Assisted reproductive technology and the risk of preeclampsia: an updated systematic review and meta-analysis

Amir Almasi-Hashiani 1, Reza Omani-Samani 2, Maryam Mohammadi 2, Payam Amini 3, Behnaz Navid 2, Ahad Alizadeh 2, Esmaeil Khedmati Morasae 4 and Saman Maroufizadeh 5*

Abstract

Background: The objective of this systematic review and meta-analyses was to assess the risk of preeclampsia among women who conceived with assisted reproductive technology (ART).

Methods: We searched the ISI Web of Knowledge, Medline/PubMed, Scopus, and Embase (from inception to May 2017) for English language articles using a list of key words. In addition, reference lists from identified studies and relevant review articles were also searched. Data extraction was performed by two authors, and the study quality was assessed using the Newcastle–Ottawa Scale. Random-effects model meta-analysis was applied to pool the relative risks (RR) across studies.

Results: A total of 48 studies (5 case-control studies and 43 cohort studies) were included in this meta-analysis. The Cochran Q test and I² statistics revealed substantial heterogeneity (Q = 26,313.92, d.f. = 47, p < 0.001 and I² = 99.8%). Meta-analysis showed a significant increase in preeclampsia in women who conceived by ART compared with those who conceived spontaneously (RR = 1.71, 95% CI = 1.11–2.62, p = 0.015).

Conclusions: The findings of this systematic review indicate that the use of ART treatment is associated with a 1.71-fold increase in preeclampsia.

Keywords: Assisted reproductive technology, Preeclampsia, Infertility, Meta-analysis, Systematic review

Background

Assisted reproductive technologies (ART) are used to treat infertility problems and contain methods in which oocyte and sperm are manipulated in vitro [1]. The use of ART has increased exponentially worldwide and is responsible for over than one million births annually [2, 3]. Having been treated by ART, the women who conceived had numerous adverse outcomes, both for themselves and the infants [3]. Previous studies have demonstrated that ART is associated with small for gestational age infants, preterm delivery, perinatal mortality, preeclampsia (PE), gestational diabetes, placenta previa, placental abruption, and cesarean delivery [4]. Of several adverse pregnancy consequences, hypertensive disorders affect 6–8% of all pregnancies through gestational hypertension and PE [5, 6]. In contrast to spontaneous pregnancy, pregnancies with ART are at an increased risk of PE [7]. It remained unclear whether either ART itself [in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), intratuterine insemination (IUI), oocyte donation (OD), or embryo donation (ED)] or maternal risk factors associated with ART (that is, advanced maternal age, obesity, change of partner, longer interval between births, reduced smoking, and chronic hypertension) were related to increased risk of PE [7, 8]. Some studies have shown the probability of the taking of some medications during pregnancy, such as low-dose aspirin, [9] prevents for PE in high-risk women [10–12]. Thus, identifying high-risk women during the early period of gestation will be worthwhile for the prevention and management of the pregnancy complications [13]. Finally, the lack of diagnostic criteria for pregnancy complications associated...
with hypertension, especially for PE, make the research in this field more complicated [14].

In the present paper, the authors conducted a comprehensive systematic review of ART procedures and PE. The aim of this review was to investigate whether ART mediated pregnancies (i.e., IUI, IVF, ICSI, OD, and ED) increased the incidence of PE in pregnancy compared with spontaneous pregnancies.

**Methods**

**Search strategy**

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist [15]. We conducted a systematic literature search in Medline/PubMed, Embase, Scopus, and the ISI Web of Knowledge from inception through June 2017 for studies examining the association between ART and PE. In addition, reference lists from all retrieved papers were checked. Table 1 provides more details about the search strategy.

**Inclusion and exclusion criteria**

We included published case-control studies and cohort studies evaluating the association between ART and PE risk. No geographic restrictions were used. The following types of studies were excluded: (a) non-English full-text studies, (b) animal studies, (c) repeated or overlapping studies, (d) reviews, meta-analysis and cross-sectional articles, case reports, editorials, and letters to the editor, (e) abstract-only publications or unpublished studies. There were five case-control studies added to the study. However, it was not substantially possible to estimate the relative risk (RR) with case-control design due to the fact that the marginal probabilities were not available; under the rare disease assumption, the odds ratio will be approximate the RR.

**Outcome and exposure**

In the present study, all types of ART treatments were considered as the interested exposure variable. Our outcome was PE defined as “elevated blood pressure (BP) (more than 140/100 mmHg) and proteinuria (0.3 g over 24 hours or more).”

**Data extraction**

Two authors (MM and SM) independently extracted the following data from all studies meeting the inclusion criteria: first author’s name, year of publication, location, study period, design, sample size, and study results. In addition, outcome data were extracted from each study in a 2 × 2 table, and the results were expressed as RR with their respective 95% confidence intervals (CIs) [9].

