Post-partum depressive symptoms and medically assisted conception: a systematic review and meta-analysis

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STUDY QUESTION: Does medically assisted conception increase the risk of post-partum depressive symptoms?

SUMMARY ANSWER: Our literature review and meta-analysis showed no increased risk of post-partum depressive symptoms in women after medically assisted conception.

WHAT IS KNOWN ALREADY: Women who conceive with medically assisted conception, which can be considered as a stressful life event, could face an increased risk of depressive symptoms. However, no previous meta-analysis has been performed on the association between medically assisted conception and post-partum depressive symptoms.

STUDY DESIGN, SIZE, DURATION: A systematic review with electronic searches of PubMed, ISI Web of Knowledge and PsycINFO databases up to December 2014 was conducted to identify articles evaluating post-partum depressive symptoms in women who had benefited from medically assisted conception compared with those with a spontaneous pregnancy. Meta-analyses were also performed on clinically significant post-partum depressive symptoms according to PRISMA guidelines.

PARTICIPANTS/MATERIALS, SETTING, METHODS: From 569 references, 492 were excluded on title, 42 on abstract and 17 others on full-text. Therefore, 18 studies were included in the review and 8 in the meta-analysis (2451 women) on clinically significant post-partum depressive symptoms after medically assisted conception compared with a spontaneous pregnancy. A sensitivity meta-analysis on assisted reproductive technologies and spontaneous pregnancy (6 studies, 1773 women) was also performed. The quality of the studies included in the meta-analyses was evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology Statement for observational research. The data were pooled using RevMan software by the Cochrane Collaboration. Heterogeneity between studies was assessed from the results of the $\chi^2$ and $I^2$ statistics. Biases were assessed with funnel plots and Egger’s test. A fixed effects model was used for the meta-analyses because of the low level of heterogeneity between the studies.

MAIN RESULTS AND THE ROLE OF CHANCE: The systematic review of studies examining post-partum depressive symptoms after medically assisted conception compared with spontaneous pregnancy is not in favor of an association. Our meta-analysis on clinically significant post-partum depressive symptoms showed no significant difference between women who used medically assisted conception and those with spontaneous pregnancy: odds ratio (OR) = 0.93 (0.67 – 1.31), $Z = 0.40$, $P = 0.69$. The sensitivity meta-analysis reported no significant difference either: OR = 1.04 (0.71 – 1.52), $Z = 0.18$, $P = 0.86$.

LIMITATIONS, REASONS FOR CAUTION: The literature on post-partum depressive symptoms and medically assisted conception is sparse. Only eight studies were available for our meta-analysis taking into account the rates of clinically significant post-partum depressive symptoms after medically assisted conception. However, the quality of the studies was high and the heterogeneity between trials was not significant. Whilst post-partum anxiety is more prevalent than depressive states and they can co-occur, it was not considered in these review and meta-analyses. In addition, other risk factors, such as maternal age, socio-demographic data or obstetric factors, are important for the assessment of post-partum depressive symptoms. Our review reported that several of these confounding risk factors were, however, analyzed and controlled for in the studies.
Introduction

The World Health Organization recognizes infertility as a public health issue. It is defined by ‘the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse’ and affects ~10% of couples (Boivin et al., 2007). The use of medically assisted conception (all fertility treatments including hormone treatment) and especially assisted reproductive technologies (ART) is increasing. In 2006, according to the International Committee for Monitoring ART (ICMART) World Report, there were ~1 050 300 ART procedures and 256 668 births resulting from ART worldwide (Mansour et al., 2014). Several technologies are used depending on the causes of infertility: ovulation induction, artificial insemination, IVF and IVF–ICSI, with or without gamete donation. While no significant differences are found in the psychological state of a couple beginning a process of medically assisted conception compared with the general population (Hearn et al., 1987; Edelmann et al., 1994), the experience of infertility and its treatments can be a source of stress (Eugster and Vingerhoets, 1999).

They can also alter the couple’s relationship: lower marital satisfaction was reported to be very common among infertile women compared with their partners or to fertile women (Tao et al., 2012). In addition, infertility can have adverse effects on self-esteem, which might persist during pregnancy and the post-partum period (McMahon et al., 1997; Gibson et al., 2000). During pregnancy, the anxiety of losing a child or the fear of fetal diseases can be significantly greater for couples undergoing medically assisted conception (Hjelmstedt et al., 2003). Moreover, IVF increases the risk of multiple pregnancies—especially if several embryos are implanted—prematurity, low birthweight and operative births (Eugster and Vingerhoets, 1999). Women conceiving through ART could also have a more intense emotional attachment to the fetus than women with a spontaneous pregnancy (Fisher et al., 2008; McMahon et al., 2011b). It has been suggested that because of the long periods of time spent wanting a pregnancy and the high investment in achieving it, parents may develop unreasonable high expectations toward the child (Colpin et al., 1999). In addition, women with assisted conception pregnancies might idealize parenthood and might not be prepared for the difficulties that it brings (Hammarberg et al., 2008). They might also have a lowered sense of entitlement to complain or seek help (Fisher et al., 2005). Moreover, with first-time mothers who have a history of infertility compared with naturally conceiving first-time mothers, higher stress scores for parental competence and health, lower psychosocial well-being (Colpin et al., 1999) and more marked dysregulated infant behaviors (Hammarberg et al., 2009) have been reported. Thus, women with medically assisted conception may experience difficulties adjusting to mothering. The post-partum period is therefore a time of psychological vulnerability and of increased risks for developing or exacerbating psychiatric disorders.

