Human Reproduction Update, Vol.26, No.4, pp. 514–544, 2020
Advance Access Publication on May 22, 2020 doi:10.1093/humupd/dmaa011

human reproduction update

Risk of gestational diabetes mellitus in women achieving singleton pregnancy spontaneously or after ART: a systematic review and meta-analysis

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Submitted on October 9, 2019; resubmitted on February 6, 2020; editorial decision on February 25, 2020

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BACKGROUND: Women who achieve pregnancy by ART show an increased risk of obstetric and perinatal complications compared with those with spontaneous conception (SC).

OBJECTIVE AND RATIONALE: The purpose of this systematic review and meta-analysis was to synthesize the best available evidence regarding the association between ART and gestational diabetes mellitus (GDM) in women with singleton pregnancies. The research question

asked was whether the risk of GDM is higher in women achieving singleton pregnancy by ART compared with those achieving singleton pregnancy spontaneously.

SEARCH METHODS: A literature search, in MEDLINE, Scopus and Cochrane databases, covering the period 1978–2019, was performed aiming to identify studies comparing the risk of GDM in singleton pregnancies after ART versus after SC. Both matched and unmatched studies were considered eligible. Meta-analysis of weighted data was performed using the random effects model. Results were reported as risk ratio (RR) with 95% CI. Heterogeneity was quantified with the I^2 index.

OUTCOMES: The study reports on 63 760 women who achieved a singleton pregnancy after ART (GDM was present in 4776) and 1 870 734 women who achieved a singleton pregnancy spontaneously (GDM in 158 526). Women with singleton pregnancy achieved by ART showed a higher risk of GDM compared with those with singleton pregnancy achieved spontaneously (RR 1.53, 95% CI 1.39–1.69; I^2 78.6%, $n = 37$, 1 893 599 women). The direction or the magnitude of the effect observed did not change in subgroup analysis based on whether the study was matched ($n = 17$) or unmatched ($n = 20$) (matched: RR 1.42, 95% CI 1.17–1.72; I^2 61.5%—unmatched: RR 1.58, 95% CI 1.40–1.78; I^2 84.1%) or whether it was prospective ($n = 12$) or retrospective ($n = 25$) (prospective studies: RR 1.52, 95% CI 1.27–1.83, I^2 62.2%—retrospective studies: RR 1.53, 95% CI 1.36–1.72, I^2 82.5%). Regarding the method of fertilization, a higher risk of GDM after ART versus SC was observed after IVF ($n = 7$), but not after ICSI ($n = 6$), (IVF: RR 1.95, 95% CI 1.56–2.44, I^2 43.1%—ICSI: RR 1.42, 95% CI 0.94–2.15, I^2 73.5%). Moreover, regarding the type of embryo transfer (ET), a higher risk of GDM after ART versus SC was observed after fresh ($n = 14$) but not after frozen ($n = 3$) ET (fresh ET: RR 1.38, 95% CI 1.03–1.85, I^2 75.4%—frozen ET: RR 0.46, 95% CI 0.10–2.19; I^2 73.1%). A higher risk of GDM was observed after ART regardless of whether the eligible studies included patients with polycystic ovary syndrome (RR 1.49, 95% CI 1.33–1.66, I^2 75.0%) or not (RR 4.12, 95% CI 2.63–6.45, I^2 0%), or whether this information was unclear (RR 1.46, 95% CI 1.22–1.75, I^2 77.7%).

WIDER IMPLICATIONS: The present systematic review and meta-analysis, by analysing 1 893 599 women, showed a higher risk of GDM in women achieving singleton pregnancy by ART compared with those achieving singleton pregnancy spontaneously. This finding highlights the importance of early detection of GDM in women treated by ART that could lead to timely and effective interventions, prior to ART as well as during early pregnancy.

Key words: gestational diabetes mellitus / ART / spontaneous conception / singleton pregnancy / IVF/ICSI / embryo transfer

Introduction

The number of pregnancies resulting from ART is continuously increasing worldwide. Not unexpectedly, the interest in the potential risks to the mothers and children born after ART has also increased. Currently, a higher risk of obstetric and perinatal complications appears to be present in women achieving pregnancy after ART compared with those achieving pregnancy spontaneously (Nassar *et al.*, 2003, Jackson *et al.*, 2004, Pandey *et al.*, 2012, Qin *et al.*, 2015, Vermey *et al.*, 2019).

