Assisted reproductive technology and the risk of gestational diabetes mellitus: a systematic review and meta-analysis

Maryam Mohammadi 1,2, Esmaeil Khedmati Morasae 3, Saman Maroufizadeh 4*, Amir Almasi-Hashiani 5, Behnaz Navid 1, Payam Amini 6, Reza Omani-Samani 7 and Ahad Alizadeh 8*

Abstract

Background: The use of assisted reproductive technology (ART) is increasing worldwide, and observational studies have indicated that women who conceived by ART have an increased risk of pregnancy complications including gestational diabetes mellitus (GDM). We aimed to determine the risk of GDM among women who conceived with ART by systematic review and meta-analysis.

Main text: A systematic literature search was conducted in ISI Web of Knowledge, MEDLINE, Scopus, and Embase through May 2017 for English-language articles using a list of keywords. All studies comparing GDM in women conceived by ART and those who conceived spontaneously were included. Data extraction was performed by two authors independently and discrepancies were resolved by discussion. In total, 48 studies with 91,487 pregnancies conceived through ART and 2,525,234 spontaneously conceived met the inclusion criteria. There was evidence of substantial heterogeneity among these studies ($P < 0.001$, $I^2 = 98.6\%$). Random effects meta-analysis showed a significant increase in GDM among those who conceived by ART compared with those who conceived spontaneously (pooled relative risk = 1.51, 95% confidence interval = 1.18–1.93). Visual inspection of the funnel plot did not reveal any publication bias, which was supported by Egger’s test and Begg’s test.

Conclusion: The findings of this systematic review indicate that the use of ART treatment is associated with a 1.51-fold increase in GDM. Women need to be counselled carefully before undergoing ART treatment about the possibility and risk of GDM.

Keywords: Assisted reproductive technology, Gestational diabetes mellitus, Infertility, Meta-analysis, Systematic review

Background

Assisted reproductive technology (ART) is a group of medical methods for treating the infertile human in which both male and female gametes are used outside the body to achieve pregnancy [1]. To date, approximately 5 million babies are born worldwide via ART [2]. Although ART may help infertile couples, its use has increased concerns associated with pregnancy-related complications and adverse consequences [3]. It has been suggested that obstetric outcomes in gestation after ART are poor when compared with those pregnancies spontaneously conceived [4]. Moreover, evidence from meta-analyses [4–8] has revealed that singleton pregnancies after ART are at higher risk of adverse consequences than those conceived naturally. One of the outcomes followed by ART is gestational diabetes mellitus (GDM) and is known as one of the most common complications in pregnancy [9, 10]. GDM is defined as “carbohydrate intolerance of variable severity with onset or first recognition during pregnancy” [11]. GDM is a worldwide public health problem and complicates about 7% of all pregnancies [12, 13]. The cause and pathogenesis of GDM is both multifunctional and complex [14]. GDM is prone to causing a woman and her baby a wide range of complications during pregnancy and in later life [15, 16]. women with GDM are more...
likely to develop metabolic syndrome in the future, including type 2 diabetes [17]. Therefore, it is important to realize the risk factors of GDM such as family history of diabetes, obesity, high parity, advanced maternal age, previous adverse pregnancy, non-white race, history of a baby with birth weight > 3800 g, and hypothyroidism [12, 18].

In addition, studies have indicated that ART pregnancies are related to an increased risk of GDM [19–22]. Another study in Australia reported those who underwent ART are more prone to experience GDM compared to those who conceived spontaneously [23]. However, it was shown in another study that the rate of GDM was lower in women who conceived under intracytoplasmic sperm injection (ICSI) compared to those of spontaneously, in vitro fertilization (IVF) or simple ART [24]. Finally, we conducted a meta-analysis to provide an up-to-date survey of pregnancies resulting from ART and the increased risk of GDM between 1997 and 2017. We aimed to investigate the higher risk of GDM in pregnancies following ART and compare them to those of spontaneous conceptions.

Material and methods

Search strategy
This systematic review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist [25]. We searched the electronic databases ISI Web of Knowledge, MEDLINE/PubMed, Scopus, and Embase through May 2017, for studies investigating the relationship between ART and GDM. The search terms used were presented in Table 1. Reference lists from all identified studies were also searched for any relevant articles. Two authors (MM and AA) evaluated the studies, and discrepancies were resolved by discussion.