The overall prevalence of clinically significant post-partum depressive symptoms in high-income countries is 13–15% (O’Hara and Swain, 1996; Gaynes et al., 2005). This prevalence varies from 1.9 to 82.1% in low- and middle-income countries and from 5.2 to 74.0% in high-income countries, as assessed on a self-reported questionnaire. However, the wide ranges in prevalence could be attributed to several reasons: the use of different instruments, the choice of cut-off scores, the timing of the assessment and also the overestimation or underestimation of women’s responses to a self-report questionnaire according to beliefs, perceptions, culture and stigma of mental health in their communities (Norhayati et al., 2015). Based on a structured clinical interview, the prevalence is lower, ranging from 0.1% in Finland to 26.3% in India (Norhayati et al., 2015).

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), post-partum depression occurs during pregnancy or within 4 weeks following the birth; the International Classification of Diseases, 10th Edition (ICD-10) (1993) mentions a 6-week timeframe post-partum. However, most researchers consider that clinically significant post-partum depressive symptoms may occur at any time during the first post-partum year (Gaynes et al., 2005; Friedman and Resnick, 2009; Pearlstein et al., 2009). Furthermore, several authors also include minor depression in significant depressive symptoms (Gaynes et al., 2005).

Screening tools are mainly used to evaluate clinically significant post-partum depressive symptoms; the most frequently used being the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987). Researchers have not reported any major differences between puerperal and non-puerperal depressive symptoms, but the content of symptoms may focus on childbirth or the newborn baby (Robertson et al., 2004). Untreated clinically significant depressive symptoms can have adverse effects on the couple’s relationship, the mother–infant relationship and the child’s development (Murray et al., 2001; Burke, 2003). Significant post-partum depressive symptoms can be the first onset for a recurrent depressive disorder or a bipolar disorder to come (O’Hara and Swain, 1996; Wisner et al., 2004; Munk-Olsen et al., 2012). Early interactions between the mother and her baby can be affected, leading to a longer-term risk for the child of developing emotional, behavioral and/or cognitive disturbances (Murray et al., 2001; Burke, 2003). Post-partum depressive causes are multifactorial (O’Hara and Swain, 1996).
Robertson et al., 2004). In high-income countries, a history of any psychopathology, lack of social support, a poor relationship between partners and recent negative life events have been identified as risk factors. There is also an increased risk of post-partum depression in immigrant populations (Norhayati et al., 2015). The relatively high prevalence of maternal depression in low- and middle-income countries may be the result of women’s exposure to poverty and economic adversity (Parsons et al., 2012). Obstetric complications or biological and genetic factors could play a more minor but nevertheless significant role (O’Hara and Swain, 1996; Friedman and Resnick, 2009; Pearlstein et al., 2009). As described above, the experience of infertility and its treatments could be considered as a recent negative life event.

Therefore, we hypothesized an increased risk of post-partum major depressive symptoms after medically assisted conception.

This work aimed (i) to review the literature data on the association between medically assisted conception and depressive symptoms in the post-partum period; (ii) to further evaluate and understand the role of medically assisted conception in clinically significant post-partum depressive symptoms, using a meta-analysis process; (iii) to perform a sensitivity analysis on ART.

Materials and Methods

Search strategies

The review was conducted on the basis of the items outlined in the PRISMA statement (Moher et al., 2009). An electronic search of the literature was performed to identify association studies that have investigated the potential influence of medically assisted conception on post-partum depressive symptoms. PubMed, ISI Web of Knowledge and PsycINFO databases were used to search for articles published up to December 2014, using the combination of the following terms: ‘depression’ or ‘depressive disorder’ or ‘depressive symptoms’ or ‘affective disorder’ or ‘mood disorder’ and ‘postpartum’ or ‘postnatal’, and ‘infertility treatment’ or ‘fertility treatment’ or ‘assisted reproductive technology’ or ‘assisted conception’ or ‘in vitro fertilization’ or ‘artificial insemination’ or ‘sperm injection’. The same search was conducted in each database. Additional articles were identified from the reference lists of included studies and relevant reviews.

