca-de Bes and S Vilska})\) provided supplementary data to be included in the meta-analysis.

**Assisted reproductive technology multiple births versus assisted reproductive technology singleton births**

**Study characteristics**

Six studies were included in the assisted reproductive technology multiple births versus assisted reproductive technology 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 assisted reproductive technology multiples and mothers of assisted reproductive technology 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 6 weeks post-partum. Roca de Bes et al. (2009, 2011) collected data at 6 months to 4 years post-partum. Ellison et al. (2005) examined depression and stress at 1 to 4 years post-partum. Olivennes et al. (2005) provided data for the time between 2 and 5 years post-partum, while Vilska et al. (2009) collected data at 2 months and 1 year post-partum \((mean 14 months post-partum)\). Finally, for all studies, the quality was good \((ranged between 4 and 5 points)\).

**Sites**

Studies were conducted in the USA \((Ellison et al., 2005)\) 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: Centres for Epidemiological Study Depression Scale \((CES-D)\) \((Ellison et al., 2005; Roca de Bes et al., 2009, 2011)\), Parenting Stress Index \((PSI)\) \((Olivennes et al., 2005)\), Cohen Perceived Stress \((Roca de Bes et al., 2009, 2011)\), Edinburgh post-natal depression scale \((EPDS)\) \((Olivennes et al., 2005; Sheard et al., 2007)\) and General Health Questionnaire \((GHQ)-36\) \((Vilska et al., 2009)\).

**Participants’ characteristics**

Comparisons by multiplicity indicated that there were no statistically significant differences between mothers of assisted reproductive technology singletons and mothers of assisted reproductive technology multiples in maternal education, pre-tax household income levels, ethnicity \((Ellison et al., 2005)\), maternal age \((Ellison et al., 2005; Roca de Bes et al., 2011; Sheard et al., 2007)\), marital status \((Roca de Bes et al., 2011)\) or regarding children without siblings \((Roca de Bes et al., 2011)\). 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 assisted reproductive technology singletons \((90.2%)\) and assisted reproductive technology multiples \((76.7%)\) included in the study of Roca de Bes et al. (2009) were primiparous \((85.7% of 37 mothers of twins and 40% of nine mothers of triplets)\).

While scoring above 12 on the EPDS cannot be seen as indicating that a mother is experiencing post-natal depression; this tool is useful to detect those mothers that experience clinically significant psychological symptoms. In Roca de Bes et al.’s (2009) study, although perceived stress and depression were higher in the mothers of assisted reproductive technology multiples, the difference was not statistically significant. A trend towards significance was also identified for assisted reproductive technology multiple birth mothers on the EPDS with 15.6% scoring above 12 compared with 5.9% of the mothers of assisted reproductive technology singletons in Sheard et al.’s (2007) study. This trend was associated with a difficult infant \((Sheard et al., 2007)\), a multiple birth \((Ellison et al., 2005; Sheard et al., 2007)\) and child-related stressors \((Vilska et al., 2009)\). In line with this, mothers of assisted reproductive technology multiple births reported feeling significantly more socially marked and devalued by their treatment decision than their assisted reproductive technology singleton counterparts \((Ellison et al., 2005; Roca de Bes et al., 2009, 2011)\). Although some studies included in this meta-analysis revealed that there was no difference between mothers of assisted reproductive technology multiples and mothers of assisted reproductive technology singletons in terms of assistance received from family members \((Olivennes et al., 2005)\), families with assisted reproductive technology multiples found it more difficult to cover basic needs \((Roca de Bes et al., 2009, 2011)\). In addition, a significantly higher proportion of mothers of assisted reproductive technology twins than mothers of assisted reproductive technology singletons were excluded for irrelevant data collection time points, use of only singleton groups \((n = 4)\), or data reported as adjusted scores or mothers’ and fathers; data not separated \((n = 8)\).
Table 1  Table of study characteristics for assisted reproduction technology multiples versus assisted reproduction technology singletons.