Inclusion and exclusion criteria
We included published studies that examined the relationship between the use of ART and the risk of GDM. No restriction criteria were imposed with regard to the size or type of the studied population, nor to the type of ART treatment. The following study types were excluded from the analyses: (a) non-English articles; (b) animal studies; (c) repeated or overlapping studies; (d) reviews, meta-analyses, case reports, editorials, and letters-to-the-editor articles; and (e) unpublished studies.

Outcome and exposure
The exposure variable was all types of ART treatment. Our outcome was GDM, defined as “carbohydrate intolerance of variable severity with onset or first recognition during pregnancy” [11].

| Table 1 Search strategy for MEDLINE (MeSH, Medical Subject Headings) |
|-----------------------------|
| Word or term                |
| 1 | Gestational Diabetes Mellitus [Text word] |
| 2 | “Gestational Diabetes Mellitus” [Text word] |
| 3 | Diabetes, Gestational [Text Word] |
| 4 | “Diabetes, Gestational” [Text Word] |
| 5 | “Diabetes, Gestational” [Mesh] |
| 6 | 1 OR 2 OR 3 OR 4 OR 5 |
| 7 | Reproductive techniques, assisted [Text word] |
| 8 | Reproductive techniques, assisted [MeSH terms] |
| 9 | 7 OR 8 |
| 10 | Cohort studies [Text word] |
| 11 | Cohort studies [MeSH terms] |
| 12 | Retrospective studies [Text word] |
| 13 | Retrospective studies [MeSH terms] |
| 14 | Prospective studies [Text word] |
| 15 | Prospective studies [MeSH terms] |
| 16 | Case-control studies [Text word] |
| 17 | Case-control studies [MeSH terms] |
| 18 | 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 |
| 19 | 6 AND 9 AND 18 |

Data extraction and quality assessment
Two reviewers (MM and AA) independently abstracted the following data from all eligible articles: first author’s name; year of publication; location; study period; design; sample size; type of ART; and study findings. Discrepancies were resolved by discussion between two reviewers. Quality assessment of included studies was performed independently by two reviewers using the Newcastle–Ottawa Scale (NOS) [26]. The NOS assesses the methodological quality of the observational studies according to three domains: (a) selection of study groups; (b) comparability of groups; and (c) ascertainment of exposure and outcomes. Total scores range from 0 (lowest quality) to 9 (highest quality).

Statistical analysis
Data were analyzed using STATA version 13.0 (Stata Corp, College Station, TX, USA). The pooled relative risk (RR) was calculated with its 95% confidence interval (CI) to assess the strength of the association between the use of ART and GDM risk. To assess between study heterogeneity, both the Cochran $Q$ test and the $I^2$ statistic (the percentage of total variation across studies attributable to heterogeneity beyond chance) were calculated [27]. $I^2$ values of 25, 50, and 75% were used as evidence of low, moderate, and high heterogeneity, respectively [27]. Subgroup analysis was performed to detect factors
that may explain heterogeneity in outcome between each study. Publication bias was assessed using visual inspection of a funnel plot, Egger’s test, and Begg’s test [28, 29]. In all statistical tests, results with $P < 0.05$ were deemed statistically significant, except for the Cochran Q test where $P < 0.10$ was used.

### Results

**Study selection**

The steps of the study selection are displayed in Fig. 1. A total of 950 related published articles were retrieved by using a search strategy in four international databases (638 from Scopus, 91 from PubMed, 62 from ISI Web of Knowledge, and 159 from Embase) and also seven records were identified from Google Scholar and reference lists of final included papers in the meta-analysis. In this study, 829 papers remained after removing duplicate papers using EndNote software. After title and abstract screening, 278 relevant articles were recognized as eligible and they were considered for additional full-text screening. After excluding 230 non-eligible studies, finally, 48 studies (four case-control studies, three cross-sectional studies, and 41 cohort studies) were included in this meta-analysis.

**Study characteristics**

The study characteristics of the included studies are summarized in Table 2. In total, we included 48 studies published from 1987 to 2017. Observational studies (i.e., cross-sectional, case control and cohort studies) were included in the meta-analysis, whereas non-English studies and studies without relevant data or partial data were excluded. Sample size in the ART group ranged from 31 to 21,615 cases and in the non-ART group it ranged from 20 to 595,168 cases. Of the 48 studies, 19 were conducted in Asia, 17 in Europe, and 12 in America. Fourteen studies were published before 2011 and 34 studies were published from 2011 to 2017.