**Quality assessment**

Two authors (MM and SM) independently assessed the quality of studies using the Newcastle–Ottawa Scale (NOS) [16]. This scale assesses methodology in three domains: (a) selection of study groups, (b) comparability of groups, and (c) ascertainment of exposure and outcomes. Total score ranged from 0 to 9 with a score of ≥8 indicating high quality.

**Statistical analysis**

Statistical analysis was conducted using Stata version 13.0 (Stata Corp, College Station, TX, USA). The RR was used as the effect size of association across studies. The Cochran Q test and the I² statistic were used to evaluate heterogeneity among studies [17]. Concerning the Cochran Q test, P < 0.10 was deemed statistically significant for heterogeneity. The I² statistic indicates the percentage of total variation across studies that is due to heterogeneity rather than chance and is classified as mild (25%), moderate (50%), or high (75%) [17]. The Galbraith plot was used to detect the potential sources of heterogeneity [18]. The pooled RR estimate and corresponding 95% CI were calculated by using the random-effect model incorporating between-study variability. The Begg’s rank correlation test, Egger’s weighted regression test, and visual inspection of a funnel plot were used to assess publication bias [19, 20]. All tests were two-tailed and a P value of < 0.05 was deemed statistically significant.

**Table 1 Search strategy for MEDLINE (MeSH, Medical Subject Headings)**

| 1 | Preeclampsia [Text Word] |
|---|----------------------------|
| 2 | Pre-Eclampsia [Text Word] |
| 3 | “Pre-Eclampsia” [Text Word] |
| 4 | “Pre-Eclampsia” [MeSH Terms] |
| 5 | 1 OR 2 OR 3 OR 4 |
| 6 | Reproductive Techniques, Assisted [Text Word] |
| 7 | Reproductive Techniques, Assisted [MeSH Terms] |
| 8 | 6 OR 7 |
| 9 | Cohort Studies [Text Word] |
| 10 | Cohort Studies [MeSH Terms] |
| 11 | Retrospective Studies [Text Word] |
| 12 | Retrospective Studies [MeSH Terms] |
| 13 | Prospective Studies [Text Word] |
| 14 | Prospective Studies [MeSH Terms] |
| 15 | Case-Control Studies [Text Word] |
| 16 | Case-Control Studies [MeSH Terms] |
| 17 | 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 |
| 18 | 5 AND 8 AND 17 |
Results
Study selection
The process of study selection is illustrated in Fig. 1. A total of 1244 relevant papers were identified using diverse search strategies in four databases (113 from PubMed, 140 from Embase, 897 from Scopus, and 94 from Web of Knowledge) and three records of gray literature. After removing duplicates, 1057 papers remained, and 749 papers were deemed ineligible after title and abstract screening, and 308 relevant papers were considered for further screening through full-text reading. After the exclusion of all non-eligible studies ($n = 260$), a total of 48 studies (5 case-control studies and 43 cohort studies) were included in this meta-analysis.

Study characteristics
For each study, sample size, total number of ART and non-ART group, number of PE cases in each group, publication date, first author, target country, type of study, and participant mean age of each group were extracted. Cross-sectional studies and non-English studies were excluded from the meta-analysis. All of the primary studies were published between 1999 and 2017 and out of 48 studies, 11 were carried out in the United States, 11 in Asia, and 26 in Europe. The characteristics of studies considered in the meta-analysis are presented in Table 2.

Quantitative data synthesis
A total of 156,246 ART cases (with 14,560 cases of PE) and 6,558,249 non-ART cases (with 202,064 cases of PE) were included in the analysis. Risk ratios and their 95% CIs were reported using the Mantel–Haenszel method. The relationship of ART and the risk of PE were estimated using the 48 primary included studies. The pooled estimate of RR in this meta-analysis revealed that ART was significantly associated with a higher risk of PE (pooled RR = 1.708, 95% CI = 1.111–2.624, $z = 2.44$, $p = 0.015$), that is, the PE risk in ART group was 1.687 times greater compared to the non-ART group (Fig. 2, Table 3).

Heterogeneity analysis
Chi-square analysis showed that there was substantial heterogeneity between primary studies (heterogeneity $\chi^2 = 26,313.92$, $p < 0.001$, $I^2 = 99.8\%$, and $\tau^2 = 2.17$). Therefore, we concluded that the random-effect model was
Table 2 Characteristics of the primary studies included in the meta-analysis