The search was repeated by two separate reviewers (F.G. and A.L.).

Inclusion and exclusion criteria

For the review, studies were included if (a) they were published, (b) they were in English or French, (c) they included a medically assisted conception population (all fertility treatments including hormone treatment), (d) they examined the association between depressive symptoms and medically assisted conception, (e) they included controls, (f) depressive symptoms were evaluated between 2 weeks and 1 year after giving birth. Articles were excluded if (a) they were case reports, (b) they reported only case series.

The full text was screened to detect relevant studies. For each study, the following information was extracted: the first author, the publication year, the design, the sample size, the assessment time after birth, the scales used, clinically significant depressive symptom frequencies and/or the mean scale scores in both groups when they were available and the results.

For the primary meta-analysis, studies were included if (a) they were published studies, (b) they were in English or French, (c) they were studies evaluating the association between clinically significant post-partum depressive symptoms and medically assisted conception, (d) they reported data on rates of clinically significant post-partum depressive symptoms in both groups, (e) the data were not extracted from the same cohorts, or data had not been published before, (f) rates of clinically significant depressive symptoms were evaluated using standard scales. Studies were excluded if they were performed with no control groups. For each selected study, the data were extracted. When no data were given in articles, we asked for this information from the authors. We then performed a sensitivity analysis on data taking into account ART only.

Risk of bias and quality assessment of the studies

We incorporated the risks of a biased assessment into our analyses by evaluating the sources of bias that could affect the overall estimations. The quality of the studies included in the meta-analyses was evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for observational research (Vandenbroucke et al., 2007).

Data analysis

To perform the meta-analyses, data were entered and analyzed using the Cochrane Collaboration Review Manager Software (RevMan version 5.3). Individual and pooled odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated. The heterogeneity between studies was assessed using the $I^2$ test for fit and $I^2$. The significance of the pooled effect size was determined using a Z-test. Data were analyzed using a fixed effects framework in the case of absence of between-study heterogeneity and a random effects framework in the case of significant between-subject heterogeneity. A funnel plot was produced to reveal selective reporting— the preferential publication of statistically significant results—by plotting the natural logarithm of individual study effect size. Publication bias was also assessed using Egger’s test (Egger et al., 1997) in the R statistics environment (http://www.R-project.org) version 2.14.1, ‘metafor’ package.

In the first analysis, we included all studies on the rates of clinically significant post-partum depressive symptoms and medically assisted conception. Then we performed a sensitivity analysis taking into account only ART data.

Results

The PubMed database yielded 563 records. Six additional records were identified from other sources. In total, 492 references were excluded on title and 42 on abstract. Thirty-five full-text articles were assessed for eligibility (Fig. 1). Seventeen were excluded: five were literature reviews (Garner, 1985; Klock, 2004; Health Quality Ontario, 2006; Hammarberg et al., 2008; Ross et al., 2011), one was a case report (McIntosh and Ferrando, 2010), two were not on depressive symptoms (Cox et al., 2006; Monti et al., 2008), two reported data only on mental health in women preparing for IVF (Yager et al., 2010; Lewis et al., 2013), four concerned only pregnancy (Harf-Kashdai and Kaitz, 2007; Fisher et al., 2008; Fisher et al., 2013a, b), three had no control population (Sheard et al., 2007; Lee et al., 2011; Darwiche et al., 2013). Finally, 18 studies were included in the review (Table I).

Regarding depressive symptoms, only one study reported higher EPDS scores in the ART group compared with the control group at 3 months post-partum (5.76 versus 3.87, $P < 0.05$; Monti et al., 2009). However, the proportion of women with major depressive symptoms (EPDS score ≥ 12) was not significantly different between the two groups. The rest of the studies did not find any significant differences between ART groups and spontaneous pregnancy groups for depressive symptoms (McMahon et al., 1997; Colpin et al., 1999; Gibson et al., 2000; Glazebrook et al., 2000; Greenfeld and Caruso Klock, 2001; Chatzizanidou et al., 2003; Glazebrook et al., 2004; Fisher et al., 2005; Repokari et al.,...
However, two studies reported very low mean depressive scores (Chatziandreou et al., 2003; Tallandini et al., 2012 on preterm birth). Interestingly, Fisher et al. (2005) conducted their study in a joint mother and baby unit and reported more admissions of women after ART than after spontaneous pregnancies ($P = 0.001$), with a relative risk of 4 (95% CI $= 3–5.4$). However, the difference was not significant when they studied major depressive symptoms.