**Quantitative data synthesis**

In the present study, 91,487 ART cases (with 6819 cases of GDM) and 2,525,234 non-ART cases (with 113,505 cases of GDM) were included in the analysis. RRs and their 95% CIs were calculated using the Mantel–Haenszel method and, because of significant heterogeneity
Table 2: Characteristics of the primary studies included in the meta-analysis

| First author | DOP     | Country | Period       | Design   | Mean of age | Type of ART | # of GDM in ART group | # of GDM in non-ART group |
|--------------|---------|---------|--------------|----------|-------------|--------------|-----------------------|--------------------------|
| Varma TR    | 1987    | UK      | 1983–1985   | Cohort   | NA          | NA           | 7                     | 362                      |
| Vollenhoven B| 2000    | Australia| 1990–1997   | Case–Control | NA         | NA          | 22                    | 60                       |
| Bjercke S   | 2002    | Norway  | 1993–1998   | Cohort   | 31.32       | 32.7        | IVF                   | 4                        |
| Koivurova S | 2002    | Finland | 1990–1995   | Cohort   | 31.8        | 31.8        | IVF                   | 12                       |
| Nassar AH   | 2003    | USA     | 1995–2000   | Cohort   | 35          | 36          | IVF                   | 3                        |
| Pinborg A   | 2004    | Denmark | 1997       | Cohort   | 33.1        | 30.5        | IVF/ICSI              | 13                       |
| Shevell T   | 2005    | USA     | 1999–2002   | Cohort   | 33.19       | 29.9        | IVF/IOI               | 92                       |
| Saygan-Karamürsel B | 2006 | Turkey | 1999–2003   | Case–Control | 31.45      | 28.94       | ICSI                  | 22                       |
| Buckett WM  | 2007    | Canada  | 1998–2003   | Cohort   | 34.75       | 34          | IVF/ICSI/IVM          | 39                       |
| Adler-Levy Y| 2007    | Israel  | 1988–2002   | Case–Control | 30.27      | 29.4        | IVF/IOI               | 96                       |
| Eskandar M  | 2007    | Saudi Arabia | 2004–2006 | Cohort   | 28.29       | 26.44       | ICSI                  | 3                        |
| Krieg SA    | 2008    | USA     | 2001–2005   | Cohort   | 42.7        | 41.3        | IVF                   | 10                      |
| Vasario E   | 2010    | Italy   | 2004–2008   | Cohort   | 31.5        | 33.5        | IVF                   | 10                       |
| Suzuki S    | 2010    | Japan   | 2000–2007   | Cohort   | 37.8        | 37.9        | IVF                   | 1                        |
| Tepper NK   | 2011    | USA     | 1997–2004   | Cohort   | 36          | 30          | NA                    | 112                      |
| Montoya JB  | 2012    | Mexico  | 2005–2009   | Cohort   | 32.5        | 31.6        | NA                    | 7                        |
| Moini A     | 2012    | Iran    | 2008–2010   | Cohort   | 30.6        | 27.3        | IVF/ICSI              | 21                       |
| Bamberg C   | 2012    | Germany | 1998–2008   | Cohort   | 32.5        | 30.1        | IVF/ICSI              | 19                       |
| Le Ray C    | 2012    | France  | 2008–2010   | Cohort   | >43         | >43         | IVF/OD                | 11                       |
| Werder E    | 2013    | USA     | 2002–2008   | Cohort   | NA          | NA          | IVF                   | 155                      |
| Wang Y      | 2013    | Australia | 2007–2009  | Cross–Sectional | NA    | NA          | 1044                  | 13,732                  |
| Farhi A     | 2013    | Israel  | 2006–2008   | Cohort   | NA          | NA          | IVF/ICSI              | 61                       |
| Toshimitsu M| 2014    | Japan   | 2006–2010   | Cohort   | NA          | NA          | IVF/ICSI              | 0                        |
| Castera D   | 2014    | Italy   | 2007–2011   | Cohort   | 38.5        | 33.5        | IVF/ICSI              | 14                       |
| Ashrafi M   | 2014    | Iran    | 2011–2012   | Cross–Sectional | 30     | 26.4        | IVF                   | 174                      |
| Ashrafi M   | 2014    | Iran    | 2011–2012   | Cross–Sectional | 30.35    | 26.6        | ICSI/IVF/IV/UID       | 13                       |
| Silberstein T| 2014  | Israel  | 1988–2006   | Cohort   | 30.9        | 28.49       | IVF/IOI               | 492                      |
| Yang X      | 2014    | China   | 2011       | Cohort   | NA          | NA          | ART                   | 172                      |
| Domingues A | 2014   | Portugal| 1996–2011   | Cohort   | NA          | NA          | IVF/ICSI              | 15                       |
| Stern JE    | 2015    | USA     | 2004–2008   | Cohort   | NA          | NA          | 81                    | 3689                     |
| Jie Z       | 2015    | China   | 2010–2013   | Cohort   | 32.53       | 29.87       | IVF                   | 48                       |
| Nunes F     | 2015    | NA      | Case–Control| NA      | 34.3        | 31.4        | NA                    | 11                       |
| Barua S     | 2016    | Australia| 2007–2010  | Cohort   | 32.1        | 29.2        | ART                   | 224                      |
| Zhu L       | 2016    | China   | 2006–2014   | Cohort   | 31.84       | 31.73       | IVF/ICSI              | 309                      |
| Martin AS   | 2016    | USA     | 2008–2012   | Cohort   | NA          | NA          | ART                   | 397                      |
| Luke B      | 2016    | USA     | 2004–2010   | Cohort   | 36.65       | 30.1        | ART                   | 93                       |
| Bashmakova NV| 2016  | Russia  | NA          | Cohort   | NA          | NA          | ART                   | 12                       |
| Rosato E    | 2016    | Italy   | 2010–2011   | Cohort   | 44.2        | 44.1        | ART                   | 6                        |
| Valenzuela-lcaraz B | 2016  | Spain | 2004–2010  | Cohort   | 33.46       | 31          | IVF/ICSI/IOI          | 17                       |
| Marton V    | 2016    | Sweden  | 1994–2014   | Cohort   | 35.25       | 33.275      | IVF/ICSI              | 54                       |
| Beyer DA    | 2016    | Germany | NA          | Cohort   | 39          | 39          | IVF/ICSI              | 4                        |
| Pourali L   | 2016    | Iran    | 2009–2014   | Cohort   | 28.9        | 27.1        | ART                   | 8                        |
Table 2 Characteristics of the primary studies included in the meta-analysis (Continued)