One of the most common and important complications of pregnancy is gestational diabetes mellitus (GDM). GDM has been associated with a higher risk of pre-eclampsia, caesarean section in the mother as well as macrosomia, shoulder dystocia, hypoglycaemia and jaundice in the newborn (Ashrafi *et al.*, 2014). In women undergoing ART, major risk factors for GDM, such as advanced maternal age, obesity, multiple pregnancy and polycystic ovary syndrome (PCOS) are often encountered, suggesting a potential association between GDM and ART (Szymanska *et al.*, 2011). Support for this association was offered by a meta-analysis published in 2012 (Pandey *et al.*, 2012), including, however, a limited number of studies ($n = 7$). Since the publication of that meta-analysis, several studies evaluating the association between GDM and ART have been published (Farhi *et al.*, 2013, Stojnic *et al.*, 2013, Ashrafi *et al.*, 2014, Silberstein *et al.*, 2014, Xu *et al.*, 2014, Xu *et al.*, 2015, Beyer and Amari, 2016, Valenzuela-Alcaraz *et al.*, 2016, Zhu *et al.*, 2016, Cai *et al.*, 2017, Luke *et al.*, 2017, Qin *et al.*, 2017, Dayan *et al.*, 2018, Frankenthal *et al.*, 2018, Harlev *et al.*, 2018, Lee *et al.*, 2018, Nagata *et al.*, 2019, Szymusik *et al.*, 2019, Yang *et al.*, 2019), with some of them including thousands of patients (Xu *et al.*, 2014, Luke *et al.*, 2017), allowing for more precise estimates to be obtained. Moreover, this is the first systematic review and meta-analysis evaluating the influence of various moderators, such as the method of fertilization and type of embryo transfer (ET), as well as of various confounders, such as study type, in the association between GDM and ART.

The purpose of this systematic review and meta-analysis was to synthesize the best available evidence regarding the association between ART and GDM in singleton pregnancies. The specific research question asked was whether the risk of GDM is higher in women achieving singleton pregnancy by ART compared with those achieving singleton pregnancy spontaneously. In addition, the influence of various moderators, such as the method of fertilization (IVF or ICSI) and type of embryo transfer (fresh versus frozen), as well as of various confounders, such as type of study (matched versus unmatched, prospective versus retrospective), was explored.

Methods

Identification of literature

A computerized literature search in MEDLINE, Scopus and Cochrane (CENTRAL) was performed independently by two reviewers (J.K.B and P.G.A), covering the period between 1978 and July 2019. This systematic review followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Liberati *et al.*, 2009) (PROSPERO registration number: CRD42019124251).

Search strategy

The following PICO (Population, Intervention or exposure, Comparison, Outcome) elements were applied as inclusion criteria for this systematic review: Population: singleton pregnancies; Intervention: ART; Comparator: SC; Outcome: GDM. A search strategy

with various synonyms was entered as free-text terms in the electronic databases in an attempt to maximize the sensitivity of the search strategy. The following search string was used: (microinjection[tiab] OR 'intra-cytoplasmic sperm injection'[tiab] OR ICSI[tiab] OR 'intracytoplasmic sperm injection'[tiab] OR IVF[tiab] OR 'in-vitro fertilization'[tiab] OR 'in vitro fertilization'[tiab] OR 'in-vitro fertilization'[tiab] OR 'in vitro fertilization'[tiab]) AND ('Diabetes, Gestational'[MeSH] OR 'gestational diabetes'[tiab] OR 'pregnancy complications'[tiab] OR 'obstetric complications'[tiab] OR (pregnancy[tiab] AND (diabet*[tiab] OR 'hyperglycaemia'[tiab] OR 'hyperglycemia'[tiab] OR 'high blood glucose'[tiab] OR 'high plasma glucose'[tiab]))) NOT (Animal[MeSH] NOT Human[MeSH]) NOT (letter[pt] OR comment[pt] OR editorial[pt] OR Review[pt] OR 'practice guideline'[ptyp] OR 'case reports'[ptyp]). No language limitations were applied. Institutional Board Review was not obtained as previously published data were used.

Selection of studies

Criteria for inclusion/exclusion of studies were established prior to the literature search. Studies had to fulfil the following criteria for eligibility: comparative data regarding the risk of GDM in women achieving singleton pregnancy by ART or spontaneously; ovarian stimulation, performed by gonadotropins and GnRH analogues. ART pregnancies included those achieved by IVF or ICSI, after fresh and/or frozen/thawed embryo transfer with autologous gametes. Studies were excluded if pregnancies were achieved using donor gametes, surrogacy, gamete intrafallopian transfer or zygote intrafallopian transfer. Studies performed exclusively in women with PCOS were also excluded due to the known association between PCOS and GDM (Toulis *et al*., 2009, Yu *et al*., 2016). Selection of eligible studies was performed independently by two of the reviewers (J.K.B and E.M.K). Any disagreement was resolved by discussion.