Our meta-analysis on the rates of clinically significant post-partum depressive symptoms included eight studies (Gibson et al., 2000; Fisher et al., 2005; Monti et al., 2009; Akyuz et al., 2010; McMahon et al., 2011a; Warmelink et al., 2012; Listijono et al., 2014; Raguz et al., 2014). The quality of the included studies was good (see Supplementary data, Table S1). No significant difference was reported in the incidence of significant post-partum depressive symptoms between women who used medically assisted conception and those with a spontaneous pregnancy [$OR = 0.93$ (95% CI $= 0.67, 1.31$), $Z = 0.40, P = 0.69$]. There was no significant heterogeneity between studies ($\chi^2 = 3.69, df = 7, P = 0.81, I^2 = 0\%$; Fig. 2). Egger’s test indicated no evidence of a publication bias ($t = 0.14, df = 6, P = 0.86$; see Supplementary data, Fig. S1 for the funnel plot).

In the six studies with ART only (Gibson et al., 2000; Fisher et al., 2005; Monti et al., 2009; Akyuz et al., 2010; McMahon et al., 2011a; Listijono et al., 2014), we did not find any association with post-partum depressive symptoms [$OR = 1.04$ (95% CI $= 0.71, 1.52$), $z = 0.18, P = 0.86$; Fig. 3). Egger’s test indicated no evidence of a publication bias ($t = 1.07, df = 4, P = 0.35$; see Supplementary data, Fig. S2 for the funnel plot).
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Assessment time (PP)</th>
<th>Measures</th>
<th>Main inclusion criteria</th>
<th>Group comparison for confounding factors</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>McMahon et al. (1997)</td>
<td>127: 65 IVF-ET</td>
<td>16–18 weeks</td>
<td>EPDS</td>
<td>Primiparous Singleton pregnancy Living with the father of the child Adequate English language skills Age-matched</td>
<td>IVF-ET: older maternal age, infants born earlier, weighed less, spent more time in neonatal intensive care Controls: trend to higher educational level NS: rate of Caesarean section</td>
<td>NS even after adjusting for age, educational level and birthweight of the infant</td>
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<td>Colpin et al. (1999)</td>
<td>103: 25 hormonal treatment 24 IVF or AI 54 controls</td>
<td>10–13 months</td>
<td>GHQ-30</td>
<td>Twin pregnancy</td>
<td>IVF/AI: lower presence of older children NS: Maternal and paternal age, parents education, prematurity</td>
<td>NS But for the IVF/AI and hormonal treatment: higher stress and lower psychosocial well-being among first-time mothers than mothers who already had children</td>
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<td>Glazebrook et al., 2000</td>
<td>330: 184 IVF (119 singleton, 65 multiple) 146 controls</td>
<td>6 weeks</td>
<td>EPDS</td>
<td>Depression: &gt; 11 Singleton and multiple pregnancies</td>
<td>IVF: older, in a stable relationship with their present partner for a longer time, had taken longer to conceive</td>
<td>NS</td>
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<td>Gibson et al. (2000)*</td>
<td>126: 65 IVF 61 controls</td>
<td>1 year</td>
<td>CES-D</td>
<td>Depression: ≥ 16 Singleton pregnancy Aged 28 or older Living with the father of the child Adequate English language skills</td>
<td>IVF: older maternal age, trend toward lower educational levels, more non-English-speaking white, Asian, or Pacific Islander background, poorer general marital adjustment reported by fathers</td>
<td>NS in multivariate analyses (P &gt; 0.10) EPDS ≥ 13: IVF = 4.62% Controls = 6.56%</td>
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<tr>
<td>Greenfeld and Caruso Klock (2001)</td>
<td>88: 56 IVF 32 controls</td>
<td>2 months 9 months</td>
<td>BDI</td>
<td>Singleton and multiple pregnancies First-time parent Between the ages of 21 and 44 Able to read English Married or cohabiting in a stable relationship</td>
<td>IVF: older maternal age, longer duration of marriage, fewer occasions for weekly exercise, more previous miscarriages, higher average number of ectopic pregnancies, more work outside and within the home NS: number of previous marriages, ethnic background, educational level, household income, religious affiliation, religiosity, self-rated health status, stillbirths, elective abortions, number of alcoholic beverages consumed per week, history of psychoactive medication use, length of maternity leave, type or amount of childcare used, and division of labor of childcare tasks by wives and husbands</td>
<td>NS Mean BDI scores (SD): 2 months: IVF = 7.7 (7.1) Controls = 6.8 (3.4) 9 months: IVF = 6.0 (5.1) Controls = 5.7 (3.1)</td>