| First author   | DOP Date       | Country    | Period          | Design    | Mean of age | Type of ART | # of GDM in ART group | # of GDM in Non-ART group |
|----------------|----------------|------------|-----------------|-----------|-------------|-------------|------------------------|--------------------------|
| Ben-Yaakov RD  | 2016           | Israel     | 1988–2012       | Cohort    | 30.9        | 28.7        | IVF/OI                 | 585                      | 4153, 5895, 95,138       |
| Qin J          | 2016           | China      | 2013–2016       | Cohort    | 31.3        | 29.26       | IVF                    | 165                      | 1260, 823, 4379          |
| Wang YPA       | 2016           | Australia  | 2007–2011       | Cohort    | NA          | NA          | NA                     | 1736                     | 21,615, 30,869, 574,905  |
| Korosec S      | 2016           | Slovenia   | 2004–2011       | Cohort    | 33.42       | 33.42       | IVF/ET/FET             | 43                       | 1127, 129, 3381          |
| Morency AM     | 2016           | Canada     | 2000–2013       | Cohort    | 33          | 31.4        | ART                    | 4                        | 49, 19, 181              |
| Luke B         | 2017           | USA        | 2004–2010       | Cohort    | 35.3        | 30.4        | IVF                    | 378                      | 3538, 493, 6090          |

DOP: date of publication, GDM: gestational diabetes mellitus, ART: assisted reproductive technology, Non-ART: non-assisted reproductive technology, NA: not available.

![Forest plot showing the risk of GDM following ART](image-url)
between studies, random effect models were also used. The relationship of ART and the risk of GDM was estimated using 48 included primary studies. The summary estimate of RR in this meta-analysis suggested that ART significantly was associated with higher risk of GDM (pooled RR = 1.51, 95% CI = 1.18–1.93, \(P = 0.001\)); that is, the risk of GDM in the ART group is 1.51 times compared to that in the non-ART group (Fig. 2 and Table 3).