| Author | DOP | Country | Period      | Design     | PE in ART | ART group | PE in NART | NART group |
|--------|-----|---------|-------------|------------|-----------|-----------|------------|------------|
| Julie Hoy [42] | 1999 | Australia | 1982–1995 | Cohort    | 131       | 1552      | 399        | 7717       |
| O'Saitha [43] | 1999 | UK       | 1992–1997  | Cohort    | 13        | 112       | 1          | 112        |
| A. Geipel [44] | 2001 | Germany | 1995–1999  | Cohort    | 6         | 114       | 11         | 114        |
| Anne Lynch [45] | 2002 | USA     | 1994–2000  | Cohort    | 27        | 198       | 40         | 330        |
| Syeda Zailb-un-Nisa [46] | 2003 | Emirates | 1997–2001  | Cohort    | 4         | 36        | 4          | 96         |
| Pinborg [47] | 2004 | Denmark | 1997      | Cohort    | 71        | 870       | 49         | 566        |
| Barbara Luke [48] | 2004 | USA     | 1990–2002  | Cohort    | 25        | 228       | 24         | 725        |
| Bengt Kallen [49] | 2005 | Sweden | 1982–2001  | Cohort    | 978       | 13,261    | 55,728     | 2,013,633  |
| Fiona Thomson [50] | 2005 | Scotland | 1989–1999  | Cohort    | 70        | 1437      | 556        | 21,688     |
| Sonia Hernandez-Diaz [51] | 2006 | USA & Canada | 1998–2006  | Cohort    | 18        | 349       | 115        | 4762       |
| Anne Lynch [52] | 2006 | Israel | 1988–2002  | Cohort    | 51        | 292       | 193        | 2336       |
| Prefumo [53] | 2007 | UK       | NA         | Case Control | 1        | 31        | 1          | 62         |
| Apantaku [54] | 2008 | UK       | 1999–2004  | Cohort    | 6         | 88        | 7          | 88         |
| Chen [55] | 2009 | Canada | 2005      | Cohort    | 34        | 1357      | 77         | 5190       |
| Sun [56] | 2009 | Canada | 2004–2007  | Cohort    | 31        | 2118      | 112        | 8420       |
| Mercol [57] | 2010 | France | 2001–2005  | Cohort    | 12        | 104       | 13         | 173        |
| Miyake [58] | 2010 | Japan   | 2005–2007  | Cohort    | 15        | 20        | 111        | 230        |
| Suzuki [59] | 2010 | Japan   | 2000–2007  | Cohort    | 4         | 64        | 9          | 87         |
| Lehmen [60] | 2011 | Germany | 2000–2009  | Cohort    | 10        | 74        | 8          | 305        |
| Yang [61] | 2011 | Korea   | 1995–2008  | Cohort    | 9         | 67        | 22         | 143        |
| Kiavasvari-Prirnien [62] | 2012 | Finland | 1996–2007  | Cohort    | 16        | 255       | 967        | 26,870     |
| Bamberg [63] | 2012 | Germany | 1998–2008  | Cohort    | 14        | 426       | 24         | 813        |
| Lubovnik [64] | 2012 | Slovenia | 1997–2009  | Case Control | 55       | 246       | 126        | 477        |
| Sazonova [65] | 2012 | Sweden | 2002–2006  | Cohort    | 520       | 11,292    | 15,984     | 571,914    |
| Mohammed [66] | 2012 | Qatar   | 2002–2011  | Cohort    | 27        | 145       | 30         | 175        |
| Le Ray [67] | 2012 | France | 2008–2010  | Cohort    | 24        | 144       | 9          | 236        |
| Emily Werder [68] | 2013 | USA     | 2002–2008  | Cohort    | 45        | 215       | 62         | 232        |
| Sara S. Malcha [69] | 2013 | Denmark | 1995–2010  | Cohort    | 1185      | 24,305    | 2519       | 56,022     |
| Rocic Revella [70] | 2013 | Italy   | 2000–2010  | Cohort    | 28        | 88        | 14         | 59         |
| Sari Raisanen [71] | 2013 | Finland | 2006–2010  | Cohort    | 90        | 5647      | 3138       | 285,357    |
| Alex Fong [72] | 2014 | USA     | 2009       | Case Control | 29       | 551       | 7487       | 406,334    |
| Nathan S. Fox [73] | 2014 | USA     | 2005–2012  | Case Control | 61       | 376       | 15         | 137        |
| Tandberg [74] | 2014 | Norway  | 1967–2009  | Cohort    | 5516      | 8549      | 24,971     | 493,217    |
| Tali Silverstein [75] | 2014 | Israel | NA         | Cohort    | 113       | 1,294     | 7889       | 171,513    |
| Cagri Arinol-Aydin [76] | 2015 | Istanbul | 2007–2010  | Cohort    | 13        | 137       | 46         | 133        |
| Anne-Maude Morency [77] | 2015 | Canada  | 2000–2013  | Cohort    | 39        | 181       | 4          | 49         |
| Robert Johnston [78] | 2015 | USA     | 2009       | Cohort    | 29        | 551       | 7847       | 406,334    |
| Malinda S. Lee [79] | 2015 | USA     | 2006–2008  | Cohort    | 17        | 108       | 176        | 2284       |
| Bay [80] | 2015 | Denmark | 1999–2003  | Cohort    | 2675      | 30,418    | 37,531     | 896,448    |
| DePietra [81] | 2016 | UK      | 1992–2009  | Cohort    | 203       | 3188      | 2341       | 52,443     |
| Nejdet [82] | 2016 | Sweden  | 2003–2012  | Cohort    | 1156      | 27,084    | 27,912     | 999,804    |
| Zhu [83] | 2016 | China   | 2006–2014  | Cohort    | 98        | 2641      | 110        | 5282       |
| Vikstrom [84] | 2016 | Sweden  | 1988–2012  | Case Control | 607      | 10,412    | 822        | 18,624     |
| Ben-Yaakov [85] | 2016 | Israel  | 1988–2012  | Cohort    | 378       | 4153      | 4471       | 95,138     |
| Sun [86] | 2016 | China   | 2010–2014  | Cohort    | 42        | 411       | 54         | 742        |
| Valenzuela-Apizac [87] | 2016 | Spain   | 2004–2010  | Cohort    | 6         | 488       | 0          | 200        |
| Rizzo [88] | 2016 | Italy   | 2007–2014  | Cohort    | 17        | 249       | 6          | 260        |
| Gullbaud [89] | 2017 | France  | 2010–2014  | Cohort    | 41        | 303       | 32         | 369        |