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<td>Study</td>
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<td>Chatziandreou et al. (2003)</td>
<td>52: 26 IVF 26 controls</td>
<td>4–6 months</td>
<td>EPDS</td>
<td>Primaiparous&lt;br&gt;Aged between 26 and 43&lt;br&gt;Among middle class&lt;br&gt;Psychiatric history: no pre-existing psychopathology requiring psychiatric treatment</td>
<td>IVF: older maternal and paternal age, trend to higher educational level&lt;br&gt;NS: number of previous failures or abortions</td>
<td>NS P = 0.69&lt;br&gt;Mean scores (SD)&lt;br&gt;IVF = 1.77 (3.0)&lt;br&gt; Controls = 2.15 (3.9)</td>
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<td>Glazebrook et al. (2004)</td>
<td>260: 131 IVF 129 controls</td>
<td>1 year</td>
<td>GHQ-12 &gt; 3</td>
<td>IVF: singleton and multiple pregnancies&lt;br&gt;Controls: primiparous, singleton pregnancy</td>
<td>Multiple IVF versus controls: older maternal age, higher years in a relationship, lower birthweight, prematurity, infant hospitalization, more Cesarean sections&lt;br&gt;Single IVF versus controls: older maternal age, higher years in a relationship, prematurity, infant hospitalization</td>
<td>NS&lt;br&gt;Psychiatric disorder: Multiple IVF = 22%&lt;br&gt; Singleton IVF = 27%&lt;br&gt; Singleton controls = 29%</td>
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<td>Fisher et al. (2005)*</td>
<td>735: 45 IVF 12 OI and AI 678 controls</td>
<td>Days 1 and 5</td>
<td>EPDS</td>
<td>Mother baby unit&lt;br&gt;Depression: &gt; 12</td>
<td>ART: older maternal age, operative and multiple births, lower birthweight&lt;br&gt;NS: multiparous, infant age at admission</td>
<td>NS&lt;br&gt;EPDS &gt; 12 (Day 5)&lt;br&gt;IVF = 13.64%&lt;br&gt;OI and AI = 15%&lt;br&gt;Controls = 15.62%</td>
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<td>Repokari et al. (2005)</td>
<td>746: 367 IVF or ICSI treatment with their own gametes 379 controls</td>
<td>2 months 1 year</td>
<td>GHQ-36</td>
<td>Singleton pregnancy&lt;br&gt;ART: maternal age, prematurity, birthweight&lt;br&gt;NS: multiparous, infant age at admission</td>
<td>ART: older paternal age, men lower socio-economic status, longer length of marriage or cohabiting partnership, fewer children&lt;br&gt;Controls: multiparous&lt;br&gt;NS: maternal age, prematurity, birthweight</td>
<td>NS in multivariate analyses&lt;br&gt;ART: fewer depressive symptoms during pregnancy than controls, but at 2 months no significant difference and same levels at 1 year</td>
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<td>Vilksa et al. (2009)</td>
<td>857: 458 IVF–ICSI: 91 twins/367 singletons 399 controls: 20 twins/379 singletons</td>
<td>2 months 1 year</td>
<td>GHQ-36</td>
<td>Singleton and twin pregnancies&lt;br&gt;Same cohort as Repokari et al. (2005)</td>
<td>ART: tendency for longer partnerships, primiparity&lt;br&gt;ART mothers of twins: younger than other mothers&lt;br&gt;The ART and control parents of twins: more prematurity, lower birthweight, earlier separation from the mother and more frequent admittance to an NICU&lt;br&gt;NS: paternal age</td>
<td>NS ART versus controls&lt;br&gt;Both ART and control mothers of twins: more symptoms of depression than mothers of singletons&lt;br&gt;Means for Depression (SE) 2 months&lt;br&gt;ART: Singletons = 1.19 (0.01)&lt;br&gt;Twins = 1.30 (0.03)&lt;br&gt;Controls: Singletons = 1.23 (0.03)&lt;br&gt;Twins = 1.34 (0.06)&lt;br&gt;1 year:&lt;br&gt;ART: Singletons = 1.27 (0.02)&lt;br&gt;Twins = 1.40 (0.04)&lt;br&gt;Controls: Singletons = 1.30 (0.02)&lt;br&gt;Twins = 1.54 (0.08)</td>
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<td>Study</td>
<td>Sample Size</td>
<td>Follow-Up</td>
<td>Screening Tool</td>
<td>Screening Criteria</td>
<td>Comparison</td>
<td>Mode of Conception</td>
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<td>Monti et al. (2009)*</td>
<td>64: 25 ART 39 controls</td>
<td>3 months</td>
<td>EPDS</td>
<td>Depression: ≥ 12</td>
<td>ART: older maternal age, more years of co-habitation</td>
<td>NS: educational level, profession, social classes, marital status, religion, parity, antenatal classes, vaginal delivery</td>
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<td>Akyuz et al. (2010)*</td>
<td>156: 51 primary infertility-treated women 105 controls</td>
<td>4–6 weeks</td>
<td>PDSS</td>
<td>Depression: ≥ 65</td>
<td>Infertility: older maternal age, lower educational status, higher duration of marriage, tendency toward unemployment</td>