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Response rate</th>
<th>Outcome measurements</th>
<th>Time of measurements</th>
<th>Results</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellison et al. (2005) US</td>
<td>128 Singleton ART mothers 111 Twin ART mothers 10 Triplet ART mothers</td>
<td>64%</td>
<td>Stress: Cohen Perceived Stress scale (PSS) Depression: Centres for Epidemiological Study Depression Scale (CES-D)</td>
<td>1–4 years post-partum Mean time 22 months.</td>
<td>Stress: 7.1% of singletons mothers report stress 13.8% of twins mothers reported stress 10% of triplets mothers reported stress (NS) Depression: 15.9% of singletons mothers reported depression 22.9% of twins mothers reported depression 40% of triplets mothers reported depression (P &lt; 0.05)</td>
<td>5</td>
</tr>
<tr>
<td>Olivennes et al. (2005) France</td>
<td>344 Singleton ART mothers 344 Twin ART mothers</td>
<td>86% for multiples and 87% for singletons</td>
<td>Depression: Edinburgh Postnatal Depression Scale (EPDS) Stress: Parenting Stress Index (PSI)</td>
<td>2–5 years post-partum</td>
<td>Stress: Mean 67.76 (SD 15.13) Singleton mothers Mean 70.94 (SD 16.82) Multiple mothers (P &lt; 0.01) Depression: Mean 6.94 (SD 4.14) singleton Mothers Mean 7.52 (SD 4.43) Multiples mothers (P &lt; 0.05)</td>
<td>4</td>
</tr>
<tr>
<td>Roca de Bes et al. (2009) Spain</td>
<td>77 Singleton ART mothers 37 Twin ART mothers 9 Triplet ART mothers</td>
<td>57.47%</td>
<td>Stress: Cohen Perceived Stress scale (PSS) Depression: Spanish version of the Epidemiological Studies Depression Scale (CES-D)</td>
<td>Between 6 months and 4 years post-partum</td>
<td>Stress: 12.2% of singletons mothers report stress 9.5% of twins mothers reported stress 20% of triplets mothers reported stress (NS) Depression: 34.1% of singletons mothers reported depression 19% of twins mothers reported depression 60% of triplets mothers reported depression (NS)</td>
<td>4</td>
</tr>
<tr>
<td>Roca de Bes et al. (2011) Spain</td>
<td>66 Singleton ART mothers 73 Multiples ART mothers</td>
<td>44.86%</td>
<td>Stress: Cohen Perceived Stress scale (PSS) Depression: Spanish version of the Epidemiological Studies Depression Scale</td>
<td>Between 6 months and 4 years post-partum</td>
<td>Stress: Mean 16.7 (SD 5.4) Singleton mothers Mean 16.8 (SD 4.4) Multiple mothers (NS) Depression: Mean 12.1 (SD 11.1) singleton Mothers Mean 12.9 (SD 10.7) Multiples mothers (P = 0.031)</td>
<td>5</td>
</tr>
<tr>
<td>Sheard et al. (2007) UK</td>
<td>102 Singleton ART mothers (three participants’ EPDS data missing from n = 105) 45 Multiple ART mothers (one participant’s EPDS data missing from n = 46)</td>
<td>84.5% completed follow-up</td>
<td>Depression: Edinburgh postnatal depression scale (EPDS)</td>
<td>6 weeks post-partum</td>
<td>Depression: Mean 5.68 (SD 4.11) Singleton mothers Mean 7 (SD 4.75) Multiple mothers (P &lt; 0.05)</td>
<td>5</td>
</tr>
<tr>
<td>Vilska et al. (2009) Finland</td>
<td>316 Singleton ART mothers 70 Multiples ART mothers &gt;1 year post-partum: 265 Singleton ART mothers 54 Multiples ART mothers</td>
<td>67% Over 79% completed at 2 months post-partum and &gt;60% completed at 1 year post-partum</td>
<td>Depression and anxiety scores taken from General Health Questionnaire (GHQ-36)</td>
<td>2 months post-partum (mean = 14 months post-partum)</td>
<td>Depression: Mean 1.186 (SD 0.218) singleton Mothers Mean 1.295 (SD 0.362) Multiples mothers (P &lt; 0.05) &gt;1 year postpartum: Depression: Mean 1.412 (SD 0.438) singleton mothers Mean 1.273 (SD 0.266) Multiples mothers (P &lt; 0.05)</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: *Multiple reporting – Olivennes et al. (2005) was selected over Freeman et al. (2007) and Golombok et al. (2007) because Olivennes reported a larger sample.*