DOP: Date of publication, PE: Preeclampsia, ART: Assisted Reproductive Technology, NART: Non-Assisted Reproductive Technology
to pool the studies. To discover the source of heterogeneity, subgroup analysis was carried out on the basis of study design (case control and cohort), study region (United States, Asia, and Europe), and study period (1999–2010 and 2010–2017) (Figs. 3, 4 and 5, and Table 3). After subgroup analysis, heterogeneity

![Forest plot showing effect of ART on preeclampsia](image)

**Fig. 2** Forest plot showing effect of ART on preeclampsia

| Study ID          | RR (95% CI)       | % Weight |
|------------------|-------------------|----------|
| O. Salha (1999)  | 13.00 (1.73, 97.71) | 1.49     |
| Julie Hoy (1999) | 1.63 (1.35, 1.97)  | 2.20     |
| A. Geipel (2001) | 0.55 (0.21, 1.42)  | 1.99     |
| Anne Lynne (2002)| 1.13 (0.71, 1.77)  | 1.16     |
| Syeda Zain-un-Nisa (2003) | 2.67 (0.70, 10.10) | 1.83     |
| Barbara Luke (2004)| 3.31 (1.93, 5.68)  | 2.14     |
| Pinborg (2004)   | 0.94 (0.67, 1.34)  | 2.18     |
| Fiona Thomson (2005)| 1.90 (1.49, 2.42)  | 2.20     |
| Bengt Kallen (2005)| 2.66 (2.51, 2.83)  | 2.21     |
| Sonia Hernandez-Diaz (2006)| 2.14 (1.32, 3.47)  | 2.15     |
| Erez (2006)      | 2.11 (1.59, 2.81)  | 2.19     |
| Prefumo (2007)   | 2.00 (0.13, 30.91) | 1.17     |
| A. Pari (2008)   | 0.86 (0.30, 2.45)  | 1.96     |
| Chen (2009)      | 1.69 (1.13, 2.52)  | 2.17     |
| Sun (2009)       | 1.71 (0.47, 1.63)  | 2.17     |
| Miyake (2010)    | 1.55 (1.17, 2.07)  | 2.19     |
| Morcel (2010)    | 1.74 (0.53, 3.24)  | 2.07     |
| Suzuki (2010)    | 0.91 (0.37, 2.86)  | 2.17     |
| Lehnen (2011)    | 5.15 (2.12, 12.60) | 2.02     |
| Yang (2011)      | 0.87 (0.43, 1.79)  | 2.08     |
| Barnberg (2012)  | 1.11 (0.58, 2.13)  | 2.11     |
| Kuivasaari-Pinnen (2012)| 1.74 (1.08, 2.81)  | 2.15     |
| Lubovnik (2012)  | 0.85 (0.84, 1.12)  | 2.19     |
| Mohammed (2012)  | 1.09 (0.68, 1.74)  | 2.16     |
| Saxonova (2012)  | 1.65 (1.51, 1.79)  | 2.21     |
| Le Ray (2012)    | 4.37 (2.08, 9.14)  | 2.16     |
| Emily Werder (2013)| 0.58 (0.56, 1.10)  | 2.18     |
| Sari Rasaneh (2013)| 1.45 (1.18, 1.78)  | 2.20     |
| Rocio Revuelo (2013)| 1.34 (0.77, 2.32)  | 2.14     |
| Sara S. Mal chu (2013)| 1.08 (0.11, 1.16)  | 2.21     |
| Alex Fong (2014) | 2.86 (2.00, 4.07)  | 2.18     |
| Tandberg (2014)  | 12.74 (12.49, 13.00)| 2.21     |
| Tal Silberstein (2014)| 1.90 (1.59, 2.27)  | 2.21     |
| Nathan S. Fox (2014)| 1.48 (0.87, 2.52)  | 2.14     |
| Robert Johnston (2015)| 2.73 (1.91, 3.89)  | 2.18     |
| Cagni Anoglu Aydin (2015)| 0.27 (0.16, 0.48)  | 2.13     |
| Anne-Maude Morenc (2015)| 2.64 (0.99, 7.03)  | 1.99     |
| Malinda S. Lee (2015)| 2.04 (1.29, 3.23)  | 2.16     |
| Bay (2016)       | 2.10 (2.02, 2.18)  | 2.21     |
| Ben-Yaakov (2016) | 1.94 (1.75, 2.14)  | 2.21     |
| DoPlera (2016)   | 1.43 (1.24, 1.64)  | 2.21     |
| Nejdet (2016)    | 1.53 (1.44, 1.62)  | 2.21     |
| Sun (2016)       | 1.40 (0.96, 2.06)  | 2.17     |
| Valenzuela-Acaraz (2016)| 5.34 (0.30, 94.41)| 1.11     |
| Vikstrom (2016)  | 1.32 (1.19, 1.46)  | 2.21     |
| Zhu (2016)       | 1.78 (1.36, 2.33)  | 2.19     |
| Rizzo (2016)     | 2.83 (1.13, 7.07)  | 2.01     |
| Guibaud (2017)   | 1.56 (1.01, 2.41)  | 2.16     |
| Overall (%-squared = 99.8%, p = 0.000) | 1.71 (1.11, 2.62) | 100.00   |