<td>NS even in multivariate analyses</td>
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<tr>
<td>McMahon et al. (2011a, b)*</td>
<td>541: 275 ART 266 controls</td>
<td>4 months</td>
<td>EPDS</td>
<td>Depression: MINI</td>
<td>Primiparous Stratified by age Adequate English language</td>
<td>Mode of conception correlated with marital status, previous marriage, home ownership, prior miscarriage, time to become pregnant, likelihood of multiple pregnancy, gestational complications.</td>
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<tr>
<td>Tallandini et al. (2012)</td>
<td>94: 41 infertility treatment 53 controls</td>
<td>1 month</td>
<td>BDI</td>
<td>Preterm delivery Absence of malformations Absence of medical and/or psychiatric maternal pathology Presence of parental couple at birth</td>
<td>ART: higher parity NS: maternal age, educational level, occupation, gestational age, birthweight, neonatal characteristics, length of hospital stay, infant gender</td>
<td>NS with repeated ANOVA measures. Means (SD) 1 month Infertility treatment = 5.33 (4.69) Controls = 5.98 (5.37) 3 months: Infertility treatment = 4.44 (4.03) Controls = 4.93 (5.12)</td>
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<tr>
<td>Warmelink et al. (2012)*</td>
<td>428: 15 AI or IUI 17 IVF/IVF–ICSI 396 controls</td>
<td>2–6 months</td>
<td>HADS</td>
<td>Depression: ≥ 8</td>
<td>Cross-sectional multicenter study</td>
<td>Assisted conception: older maternal age, more twins, hypertension during pregnancy NS: education, marital status, country of origin, primiparity, history of miscarriages, history of terminations of pregnancy, history of ectopic pregnancy, pregnancy complications except for hypertension, percentage of women delivered in a primary care setting, delivery complications</td>
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<td>Raguz et al. (2014)*</td>
<td>228: 76 fertility treatment 152 controls</td>
<td>4 months</td>
<td>EPDS</td>
<td>Depression: ≥ 13</td>
<td>Singleton pregnancy</td>
<td>ART: older maternal age NS: annual household income, educational level, time living in Canada, ethnicity, marital status, parity—birth to a fetus ≥ 24 weeks, parity, delivery method, preterm birth, previous history of abuse, history of mental disorders</td>
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<td>Study</td>
<td>Sample size</td>
<td>Assessment time (PP)</td>
<td>Measures</td>
<td>Main inclusion criteria</td>
<td>Group comparison for confounding factors</td>
<td>Results</td>
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<td>Lynch and Prasad</td>
<td>40,337</td>
<td>2–4 months</td>
<td>PRAMS</td>
<td>Cross-sectional population-based study</td>
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<td>NS even after adjustment for confounders</td>
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<td>Akyüz et al. (2010)</td>
<td>200</td>
<td>6 weeks</td>
<td>Depression:</td>
<td>Retrospective study</td>
<td></td>
<td>Depression: ART = 7.45%, Controls = 7.37%</td>
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<td>Modified EPDS</td>
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<tr>
<td>McMahon et al. (2011a)</td>
<td>105</td>
<td>6 weeks</td>
<td>Depression:</td>
<td>Retrospective study</td>
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<td>NS</td>
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<td>Modified EPDS</td>
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<tr>
<td>Listijono et al. (2014)*</td>
<td>189</td>
<td>4 weeks</td>
<td>Depression:</td>
<td>Retrospective study</td>
<td></td>
<td>NS</td>
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<td></td>
<td>94 ART</td>
<td></td>
<td>Modified EPDS</td>
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<td></td>
<td>95 controls</td>
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AI, artificial insemination; ART, assisted reproductive technologies; ANOVA, analysis of variance; BDI, beck depression inventory; CES-D, center for epidemiological studies of depression scale; EPDS, Edinburgh postnatal depression scale; GHQ, general health questionnaire; HADS, hospital anxiety and depression scale; IUI, intrauterine insemination; MINI, mini international neuropsychiatric interview; NS, non-significant; NICU, neonatal intensive care unit; OI, ovulation induction; PDSS, postpartum depression screening scale; PP, postpartum; PRAMS, pregnancy risk assessment monitoring system; *, included in our meta-analyses.