Data extraction

Data extraction was performed independently by two of the reviewers (J.K.B and E.M.K). When a study provided data separately for the method of fertilization and type of ET, the relevant datasets were used for subgroup analyses. Any disagreement between the two reviewers responsible for data extraction was resolved by discussion. In case of missing data or ambiguities in study design or trial conduction, the study authors were contacted by e-mail to request additional information.

Risk of bias and study quality assessment

The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of each study. Briefly, this system evaluates studies based on three criteria: participant selection; comparability of study groups; and assessment of outcome or exposure. A study can be awarded a maximum of four stars for the selection category, a maximum of two stars for the comparability category and a maximum of three stars for the outcome/exposure category (Wells *et al*., 2014).

Subgroup analyses and meta-regression

The influence of various factors, such as type of study (matched versus unmatched, prospective versus retrospective) method of fertilization (IVF or ICSI), type of ET (fresh or frozen), inclusion or not of patients with PCOS and study quality ('good quality' versus 'poor quality' studies), was explored by performing pre-planned subgroup analyses and meta-regression.

Statistical analysis

The dichotomous data results for each of the eligible studies were expressed as risk ratio (RR) with 95% CI. These results were combined for meta-analysis using the random effects model (DerSimonian and Laird, 1986). Study-to-study variation was assessed by using the Chi^2 statistic (the hypothesis tested was that the studies are all drawn from the same population, i.e. from a population with the same effect size). In addition, the use of the I^2 statistic was employed to indicate heterogeneity between studies that could not be attributed to chance, with $I^2 \geq 40\%$ (Higgins and Green, 2011) indicating significant heterogeneity. The presence of publication bias was tested by using the Harbord–Egger's test (Harbord *et al*., 2006). Statistical significance was set at a P level of 0.05. A meta-analysis of weighted average effect sizes was performed using STATA v14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX, USA: StataCorp LP).

Results

Identification of literature

The initial literature search yielded 1356 studies, 73 of which were further evaluated by retrieving their full text and 34 of these were excluded (Supplementary Table SI). Eventually, 38 eligible studies were included in the systematic review, 37 of which offered extractable data for the meta-analysis. A flow diagram of this process is present in Fig. 1.

Systematic review

Thirty-eight cross-sectional studies (17 matched and 21 unmatched; 13 prospective and 25 retrospective), published between 1995 and 2019, were eligible for the systematic review, including a total of 1 934 494 women. Characteristics of the studies included in the systematic review are presented in Table I. Of the 38 studies, 24 were graded as being of 'good quality' and 14 of 'poor quality', according to the NOS (Supplementary Table SII). The definition of GDM was reported in 12 out of the 38 studies. After communication with the corresponding authors, further data on the definition of GDM was obtained for 23 studies (Table I).

In the current systematic review and meta-analysis, studies including only patients with PCOS were excluded, as per protocol. In two of the eligible studies, no patients with PCOS were included (Suzuki and Miyake, 2007, Ashrafi *et al*., 2014), while in 15 studies, they were included in the population analysed (Reubinoff *et al*., 1997, Koivurova *et al*., 2002, Ochsenkuhn *et al*., 2003, Katalinic *et al*., 2004, Sazonova *et al*., 2011, Farhi *et al*., 2013, Stojnic *et al*., 2013, Machtinger *et al*., 2015, Cai *et al*., 2017, Luke *et al*., 2017, Dayan *et al*., 2018, Frankenthal *et al*., 2018, Harlev *et al*., 2018, Nagata *et al*., 2019, Yang *et al*., 2019). In the remaining 21 eligible studies, it was unclear whether patients with PCOS were included or not (Verlaenen *et al*., 1995, Maman *et al*., 1998, Isaksson *et al*., 2002, Zadori *et al*., 2003, Barros Delgadillo *et al*., 2006, De Geyter *et al*., 2006, Schieve *et al*., 2007, Caserta *et al*., 2008, Knoester *et al*., 2008, Sebastiani