NOTE: Weights are from random effects analysis
across studies did not decrease effectively; therefore, all estimations of RR were made by the random-effect model.

**Risk of publication bias**
Both graphical and statistical assessments were performed to check for the presence of publication bias. On the basis of the asymmetrical funnel plot (Fig. 6) and Begg’s test ($p = 0.001$), there was evidence of publication bias in this study. Accordingly, we excluded non-English papers from the meta-analysis and this can lead to bias.

**Discussion**
This study aimed to evaluate whether several studies agree with the effect of ART on the presence of PE. In this meta-analysis, 6,714,495 cases were recruited (156,246 ART cases and 6,558,249 non-ART cases). To detect the risk of PE regarding the use of ART, the heterogeneity among the studies was assessed, and the appropriate statistical tool was applied. To increase the validity of the results, the risk of publication bias was checked. Analysis of the important subgroups, such as publication date, type of study, and region, was performed.

Similar to the results achieved from our study, most of the studies have introduced the use of ART as a significant risk factor for placental abruption, low and very low birth weight in infants, placenta previa, gestational hypertension, risk of cesarean section, and PE [21, 22]. However, not all the investigators agree with the adverse effect of ART on pregnancy outcomes [23, 24]. Most of previous studies have proven the important impact of using ART on PE [25–28]. The positive association between ART and PE is well demonstrated by the included studies. Regarding the magnitude of the effect size, the pooled results from case-control studies were in compliance with those of cohort studies. However, in contrast to the cohort studies, the pooled RR from the case-control studies was not statistically significant. Moreover, the impact of ART on PE did not differ in two distinct periods of time (2010 as the cut-off point). Although consistent results were observed among different regions, the pooled RR from the European studies was not significant. Moreover, the effect size of the Asian and United States studies was higher than that of Europe.

We found that the use of ART was a significant risk factor for PE. The application of ART has increased across many countries around the world as a way to cope with infertility problems. The prevalence of using ART differs among countries. Annually, more than 1.5% of all births in the United States are the result of ART. The prevalence of PE is almost 10% in Africa and 15% in China [29–32]. In addition, the prevalence of PE has an increasing slope. Numerous factors, including the use of ART, hypertension, diabetes, obesity, and early diagnosis problems, are responsible for the ascending trend of PE prevalence [30, 33]. The adverse outcomes after ART cause damage to body organs, such as the kidney and liver, through PE as well as maternal mortality, perinatal deaths, preterm birth, intrauterine growth restriction, bleeding problems, and fetal growth retardation [34, 35]. In addition to ART, other factors such as anti-phospholipid syndrome, previous PE, family history of PE, insulin-dependent diabetes, obesity, multiple pregnancies, and nulliparity can affect PE [36]. The mechanism in which ART affects PE is not well known. However, it has been argued that abnormal placentation can influence PE. In some ART procedures, the blood flow is compromised and is diminished, which is then followed by obstetric complications. Moreover, placental