Interestingly, several studies compared the variations in depressive symptoms between ART groups and control groups during pregnancy and the postpartum period. Repokari et al. (2014) reported lower depressive symptoms between ART groups and control groups during the postpartum period. However, these differences were not significant. In addition, some studies performed multivariate analyses, taking into account variables thought likely to influence the measures of adjustment. Several studies performed bivariate analyses on potential confounding factors and did not report any association between depressive symptoms and the outcome of interest. In conclusion, further research is needed to determine the role of ART in the development of depressive symptoms during pregnancy and the postpartum period.
et al., 2005; Akyuz et al., 2010; Tallandini et al., 2012; Lynch and Prasad, 2014).

Interestingly, two studies reported no difference in terms of depressive symptoms when taking into account the use of donated gametes and/or the number of previous failed cycles (McMahon et al., 1997, 2011a).

Further to this, several studies have focused on depressive symptoms in case of multiple births whether or not with assisted conception. Colpin et al. (1999) compared patients who gave birth to twins after medical treatment and those without any treatment. They did not find significant differences (GHQ-30 score). However, only in the ART group were the GHQ-30 scores significantly higher among primiparous than among multiparous women. Glazebrook et al. (2004) showed a significant difference among women reporting depressive symptoms between singleton births after ART (26%), multiple births after ART (47%) and spontaneous pregnancies (41%) (P < 0.03). However, the groups did not differ in terms of GHQ scores. Vilska et al. (2009), using the same cohort as Repokari et al. (2005), reported more frequent depressive symptoms in mothers of twins, regardless of the mode of conception compared with a singleton birth at 2 months (P < 0.05) and 1 year (P < 0.01). They concluded that the risk of depression was associated with the plurality of births rather than the mode of conception.

**Discussion**

The main aim of our study was to summarize the literature regarding the possible association between post-partum depressive symptoms and medically assisted conception, and then to conduct a primary
meta-analysis on the rates of clinically significant post-partum depressive symptoms after medically assisted conception, and a sensitive analysis on ART only. To our knowledge, this is the first meta-analysis investigating the association between medically assisted conception and post-partum depressive symptoms with the aim of shedding light on previous results. Indeed, although two earlier meta-analyses (O’Hara and Swain, 1996; Beck, 2001) searched for antenatal risk factors for significant post-partum depressive symptoms, neither analyzed the association between assisted conception and post-partum depressive symptoms. Only one systematic review (with no meta-analysis) on nine studies published up to April 2009 had been previously published, showing no increased risk of depressive symptoms after medically assisted conception (Ross et al., 2011). Another review of 28 studies published up to November 2007 focused on the psychological and social aspects of pregnancy, childbirth and early parenting after assisted conception. They reported inconclusive or contradictory results on the adjustment to parenthood, the experience of childbirth and the perceptions of infant temperament and behavior (Hammarberg et al., 2008).

Thus, data in the literature demonstrates no increased risk for significant post-partum depressive symptoms after medically assisted conception, and this is strengthened by the results of our meta-analyses.

Further to this, although multiple births seemed to be a risk factor for significant post-partum depressive symptoms (Choi et al., 2009), studies focusing on populations of multiple pregnancies showed that ART did not appear to induce greater risk for post-partum depressive symptoms (Sheard et al., 2007; Vilksa et al., 2009).

There are several limitations to our study. First, only six studies analyzed the incidence of significant post-partum depressive symptoms between women who used medically assisted conception and those with a spontaneous pregnancy. However, data remained unknown for only one (Glazebrook et al., 2000). The studies were heterogeneous in design, recruitment strategies (type of medically assisted conception, parity, single or multiple pregnancies), time of assessment, sample size, measurement scales and consideration of psychiatric history. Moreover, one of the studies included in the meta-analyses (Fisher et al., 2005) evaluated the EPDS scores at Days 1 and 5 of the treatment program. Although the assessment time could be different between the mothers, the EPDS score evaluates the past 7 days, and the authors mentioned that the hospitalization took place in the first 12 months post-partum (Fisher et al., 2005). However, our meta-analyses showed no statistically significant heterogeneity.

Secondly, post-partum anxiety is more prevalent than depressive states and can co-occur with them, but this was not considered in this review or the meta-analyses. However, regarding anxiety, no significant difference between medically assisted conception groups and control groups was reported in five studies on the Spielberger State-Trait Anxiety Inventory (STAI) (Gibson et al., 2000; Greenfeld and Caruso Klock, 2001; McMahon et al., 2011a; Raguz et al., 2014) or the Hospital Anxiety and Depression scale (HADS) (Warmelink et al., 2012). However, two studies suggested lower anxiety symptoms in the group with infertility treatment [Repokari et al., 2003 on STAI; Tallandini et al., 2012 on BAI (Beck Anxiety Inventory)].

Older maternal age and sometimes higher socio-economic levels have been reported in medically assisted conception populations (McMahon et al., 1997; Chatziandreou et al., 2003). These factors have been documented as protective against the occurrence of post-partum depressive symptoms, except higher maternal age (over 35 years) (Astbury et al., 1994). However, several variables were controlled for in the studies.

Fourthly, the studies included in our review and meta-analyses were only conducted in high-income countries. Our results need to be confirmed by studies in other countries and in low socio-economic samples.