**Heterogeneity analysis**
To check the heterogeneity between studies, chi-square test, \(I^2\)-squared, and Tau-squared were conducted. Chi-square analysis revealed that there was a significant heterogeneity between primary studies (\(P < 0.001, \chi^2 = 98.6\%\)); consequently, to pool the effect sizes in this study, a random effect model was used. To find the source of heterogeneity between studies, subgroup analyses were performed on the basis of study design, study region, and study period (Table 3). Even after the aforementioned subgroup analyses, heterogeneity across the studies did not diminish successfully in all subgroups; for that reason, some estimations of pooled RR were measured by the random effects model and only pooled RR for case control studies and the papers that were published between 1987 and 2010 were estimated by a mixed-effect model (Figs. 3, 4 and 5).

**Risk of publication bias**
Graphical (funnel plot) and statistical tools (Begg’s and Egger’s test) were done to test the existence of publication bias in the studies. The results of the symmetrical funnel plot (Fig. 6), Egger’s test (\(P = 0.331\)), and Begg’s test (\(P = 0.810\)) suggested that there was no significant publication bias in this study.

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

| Groups          | # of studies | Test of association          | \(P\)  | Model | Heterogeneity |
|-----------------|--------------|------------------------------|--------|-------|---------------|
| Total studies   | 48           | 1.51 (1.18–1.93)             | 0.001  | Random| < 0.001       | 98.9%          |
| Study design    |              |                              |        |       |               |
| Cohort          | 41           | 1.44 (1.07–1.95)             | 0.021  | Random| < 0.001       | 98.8%          |
| Case control    | 4            | 2.04 (1.65–2.51)             | 0.001  | Fixed | 0.445         | 0              |
| Cross-sectional | 3            | 1.99 (0.93–4.26)             | 0.095  | Random| < 0.001       | 88.1%          |
| Time period     |              |                              |        |       |               |
| 1987–2010       | 14           | 1.75 (1.50–2.05)             | < 0.001| Fixed | 0.343         | 10.1%          |
| 2011-2017       | 34           | 1.42 (1.05–1.90)             | 0.022  | Random| < 0.001       | 99.0%          |
| Region          |              |                              |        |       |               |
| Europe          | 16           | 1.75 (1.31–2.34)             | < 0.001| Random| < 0.001       | 65.3%          |
| Asia            | 19           | 1.70 (1.45–1.98)             | < 0.001| Random| < 0.001       | 94.2%          |
| America         | 12           | 1.07 (0.46–2.52)             | < 0.001| Random| < .01         | 99.4%          |

**Discussion**
The current study aimed to assess the impact of ART on GDM using a systematic review of related articles. This meta-analysis included 344,021 cases, in which 91,487 cases used ART to achieve pregnancy. Statistical approaches were determined based on the heterogeneity of the included studies and publication bias was checked. Several subgroups were defined based on the study design, time period, and region.

The results from this meta-analysis revealed that GDM is strongly affected by the use of ART. The relative risk of GDM was significant regarding the use of ART. Regarding the magnitude of the RR, the results from different study designs were in accordance. However, the included cross-sectional studies did not report a significant pooled RR in contrast to cohort and case-control studies and this might be due to the lower number of cross-sectional studies. Moreover, the impact of ART on GDM did not differ in two distinct periods of time (2010 as the cut-off point). In contrast to America, consistent results were found in two regions of Asia and Europe. The pooled RR resulting from American studies showed a higher risk of GDM among those in the non-ART group.