### Table 3 Summary of meta-analysis results and subgroups analysis

| Groups         | Tests of association | Heterogeneity | I² Percentage |
|----------------|----------------------|---------------|--------------|
|                | RR (95% CI)          | P value       | Model        |                |
| Total studies  | 1.71 (1.11–2.62)     | 0.015         | Random       | 2.44           |
|                |                      |               |              | 26,313.92      | < 0.001         | 99.8%           |
| Subgroup analyses |                    |               |              | 99.8%           | < 0.001         | 99.8%           |
| Study design   |                      |               |              | 85.9%           | < 0.001         | 85.9%           |
| Cohort         | 1.73 (1.10–2.72)     | 0.018         | Random       | 2.36           |
|                |                      |               |              | 25,159.19      | < 0.001         | 99.8%           |
| Case control   | 1.46 (0.97–2.20)     | 0.070         | Random       | 1.81           |
|                |                      |               |              | 28.38          | < 0.001         | 85.9%           |
| Time Period    |                      |               |              |                |                |                |
| 1999–2010      | 1.64 (1.31–2.05)     | < 0.001       | Random       | 4.29           |
|                |                      |               |              | 117.09         | < 0.001         | 85.5%           |
| 2010–2017      | 1.74 (0.97–3.09)     | 0.062         | Random       | 1.87           |
|                |                      |               |              | 25,671.51      | < 0.001         | 99.9%           |
| Region         |                      |               |              |                |                |                |
| Asia           | 1.71 (1.53–1.92)     | < 0.001       | Random       | 9.38           |
|                |                      |               |              | 17.12          | 0.072           | 41.6%           |
| Europe         | 1.74 (0.95–3.21)     | 0.075         | Random       | 1.78           |
|                |                      |               |              | 25,090.51      | < 0.001         | 99.9%           |
| America        | 1.78 (1.31–2.41)     | < 0.001       | Random       | 3.70           |
|                |                      |               |              | 52.30          | < 0.001         | 80.9%           |

**RR** Relative Risk, **CI** Confidence Interval
Fig. 3 Forest plot showing effect of ART on preeclampsia based on study design.
insufficiency is caused by the transfer of the conceptus into the uterine cavity and the impact of the altered hormonal environment in the endometrium where the development of the maternal–fetal interface can be influenced [37, 38]. It has been argued that ART may have epigenetic effects. The pregnancies from ART are

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| Study ID | RR (95% CI) | % Weight |
|----------|-------------|----------|
| Lehnen (2011) | 5.15 (2.11, 12.60) | 2.02 |
| Yang (2011) | 0.87 (0.43, 1.79) | 2.08 |
| Bamberg (2012) | 1.11 (0.58, 2.13) | 2.11 |
| Kuivasaari-Pitren (2012) | 1.74 (1.08, 2.81) | 2.15 |
| Lubovnik (2012) | 0.85 (0.64, 1.12) | 2.19 |
| Mohammad (2012) | 1.08 (0.68, 1.74) | 2.16 |
| Sazonova (2012) | 1.65 (1.51, 1.79) | 2.21 |
| Le Ray (2012) | 4.37 (2.09, 9.14) | 2.08 |
| Emily Weder (2013) | 0.78 (0.56, 1.10) | 2.18 |
| Sari Raisanen (2013) | 1.45 (1.18, 1.78) | 2.20 |
| Roclo Revelli (2013) | 1.34 (0.77, 2.32) | 2.14 |
| Sara S. Malcha (2013) | 1.08 (1.01, 1.16) | 2.21 |
| Alex Fong (2014) | 2.86 (2.00, 4.07) | 2.18 |
| Tandberg (2014) | 12.74 (12.49, 13.00) | 2.21 |
| Tal Silberstein (2014) | 1.90 (1.59, 2.27) | 2.21 |
| Nathan S. Fox (2014) | 1.48 (0.87, 2.52) | 2.14 |
| Robert Johnston (2015) | 2.73 (1.91, 3.89) | 2.18 |
| Cagri Anoglu Aydin (2015) | 0.27 (0.16, 0.48) | 2.13 |
| Anne-Maude Morency (2015) | 2.64 (0.98, 7.03) | 1.99 |
| Malinda S. Lee (2016) | 2.04 (1.20, 3.32) | 2.16 |
| Bay (2016) | 2.10 (2.02, 2.18) | 2.21 |
| Ben-Yaakov (2016) | 1.94 (1.75, 2.14) | 2.21 |
| DoPierala (2016) | 1.43 (1.24, 1.64) | 2.21 |
| Nejdet (2016) | 1.53 (1.44, 1.62) | 2.21 |
| Sun (2016) | 1.40 (0.96, 2.06) | 2.17 |
| Valenzuela-Alcaraz (2016) | 5.34 (3.00, 9.41) | 1.11 |
| Vikstrom (2016) | 1.32 (1.19, 1.46) | 2.21 |
| Zhu (2016) | 1.78 (1.36, 2.33) | 2.19 |
| Rizzo (2016) | 2.83 (1.13, 7.07) | 2.01 |
| Guillaud (2017) | 1.56 (1.01, 2.41) | 2.16 |
| Subtotal (I-squared = 99.9%, p = 0.000) | 1.74 (0.97, 3.09) | 63.65 |