In addition, even if the rates of depressive symptoms are the same in medically assisted conception populations and control groups, the risk factors could be different. Indeed, some of the established risk factors for post-partum depressive symptoms, such as young age, conflict within the couple, low socio-economic status, high parity or unwanted pregnancy, are very rare in infertility populations (Hammarberg et al., 2008). But on the other hand, assisted conception appears to be associated with an increased rate of early parenting difficulties (Fisher et al., 2005). The transition from infertility to motherhood might be a challenge of a psychological nature. Indeed, parenthood might be idealized after infertility. Women with a history of infertility might also feel they are not entitled to complain or to express any doubts, uncertainty or mixed feelings about their motherhood (Fisher et al., 2008). They may also be less prepared for difficulties of parenthood as a result of their idealization of it (Hammarberg et al., 2008). These psychological factors might increase depressive symptoms in women who conceive with medical assistance.

It is therefore interesting to study the characteristics of depressive symptoms in women who have resorted to medically assisted conception. Lee et al. (2011) conducted a study on 71 women who underwent treatment for infertility to identify factors associated with post-partum depressive symptoms. They found a positive correlation between the frequency of the IVF treatment, perceived stress and the rate of post-partum depressive symptoms. A multiple linear regression analysis showed that the frequency of ART treatment, Caesarean birth and poor social support were predictors of significant post-partum depressive symptoms. Another study found that marital satisfaction and the ‘divided self’ (a condition in which women present an outer, compliant self while experiencing internal anger) may be predictors of the development of post-partum depressive symptoms in first-time mothers with a history of infertility (Olshansky and Sereika, 2005).

It would be interesting to carry out further studies; for instance, assessing the influence of the type of medically assisted conception (the technique used, whether with or without a gamete donation) on the occurrence of significant post-partum depressive symptoms. The origin (paternal or maternal) and nature of the infertility could also be important points to consider. Furthermore, only a few studies have been performed evaluating psychiatric disorders in fathers after ART compared with spontaneous pregnancies (Colpin et al., 1999; Gibson et al., 2000). More studies about the risk of paternal depressive symptoms after medically assisted conception could be an area for future research.

The psychosocial consequences of medically assisted conception remain a significant public health issue. Our literature review and meta-analysis showed no increased risk of significant post-partum depressive symptoms in women after medically assisted conception. Nevertheless, the process of medically assisted conception requires individualized support. Professionals should also be careful to screen for prenatal and post-partum depressive symptoms, as for all pregnant women.
Further studies are needed to clarify the specific features of post-partum depressive symptoms in this population.

**Supplementary data**

Supplementary data are available at http://humrep.oxfordjournals.org/.

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**Authors’ roles**

F.G. designed the review. F.G. and A.L. managed the literature search. F.G., A.L. and B.F. performed the meta-analyses. F.G., A.L., O.C., A.L.S.-D., B.F. and P.H. interpreted the data. F.G. and A.L. wrote the first draft of the manuscript. All authors contributed to the review and improvement of final version. All authors have approved the final manuscript.

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**Conflict of interest**

Regarding potential conflicts of interest, all of them were indirect: F.G. has given talks for Lundbeck and Servier and received a grant from Servier. A.L., O.C. and P.H. reported no biomedical financial interests or potential conflicts of interest. A.L.S.-D. reports no financial relationships with commercial interests. B.F. has been a consultant, an expert for Genzyme, Pierre Fabre, AstraZeneca, Roche, Boehringer Ingelheim, Bayer, Almirall, Allergan, Stallergenes, Genzyme, Pierre Fabre, Astra Zeneca, Novartis, Janssen, Astellas, Biotronik, Daiichi-Sankyo, Gilead, MSD, Lundbeck. HRA, Roche, Boeringer Ingelheim, Bayer, Almirall, Allergan, Stallergene, Genzyme, Pierre Fabre, Astra Zeneca, Novartis, Janssen, Astellas, Biotronik, Daiichi-Sankyo, Gilead, MSD, Lundbeck.

**References**


Hammarberg K, Rowe HJ, Fisher JR. Early post-partum adjustment and admission to parenting services in Victoria, Australia after assisted conception. Hum Reprod 2009;24:2801–2809.


McIntosh MD, Ferrando S. Perimenopausal postpartum depression after conception by assisted reproductive technology. *Psychosomatics* 2010; **51**:345–348.


Olshansky E, Sereika S. The transition from pregnancy to postpartum in previously infertile women: a focus on depression. *Arch Psychiatr Nurs* 2005; **19**:273–280.


Ross LE, McQueen K, Vigo S, Dennis CL. Risk for postpartum depression associated with assisted reproductive technologies and multiple births: a systematic review. *Hum Reprod Update* 2011; **17**:96–106.