*Data obtained through author.*

*Authors confirmed both studies included different participants.*

*Multiple reporting – Sheard et al. (2007) was selected over Glazebrook et al. (2004) because Sheard’s sample was larger. ART = assisted reproductive technology; NS = not statistically significant.*
technology singleton found parenting difficult (Ellison et al., 2005; Olivennes et al., 2005; Roca de Bes et al., 2009). Similarly, there was a significant difference between mothers of assisted reproductive technology twins and mothers of assisted reproductive technology singletons in the amount of pleasure they 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. Assisted reproductive technology multiple birth children had greater health and developmental problems than their assisted reproductive technology singleton counterparts in two studies (Olivennes et al., 2005; Roca de Bes et al., 2011), but the difference was non-significant in two other studies (Ellison et al., 2005; Roca de Bes et al., 2009). In Olivennes et al. (2005), 10.7% of assisted reproductive technology twins and 7.3% of assisted reproductive technology 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 assisted reproductive technology were significantly more likely to experience depression than mothers who conceived singletons through assisted reproductive technology (standardized mean difference $d = 0.198$, 95% confidence interval (CI) 0.050 to 0.345, $z = 2.623$, $P = 0.009$, with moderate levels of non-significant heterogeneity $I^2 = 36.467\%$) (Figure 2).

No publication bias was revealed. Egger’s regression intercepts were non-significant, the funnel plot was symmetrical 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 ($Q = 4.664$, $df = 1$, $P = 0.031$). The effect size for depression at $\leq 1$ year was stronger ($d = 0.389$; $k = 2$: 95% CI 0.180–0.599; $z = 3.640$, $P < 0.001$; with low levels of heterogeneity $I^2 < 0.01\%$) than for depression assessed at $>1$ year ($d = 0.122$, $k = 4$: 95% CI 0.000 to 0.244, $z = 1.959$, $P < 0.05$; with low levels of heterogeneity $I^2 < 0.01\%$). However, both effect sizes remained significant. As the number of studies was small (two studies with $\leq 1$ 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, 2011). Data supported the prediction that mothers who conceived multiples through assisted reproductive technology were significantly more likely to experience stress than mothers who conceived singletons through assisted reproductive technology (standardized mean difference $d = 0.177$, 95% CI 0.049 to 0.305, $P = 0.007$; heterogeneity $I^2 = 0.01$) (Figure 3).

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

**Assisted reproductive technology multiple births versus natural conception multiple births**

**Study characteristics**

Three studies were included in the assisted reproductive technology multiple births versus natural conception multiple births meta-analysis (see Table 2). One study measured stress (Baor and Soskolne, 2010), while the other two measured depression (Vilska et al., 2009; Yokoyama, 2003). 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

### Table 2

<table>
<thead>
<tr>
<th>Study name</th>
<th>Std diff in means</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellison et al., 2005</td>
<td>0.292</td>
<td>-0.055</td>
<td>0.640</td>
<td>0.099</td>
</tr>
<tr>
<td>Olivennes et al., 2005</td>
<td>0.135</td>
<td>-0.014</td>
<td>0.285</td>
<td>0.076</td>
</tr>
<tr>
<td>Roca de Bes et al., 2009</td>
<td>-0.185</td>
<td>-0.628</td>
<td>0.258</td>
<td>0.414</td>
</tr>
<tr>
<td>Sheard et al., 2007</td>
<td>0.306</td>
<td>-0.047</td>
<td>0.658</td>
<td>0.089</td>
</tr>
<tr>
<td>Roca de Bes et al., 2011</td>
<td>0.073</td>
<td>-0.260</td>
<td>0.406</td>
<td>0.666</td>
</tr>
<tr>
<td>Vilska et al., 2009</td>
<td>0.435</td>
<td>0.174</td>
<td>0.696</td>
<td>0.001</td>
</tr>
<tr>
<td>Overall</td>
<td>0.198</td>
<td>0.050</td>
<td>0.345</td>
<td>0.009</td>
</tr>
</tbody>
</table>