**1990-2010**

| Study ID | RR (95% CI) | % Weight |
|----------|-------------|----------|
| O.Salha (1999) | 13.00 (1.73, 97.71) | 1.49 |
| Julie Hoy (1999) | 1.63 (1.35, 1.97) | 2.20 |
| A.Geipel (2001) | 0.55 (0.21, 1.42) | 1.99 |
| Anne Lynch (2002) | 1.13 (0.71, 1.77) | 2.16 |
| Syeda Zaib-un-Nisa (2003) | 2.67 (0.70, 10.10) | 1.83 |
| Barbara Luke (2004) | 3.31 (1.93, 5.68) | 2.14 |
| Pinborg (2004) | 0.94 (0.67, 1.34) | 2.18 |
| Fiona Thomson (2005) | 1.90 (1.49, 2.42) | 2.20 |
| Bengt Kallen (2005) | 2.66 (2.51, 2.83) | 2.21 |
| Sonia Hernandez-Diaz (2006) | 2.14 (1.32, 3.47) | 2.15 |
| Erez (2006) | 2.11 (1.59, 2.81) | 2.19 |
| Prefumo (2007) | 2.00 (0.13, 30.91) | 1.17 |
| Apantaku (2008) | 0.86 (0.30, 2.45) | 1.96 |
| Chen (2009) | 1.69 (1.13, 2.52) | 2.17 |
| Sun (2009) | 1.10 (0.74, 1.63) | 2.17 |
| Miyake (2010) | 1.55 (1.17, 2.07) | 2.19 |
| Morcel (2010) | 1.54 (0.73, 3.24) | 2.07 |
| Suzuki (2010) | 0.91 (0.27, 3.08) | 1.88 |
| Subtotal (I-squared = 85.5%, p = 0.000) | 1.64 (1.31, 2.05) | 36.35 |
| Overall (I-squared = 99.8%, p = 0.000) | 1.71 (1.11, 2.62) | 100.00 |

**NOTE:** Weights are from random effects analysis

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**Fig. 4** Forest plot showing effect of ART on preeclampsia based on study period
| Study ID | RR (95% CI) | Weight |
|---------|-------------|---------|
| America |             |         |
| Anne Lynch (2002) | 1.13 (0.71, 1.77) | 2.16 |
| Barbara Luke (2004) | 3.31 (1.93, 5.68) | 2.14 |
| Sonia Hernandez-Diaz (2006) | 2.14 (1.32, 3.47) | 2.15 |
| Chen (2009) | 1.69 (1.13, 2.52) | 2.17 |
| Sun (2009) | 1.10 (0.74, 1.63) | 2.17 |
| Emily Werder (2013) | 0.78 (0.56, 1.10) | 2.18 |
| Alex Fong (2014) | 2.86 (2.00, 4.07) | 2.18 |
| Nathan S. Fox (2014) | 1.48 (0.87, 2.52) | 2.14 |
| Robert Johnston (2015) | 2.73 (1.91, 3.89) | 2.18 |
| Anne-Maude Morency (2015) | 2.64 (0.99, 7.03) | 1.99 |
| Malinda S. Lee (2015) | 2.04 (1.29, 3.23) | 2.18 |
| Subtotal (I-squared = 80.9%, p = 0.000) | 1.78 (1.31, 2.41) | 23.83 |
| Europe |             |         |
| O.Saitha (1999) | 13.00 (7.37, 97.11) | 1.49 |
| A.Geipel (2001) | 0.55 (0.21, 1.42) | 1.99 |
| Pinborg (2004) | 0.94 (0.67, 1.34) | 2.18 |
| Fiona Thomson (2005) | 1.90 (1.49, 2.42) | 2.20 |
| Bengt Kallen (2005) | 2.66 (2.51, 2.83) | 2.21 |
| Prefumo (2007) | 2.00 (1.93, 2.07) | 2.08 |
| Apantaku (2008) | 0.86 (0.30, 2.45) | 1.96 |
| Morcel (2010) | 1.54 (0.73, 3.24) | 2.07 |
| Lehnen (2011) | 5.15 (2.11, 12.60) | 2.02 |
| Bamberg (2012) | 1.11 (0.58, 2.13) | 2.11 |
| Kuivasaari-Pinnem (2012) | 1.74 (1.08, 2.81) | 2.15 |
| Lubovnik (2012) | 0.85 (0.64, 1.12) | 2.19 |
| Sazonova (2012) | 1.65 (1.51, 1.79) | 2.21 |
| Le Ray (2012) | 4.37 (2.09, 9.14) | 2.08 |
| San Raisanen (2013) | 1.45 (1.16, 1.78) | 2.20 |
| Rocío Revello (2013) | 1.34 (0.77, 2.32) | 2.14 |
| Sara S. Malchau (2013) | 1.08 (0.10, 1.16) | 2.21 |
| Tandberg (2014) | 12.74 (12.49, 13.00) | 2.21 |
| Cagnì Angiolucc Aydin (2015) | 0.27 (0.16, 0.48) | 2.13 |
| Bay (2016) | 2.10 (2.02, 2.19) | 2.21 |
| DoPierala (2016) | 1.43 (1.24, 1.64) | 2.21 |
| Nejdet (2016) | 1.53 (1.44, 1.62) | 2.21 |
| Valenzuela-Alcaraz (2016) | 5.34 (0.30, 94.41) | 1.11 |
| Vikstrom (2016) | 1.32 (1.19, 1.46) | 2.21 |
| Rizzo (2016) | 2.83 (1.13, 7.07) | 2.01 |
| Guilbaud (2017) | 1.58 (1.01, 2.41) | 2.18 |
| Subtotal (I-squared = 99.9%, p = 0.000) | 1.74 (0.90, 3.21) | 53.06 |
| Asia |             |         |
| Julie Hoy (1999) | 1.63 (1.35, 1.97) | 2.20 |
| Syeda Zaib-un-Nisa (2003) | 2.67 (0.70, 10.10) | 1.83 |
| Erez (2006) | 2.11 (1.59, 2.81) | 2.19 |
| Miyake (2010) | 1.55 (1.07, 2.07) | 2.19 |
| Suzuki (2010) | 0.91 (0.72, 1.18) | 1.98 |
| Yang (2011) | 0.87 (0.43, 1.79) | 2.08 |
| Mohammed (2012) | 1.09 (0.68, 1.74) | 2.16 |
| Tali Silberstein (2014) | 1.90 (1.59, 2.27) | 2.21 |
| Ben-Yaakov (2016) | 1.94 (1.75, 2.14) | 2.21 |
| Sun (2016) | 1.40 (0.96, 2.06) | 2.17 |
| Zhu (2016) | 1.78 (1.36, 2.33) | 2.19 |
| Subtotal (I-squared = 41.6%, p = 0.072) | 1.71 (1.53, 1.92) | 23.32 |
| Overall (I-squared = 99.9%, p = 0.000) | 1.71 (1.11, 2.62) | 100.00 |