The ART has been defined as treatments including in vitro handling of oocytes and sperm, and embryos, in which establishing pregnancy is the goal [76]. There have been many debates on the efficacy and safety of using ART regarding its increasing trend of use across most countries [77, 78]. It has been shown that ART is responsible for a high number of adverse pregnancy-related complications and obstetric outcomes such as polyhydramnios, low and very low infant birth weight, pregnancy-induced hypertension, pre-eclampsia, perinatal mortality, preterm and very preterm birth, placenta
previa, antepartum hemorrhage, multiple pregnancy, congenital malformation, higher risk of ectopic pregnancy, lower odds of vaginal delivery, postpartum hemorrhage, oligohydramnios, small for gestational age, and placental abruption [36, 79–83]. As mentioned, using ART was associated with GDM, which is diabetes diagnosed during pregnancy. Pregnancy may cause insulin resistance and hyperinsulinemia and can be followed by diabetes. GDM is defined as glucose intolerance with the first recognition during pregnancy and usually progresses in the second trimester [84]. GDM is associated with a large number of risk factors, such as elevated prepregnancy body mass index, older maternal age, history of GDM, diabetes among family members, polycystic ovary syndrome (PCOS), pre-existing hypertension, weight gain during pregnancy, smoking, ART, and higher parity [85–87]. The adverse effect of ART on GDM is discussed by several studies; however, the mechanism has not been well clarified [48, 52]. Several hypotheses are introduced in which GDM is influenced by the use of ART, including the etiology of infertility, the drugs used in the treatment procedure, the hormonal levels, and metabolic and vascular factors [19, 52]. However, it has been revealed that maternal age is the most effective factor on GDM [88]. Wang et al. have discussed the association between GDM and ART through

| Name           | year | Country | RR (95% CI) | % Weight | Reference |
|----------------|------|---------|-------------|----------|-----------|
| Varma TR       | 1987 | UK      | 2.08 (0.96, 4.50) | 2.01 | 54 |
| Koivurova S    | 2002 | Finland | 1.67 (0.83, 3.34) | 2.09 | 57 |
| Bjorn Bjoergo  | 2002 | Norway  | 1.27 (0.39, 4.79) | 1.57 | 56 |
| Nasar AH       | 2003 | USA     | 1.00 (0.26, 3.86) | 1.43 | 58 |
| Pinyng A       | 2004 | Denmark | 1.90 (0.93, 3.70) | 2.07 | 59 |
| Shewell T      | 2005 | USA     | 1.50 (1.32, 1.84) | 1.33 | 33 |
| Buckett WM     | 2007 | Canada  | 1.50 (0.93, 2.43) | 2.29 | 60 |
| Eriksson M     | 2007 | Saudi Arabia | 0.90 (0.20, 3.30) | 1.48 | 62 |
| Kling OA       | 2008 | USA     | 1.60 (0.88, 2.97) | 1.63 | 63 |
| Vesaio E       | 2010 | Italy   | 1.24 (0.57, 2.72) | 2.00 | 54 |
| Suzuki S       | 2010 | Japan   | 1.35 (0.09, 21.25) | 0.61 | 65 |
| Tepper NK      | 2012 | Massachusetts | 2.39 (1.97, 2.86) | 2.47 | 66 |
| Moni A         | 2012 | Iran    | 1.03 (0.56, 1.90) | 2.15 | 66 |
| Le Ray C       | 2012 | France  | 1.47 (0.66, 3.24) | 1.89 | 70 |
| Bambang C      | 2012 | Germany | 1.38 (0.77, 2.46) | 2.20 | 69 |
| Montoya JB     | 2012 | Mexico  | 1.00 (0.37, 2.69) | 1.79 | 67 |
| Fathi A        | 2013 | Israel  | 1.10 (0.78, 1.54) | 2.39 | 72 |
| Warder E       | 2013 | USA     | 0.71 (0.49, 1.03) | 2.37 | 71 |
| Toskimatsu M   | 2014 | Japan   | 0.44 (0.03, 7.78) | 0.67 | 73 |
| Yang X         | 2014 | China   | 2.95 (2.05, 3.40) | 2.48 | 77 |
| Dominguez A    | 2014 | Portugal | 1.81 (0.50, 3.28) | 2.19 | 78 |
| Silberstein T  | 2014 | Israel  | 2.11 (1.94, 2.30) | 2.50 | 76 |
| Castera D      | 2014 | Italy   | 3.27 (1.79, 6.32) | 1.85 | 74 |
| Je Z           | 2015 | China   | 1.58 (1.17, 2.14) | 2.42 | 80 |
| Stuen JE       | 2015 | USA     | 1.95 (1.57, 2.43) | 2.48 | 79 |
| Rosato E       | 2016 | Italy   | 1.10 (0.97, 1.28) | 0.67 | 80 |
| Konvacs B      | 2016 | Slovenia | 1.00 (0.71, 1.40) | 2.39 | 95 |
| Merin AS       | 2016 | USA     | 0.14 (0.03, 0.16) | 2.50 | 94 |
| Valenzuela-Acuna B | 2016 | Spain | 1.72 (0.58, 5.04) | 1.70 | 98 |
| Wang YPA       | 2016 | Australia | 1.46 (1.39, 1.53) | 2.51 | 94 |
| Luke B         | 2016 | USA     | 1.31 (1.08, 1.61) | 2.47 | 95 |
| Pourell L      | 2016 | Iran    | 2.67 (1.98, 6.61) | 1.57 | 91 |
| Ben-Yakov RO   | 2016 | Israel  | 2.12 (1.95, 2.29) | 2.50 | 92 |
| Beyer DA       | 2016 | Germany | 0.36 (0.13, 0.93) | 1.79 | 90 |
| Monroy AM      | 2016 | Canada  | 0.79 (0.28, 2.24) | 1.74 | 95 |
| Zhu L          | 2016 | China   | 1.72 (1.48, 2.00) | 2.48 | 83 |
| Marton V       | 2016 | Sweden  | 3.21 (2.19, 4.68) | 2.37 | 89 |
| Bashmakova NV  | 2016 | Russia  | 4.16 (1.56, 10.43) | 1.86 | 85 |
| Barus S        | 2016 | Australia | 1.82 (1.60, 2.07) | 2.49 | 82 |
| Qin J          | 2017 | China   | 0.73 (0.63, 0.86) | 2.48 | 93 |
| Luke B         | 2017 | USA     | 1.29 (1.13, 1.48) | 2.47 | 97 |
| Subtotal (squared = 98.8%, p = 0.000) | | | 1.44 (1.07, 1.95) | 84.72 |
| - case-control | | | | |
| Vollehoven B   | 2000 | Australia | 1.88 (0.96, 3.69) | 2.11 | 55 |
| Stegner-Karleus B | 2006 | Turkey | 2.66 (1.28, 5.53) | 2.06 | 21 |
| Afler VS Y     | 2007 | Israel  | 2.13 (1.67, 2.73) | 2.45 | 61 |
| Nunes F        | 2015 | Portugal | 1.26 (0.84, 2.47) | 2.11 | 61 |
| Subtotal (squared = 0.0%, p = 0.445) | | | 2.04 (1.65, 2.51) | 8.72 |
| - Cross-sectional | | | | |
| Wang Y         | 2013 | Australia | 1.48 (1.10, 1.98) | 2.50 | 44 |
| Ashraf M       | 2014 | Iran    | 4.00 (2.49, 4.64) | 2.29 | 43 |
| Ashraf M       | 2014 | Iran    | 1.16 (0.42, 3.32) | 1.76 | 75 |
| Subtotal (squared = 88.1%, p = 0.000) | | | 1.99 (0.93, 4.26) | 6.56 |
| - Overall (squared = 96.5%, p = 0.000) | | | 1.51 (1.18, 1.93) | 100.00 |