**Figure 2** Forest plot for depression. Difference in means for depression in studies comparing mothers of assisted reproductive technology multiples with mothers of assisted reproductive technology singletons.
Vilska et al.’s (2009) studies were good. Yokoyama (2003) assessed stress at 6 months post-partum, while Vilska et al. (2009) and Yokoyama (2003) examined depression at 2 months and 3 years post-partum, respectively. Study quality for Baor and Soskolne (2010) and Vilska et al. (2009) was good. Yokoyama’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.

Sites and measures
Data were collected in Europe (Finland: Vilska et al., 2009) and Asia (Japan: Yokoyama, 2003; Israel: Baor and Soskolne, 2010) through self-administered measures assessing depression and stress, such as: Short form PSI (Baor and Soskolne, 2010), GHQ-36 (Vilska et al., 2009) and DSM IV (Yokoyama, 2003).

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

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 assisted reproductive technology did not score differently on psychological distress compared with mothers who conceived multiples naturally (standardized mean difference $d = 0.371$, 95% CI $-0.153$ to $0.895$; $z = 1.387$; with significant heterogeneity $I^2 = 86.962\%$, $P = 0.001$) (Figure 4).

When only depression data were used ($n = 1075$ mothers), the results were also non-significant, with non-significant heterogeneity (standardized mean difference $d = 0.152$, 95% CI $-0.179$ to $0.483$: $z = 0.901$; $I^2 = 36.918$) (Figure 5).

No publication bias was found for both depression and distress studies. Egger’s regression intercepts were non-significant, the funnel plots were symmetrical 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 assisted reproductive technology. Eight studies were included to examine depression, anxiety and stress of mothers of assisted reproductive technology twins/multiples versus mothers of natural conception twins/multiples and mothers of assisted reproductive technology twins/multiples versus mothers of assisted reproductive technology singletons. Two hypotheses informed the analytic process. The first hypothesis was partially tested, as there were not enough data on anxiety for mothers of assisted reproductive technology multiples and mothers of assisted reproductive technology singletons to run the analysis. However, results supported the predictions for depression and stress scores. To test the second hypothesis, this study adopted the methodological strategy to combine scores on stress and depression in the data analysis with assisted reproductive technology multiples and natural conception multiples, given the limited number of studies. Results did not support the second prediction.

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 assisted reproductive technology singletons versus mothers of assisted reproductive technology multiples–depression and stress analysis; assisted reproductive technology multiples depression and combined stress analysis) of the four data sets exceeded 1000 each. This allowed

<table>
<thead>
<tr>
<th>Study name</th>
<th>Std diff in means</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellison et al., 2005</td>
<td>0.394</td>
<td>-0.076</td>
<td>0.864</td>
<td>0.101</td>
</tr>
<tr>
<td>Olivennes et al., 2005</td>
<td>0.199</td>
<td>0.049</td>
<td>0.349</td>
<td>0.009</td>
</tr>
<tr>
<td>Roca de Bes et al., 2009</td>
<td>-0.034</td>
<td>-0.659</td>
<td>0.590</td>
<td>0.915</td>
</tr>
<tr>
<td>Roca de Bes et al., 2011</td>
<td>0.020</td>
<td>-0.313</td>
<td>0.353</td>
<td>0.904</td>
</tr>
<tr>
<td>Overall</td>
<td>0.177</td>
<td>0.049</td>
<td>0.305</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Figure 3  Forest plot for stress. Difference in means for stress in studies comparing mothers of assisted reproductive technology multiples with mothers of assisted reproductive technology singletons.
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Response rate</th>
<th>Outcome measurements</th>
<th>Time of measurements</th>
<th>Results</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baor and Soskolne (2010)</td>
<td>88 ART multiples mothers</td>
<td>86%</td>
<td>Parenting Stress Index (PSI)</td>
<td>6 months post-partum</td>
<td>Stress: Mean 82.63 (SD 21.53) for ART multiples Mean 66.77 (SD 13.81) for NC multiples $P &lt; 0.01$</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>98 NC multiples mothers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Israel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vilska et al. (2009)</td>
<td>70 Twins ART mothers</td>
<td>&gt;75% completed follow-up at 2 months postpartum</td>
<td>Depression and anxiety scores taken from General Health Questionnaire (GHQ-36)</td>
<td>2 months post-partum</td>
<td>Depression: Mean 1.29 (SD 0.36) for ART multiples Mean 1.34 (SD 0.339) for NC multiples NS</td>
<td>5</td>
</tr>
<tr>
<td>Finland*</td>
<td>15 NC Multiples mothers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yokoyama (2003) Japan</td>
<td>359 ART multiples mothers</td>
<td>–</td>
<td>Depression: Diagnostic and statistical manual of mental disorder (DSM-IV)</td>
<td>3 years post-partum</td>
<td>Depression: 16.1% of ART multiples reported depression 10.6% of NC multiples reported depression $P &lt; 0.05$</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>mothers and 631 NC multiples mothers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data obtained through author.