NOTE: Weights are from random effects analysis

Fig. 5 Forest plot showing effect of ART on preeclampsia based on regions
associated with PE through oxidative stress. In addition, ART has several types of reproductive dysfunction with the same strength as miscarriages. Recurrent spontaneous miscarriages, along with infertility treatments, increase the risk of PE in comparison to those without treatment [39]. Nonetheless, the excess RR in the association between ART and PE can be caused by multiple factors, such as previous fertility complications, lifestyle, smoking habits, long inter-birth intervals, multiple pregnancy, and advanced maternal age [39]. However, there are many other causal factors associated with infertility itself in which the relationship between PE and ART can be argued.

Thomopoulos et al. assessed the risk of hypertensive disorders in pregnancy following ART using an overview of the studies conducted from 1978 to 2016 [40]. Their study included papers from PubMed and the Cochrane Collaboration Library databases with a total of 32 papers with PE as an outcome. The present meta-analysis has added primary studies from other databases such as Embase, Scopus, and ISI Web of Knowledge with a total number of 48 papers up to June 2017.

The controversy of using statistical tools to determine the magnitude of heterogeneity in meta-analysis has several potential causes, including sample size and number of the included studies, the period of time, the geographical patterns, the level of development, and the types of studies, etc. In this regard, a non-significant result from a chi-square test must not be taken as evidence of a lack of heterogeneity. Furthermore, the chi-square test is very powerful when many studies are included in a meta-analysis. The other statistical tool to detect heterogeneity, the $I^2$ value, depends on the magnitude of the rates [41]. In our meta-analysis, the result of the chi-square test was confirmed by the $I^2$ test. Except for a region of Asia, significant heterogeneities were observed among the pooled and subgroup RRs. The source of heterogeneities may be due to the diversity in the ethnic and cultural conditions and uneven development regions.

However, this study has some limitations. Almost every meta-analysis study deals with uncontrolled confounders. Researchers are not able to control the analysis for the confounders unless the proper information is presented by the original articles. To overcome this problem, “individual patient or participant data (IPD)” is suggested in which requires the detailed information and data-sets from every single original article and it is not applicable in most of the cases regarding that the authors (original articles) might not be interested to present their data and other potential reasons.

This systematic review has several limitations. First, the most important limitation for this study as for other systematic review is the lack of data for subgroup analysis based on type of pregnancy (singleton versus twin pregnancy) or for data analysis controlling for known confounders. Second, our study included only English full-text papers. However, globally published papers might present higher quality research compared with those of local origin.
Conclusion
The present systematic review and meta-analysis revealed that the use of ART increases the risk of PE considerably. More attention must be paid to Asia and the United States, where the association is stronger and significant.

Abbreviations
ART: Assisted Reproductive Technology; CI: Confidence Interval; PE: Preeclampsia; RR: Relative Risk

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Availability of data and materials
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors’ contributions
SM, ROS, and AAH conceived the study. MM, PA, BN, and AAH analyzed the data, and all authors revised the manuscript and approved the final version.

Ethics approval and consent to participate
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Author details
1Department of Epidemiology, School of Health, Arak University of Medical Sciences, Arak, Iran. 2Department of Epidemiology and Reproductive Health, Reproductive Epidemiology Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran. 3Department of Biostatistics and Epidemiology, School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. 4Institute of Psychology, Health, and Society, Department of Health Services Research, University of Liverpool, Liverpool, UK. 5School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran.

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