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

Fig. 3 Forest plot showing the risk of GDM following ART on the basis of study design.
impaired glucose tolerance in comparison to those of spontaneous conceptions. Moreover, they have exposed that for singleton mothers, GDM was more common among cases that underwent ART. However, the risk increases for singleton mothers younger than 40 [48]. Double embryo transfer has been introduced as a significant factor for multiple gestational pregnancy, which is followed by an elevated risk of GDM [89, 90]. Vitthala et al. assessed the risk of monozygotic twins after ART using a systematic review and they revealed that in comparison to cleavage embryo transfer, GDM is more affected by blastocyst transfer [91]. Hammoud et al. addressed the scientific question of whether it is important to diagnose GDM by screening or symptoms. They showed that GDM is strongly related to large-for-gestational-age births [92] and Sazonova et al. showed that babies after embryo transfer have a higher large for gestational age compared to fresh embryo transfer [93]. Pre-existing hypertension is associated with GDM [87] and this might be due to higher rates of ART mothers being of high maternal age [94]. Sibai and Ross assessed the pathophysiology and long-term consequences of hypertension in GDM. They demonstrated that mothers of twins are at a higher risk of GDM in contrast to those of singletons [90]. Risk of GDM among women with PCOS was assessed by Toulis et al. in a systematic review. They showed an increased likelihood of