The maximum a study could achieve for quality assessment was 6 points. Any study that scored 4 points or higher was considered of good quality.

ART = assisted reproductive technology; NC = naturally conceived; NS = not statistically significant.
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 post-natal depression (Fisher and Stocky, 2003; Sutcliffe and Derom, 2006), such an analysis would have allowed the examination of the effects of baseline depression on depression in the post-partum. 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 et al., 2005) is substantively and theoretically distinct from generalized stress as measured by the Cohen Perceived Stress (Roca de Bes et al., 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 et al., 2009, 2011) and by the EPDS (Olivennes et al., 2005; Sheard et al., 2007). However, as previous studies indicate, there is normally a high degree of overlap between general depression scales and post-natal 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 (Rondo et al., 2003; Spielberger et al., 1970). Validated measures of depression, anxiety and emotional (psychological) subscales from quality of life questionnaires (Veltman-Verhulst et al., 2012) were used in combination too.

This study’s 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 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

### Figure 4
Forest plot for psychological distress. Difference in means for distress in studies comparing mothers of assisted reproductive technology multiples with mothers of natural conception multiples.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Std diff in means</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baor and Soskolne, 2010</td>
<td>0.887</td>
<td>0.585</td>
<td>1.189</td>
<td>0.000</td>
</tr>
<tr>
<td>Vilska et al., 2009</td>
<td>-0.130</td>
<td>-0.688</td>
<td>0.428</td>
<td>0.647</td>
</tr>
<tr>
<td>Yokoyama, 2003</td>
<td>0.253</td>
<td>0.042</td>
<td>0.464</td>
<td>0.019</td>
</tr>
<tr>
<td>Overall</td>
<td>0.371</td>
<td>-0.153</td>
<td>0.895</td>
<td>0.165</td>
</tr>
</tbody>
</table>

### Figure 5
Forest plot for depression. Difference in means for depression in studies comparing mothers of assisted reproductive technology multiples with mothers of natural conception multiples.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Std diff in means</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
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<tbody>
<tr>
<td>Vilska et al., 2009</td>
<td>-0.130</td>
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<td>0.428</td>
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<td>0.019</td>
</tr>
<tr>
<td>Overall</td>
<td>0.152</td>
<td>-0.179</td>
<td>0.483</td>
<td>0.368</td>
</tr>
</tbody>
</table>

O van den Akker et al.
basis of their specific factors, we recommend some caution in terms of the implications of our findings.

Results from this study indicate that depression and stress are more likely to occur after assisted reproductive technology multiple births compared with assisted reproductive technology singleton births, but the mechanism underpinning this process is unclear, given the constraints 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 assisted reproductive technology 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.

Since previous research has shown that assisted reproductive treatment itself can be stressful (Eugster and Vingerhoets, 1999; Williams et al., 2007), further meta-analyses were carried out comparing mothers of natural conception multiples with assisted reproductive technology multiples in an attempt to tease out the effect of multiples from the effects of assisted reproductive treatment. Only three studies (Baor and Soskolne, 2010; Vilska et al., 2009; Yokoyama, 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 sufficient data to support this could not be found. Premature multiple birth infants are often diagnosed with health problems such as respiratory and neurodevelopmental difficulties or disabilities and require extended and frequent hospitalization (Blickstein, 2002; Blickstein and Keith, 2003). Other factors such as difficulty establishing breastfeeding, and physical recovery (Fisher and Stocky, 2003) in parents of multiples may also be responsible. This studies 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 depression and distress. However, this meta-analysis focused on assisted reproductive technology versus natural conception twin perinatal outcomes.

We cannot conclude that assisted reproductive technology multiple births lead to stress and depression (Ross et al., 2011). However, different potential explanations for higher psychological problems in assisted reproductive technology 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 assisted reproductive technology 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 post-partum (Fisher and Stocky, 2003; Roca de Bes et al., 2009; Sutcliffe and Derom, 2006). In addition, maternal pre-natal distress is associated with low birthweight and prematurity (Rondo et al., 2003), although assisted reproductive treatment itself has been reported to lead to little or no increased risk for post-partum depression (Gressier et al., 2015; Ross et al., 2011). Therefore, assisted reproductive technology multiple birth mothers may not be completely comparable with the mothers of assisted reproductive technology 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 (USA – Ellison et al., 2005; Japan – Yokoyama, 2003; and Israel – Baor and Soskolne, 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 USA 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 improve support for families of multiples.

We strongly recommend that the clinical implications of multiple births specific to assisted reproductive technology should be explored further, because: (i) post-natal distress is likely to co-exist with previous pregnancy distress (Scottish Intercollegiate Guidelines Network, 2002); (ii) the consequences of distress in pregnancy are known to affect fetal growth (Henrichs et al., 2009); (iii) prematurity and low birthweight are important determinants of neonatal mortality (Shinwell et al., 2015) and neonatal, infant and childhood morbidity (De Kleine et al., 2007); (iv) the incidence of prematurity in mothers with comorbid anxiety and depression is greater than in non-depressed mothers (Field et al., 2010); and (v) 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 the children’s cognitive, social and emotional development (Murray et al., 1999). Taken together, these effects are complex and likely to pose considerable and serious public health concerns (Black and Bhattacharya, 2010).

One of the aims of this meta-analysis was to compare levels of depression in assisted reproductive technology and natural conception multiple birth mothers. There was a dearth of research into men’s psychological health and insufficient paternal data within multiple singleton, assisted reproductive technology/natural conception groups. Given the scarce identified evidence that was available even in women, it can be concluded that the psychological consequences of multiple births specifically, and assisted reproductive technology generally, are understudied (van den Akker, 2013). Vilska et al. (2009) reported ≤1 year depression data and found no
difference between mothers of assisted reproductive technology multiples and mothers of natural conception multiples, while Yokoyama (2003) found a greater level of depression in assisted reproductive technology multiple birth mothers than natural conception multiple birth mothers >1 year post-partum. This study’s findings suggest the need for more research on the psychological consequences of multiple births and assisted reproduction to allow more comprehensive meta-analyses involving moderating variables. Such an effort would contribute to the explanation and clinical implications of the associations found in this meta-analysis in terms of depression and stress in assisted reproductive technology multiple birth mothers compared with assisted reproductive technology singleton birth mothers and natural conception multiple birth mothers. Personality characteristics, such as neuroticism and specific coping strategies, for example, have recently been identified as positively associated with assisted reproductive technology distress (Rockliff et al., 2014). The same systematic review indicated that positive emotional states were rarely reported (Rockliff et al., 2014). The relative contributions of distress in pregnancy (which could not be included in this meta-analysis) and the different aetiological 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, 2005). It can be still argued that psychological research is lagging behind assisted reproductive technology practice.

Conclusion

Mothers of assisted reproductive technology multiple births exhibit significantly more stress and depression compared with mothers of assisted reproductive technology 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 assisted reproductive treatment. 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 post-partum than at > 1 year post-partum, suggesting that women need more support to cope with multiples following the first year post-delivery. Post-natal depression is more common at ≤ 1 year post-partum than after the first year and its occurrence in assisted reproductive technology 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.

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