| Name          | year | Country   | RR (95% CI)       | % Weight | Reference |
|---------------|------|-----------|-------------------|----------|-----------|
| Vanma TR      | 1987 | UK        | 2.04 (0.98, 4.50) | 2.01     | 54        |
| Volante-Brown | 2000 | Australia | 1.88 (0.96, 3.69) | 2.11     | 55        |
| Kolovratova   | 2002 | Finland   | 1.87 (0.83, 3.34) | 2.09     | 57        |
| Bjarcne S     | 2002 | Norway    | 1.27 (2.39, 67.99) | 1.17     | 56        |
| Nasser AH     | 2003 | USA       | 1.00 (0.26, 3.86) | 1.43     | 58        |
| Pincborg A    | 2004 | Denmark   | 1.90 (0.83, 3.89) | 2.07     | 59        |
| Shevlin T     | 2005 | USA       | 1.95 (12, 194)    | 1.46     | 33        |
| Saygak-Karami S | 2006 | Turkey    | 2.66 (12, 55)    | 2.06     | 21        |
| Adler-Levy Y  | 2007 | Israel    | 2.13 (1.67, 2.73) | 2.45     | 61        |
| Buswell WM    | 2007 | Canada    | 1.50 (0.83, 2.43) | 2.29     | 60        |
| Eskander M    | 2007 | Saudi Arabia | 0.90 (0.25, 3.30) | 1.48     | 62        |
| Klieg SA      | 2008 | USA       | 1.80 (0.68, 3.77) | 1.33     | 63        |
| Vassile E     | 2010 | Italy     | 1.24 (0.57, 2.72) | 2.00     | 54        |
| Suzuki S      | 2010 | Japan     | 1.35 (0.98, 21,25) | 0.61     | 65        |
| Subtotal      |      |           | 1.75 (1.50, 2,05) | 26.17    |           |

Fig. 4: Forest plot showing the risk of GDM following ART on the basis of time period.
developing GDM among women with PCOS compared with general cases [95].

The current meta-analysis revealed a significant heterogeneity among the pooled studies, the cohort and cross-sectional studies, the studies conducted during 2011–2017, and the three regions of Asia, Europe, and America. Several statistical tools are available to check the heterogeneity of included studies in a meta-analysis and its selection mechanism depends on several factors such as sample size, the frequency of included studies, etc. The two common tests for heterogeneity (chi-square and the $I^2$ value) can result in controversial conclusions regarding the number of included studies and the magnitude of the relative risks [96]. There might be many reasons for the presence of heterogeneity in the results, such as different cultural and ethnic conditions and diversity in the amount of regions’ development.

The present systematic review has several limitations that should be noted. First, the most important limitation for this study as for other meta-analysis studies is the lack of data for subgroup analysis based on type of pregnancy (singleton versus twin pregnancy), type of ART, or for data analysis controlling for known confounders. Second, there were no data on the relationship between ART and GDM for large regions such as Africa and Latin America, thus the generalizability of the

![Fig. 5 Forest plot showing the risk of GDM following ART on the basis of region](image-url)
results may be limited. Third, this study included only English papers.

In sum, the findings of the present systematic review and meta-analysis indicate that the use of ART is associated with a 1.51-fold increase in GDM. Women need to be counselled carefully before undergoing ART treatment about the possibility and risk of GDM.

Abbreviations
ART: Assisted reproductive technology; CI: Confidence interval; GDM: Gestational diabetes mellitus; NOS: Newcastle–Ottawa Scale; PCOS: Polycystic ovary syndrome; RR: Relative risk

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Authors’ contributions
AA, MM, ROS, SM, and AAH conceived the study. MM, PA, BN, SM, EKM, and AA collected the data. AAH and SM analyzed the data. All authors contributed equally to draft the manuscript. All authors revised the manuscript and approved the final version.

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The authors declare that they have no competing interests.

Author details
1Reproductive Epidemiology Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran. 2Department of Health Services Research, Institute of Psychology, Health, and Society, University of Liverpool, Liverpool, UK. 3School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran. 4Department of Epidemiology, School of Health, Arak University of Medical Sciences, Arak, Iran. 5Department of Biostatistics and Epidemiology, School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. 6Department of Medical Ethics and Law, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran. 7Metabolic Diseases Research Center, Qazvin University of Medical Sciences, Qazvin, Iran.

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