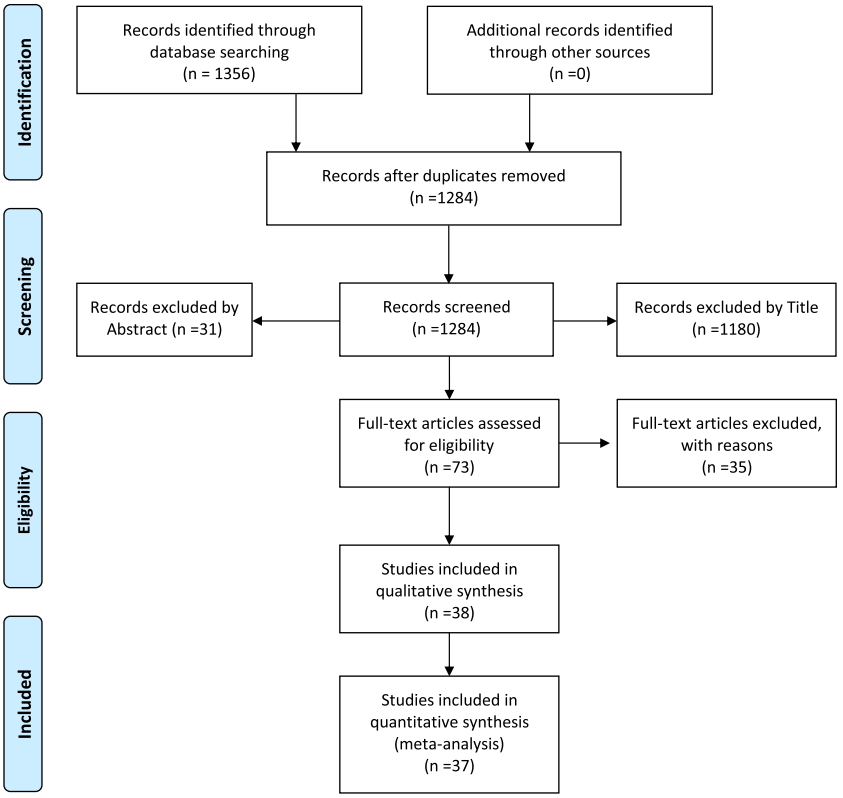

Figure 1 **Flow diagram for selection of studies on risk of gestational diabetes mellitus after spontaneous and ART pregnancies.**

et al., 2009, Chaveeva et al., 2011, Tomic and Tomic, 2011, Silberstein et al., 2014, Xu et al., 2014, Xu et al., 2015, Beyer and Amari, 2016, Valenzuela-Alcaraz et al., 2016, Zhu et al., 2016, Qin et al., 2017, Lee et al., 2018, Szymusik et al., 2019), although this specific information was requested from the corresponding authors (Table I). No data regarding the proportion of patients with PCOS were available in 12 out of the 15 studies that included women with PCOS, while this proportion was reported in the remaining three studies (Farhi et al., 2013: 12.5%, Machtinger et al., 2015: 2%, Frankenthal et al., 2018: 6.5%).

Diagnosis of GDM was present in 4776 out of 63 760 women who achieved singleton pregnancy after ART and in 158 526 out of 1 870 734 women who achieved singleton pregnancy spontaneously. In studies evaluating GDM after ART, IVF/ICSI was performed in 22 studies, IVF only in 5 and ICSI only in 3, whereas this information was not present in eight studies. Fresh and frozen ET were performed in 10 studies, fresh ET only in 11 and frozen ET only in 1, whereas this information was not present in 16 studies.

Maternal age ($n = 16$), parity ($n = 11$), ethnic origin ($n = 7$), date of delivery ($n = 6$) and BMI ($n = 3$) were the most commonly used variables for matching pregnant women after ART with their counterparts after SC. Additional matching variables included smoking ($n = 3$), social class ($n = 3$), gravidity ($n = 3$), fertility history ($n = 3$), height ($n = 2$), weight ($n = 2$), gestational age ($n = 2$), education ($n = 1$) and obstetric outcome ($n = 1$).

Meta-analysis

Main analysis

Thirty-seven studies (17 matched, 20 unmatched) provided data for the main comparison. Women with singleton pregnancies achieved by ART showed a higher risk of GDM compared with those women who achieved singleton pregnancy spontaneously (RR 1.53, 95% CI 1.39–1.69, I^2 78.6%, 1 893 599 women) (Fig. 2). No evidence for publication bias was detected using the Harbord–Egger's test for the primary outcome ($P = 0.84$).

Subgroup analyses—meta-regression

Matched versus unmatched studies. Subgroup analysis was performed according to whether the eligible studies were matched ($n = 17$) or unmatched ($n = 20$). This, however, did not change the direction or the magnitude of the effect observed regarding the type of conception and the presence of GDM (matched studies: RR 1.42, 95% CI 1.17–1.72, I^2 61.5%, 21 606 women—unmatched studies: RR 1.58, 95% CI 1.40–1.78, I^2 84.1%, 1 871 993 women) (Fig. 2). Meta-regression analysis confirmed that the type of study (matched versus. unmatched) did not have a significant effect on the association between type of conception and GDM (coefficient: 0.91, 95% CI 0.67–1.22, $P = 0.51$).

Prospective versus retrospective cross-sectional studies. Subgroup analysis was performed according to whether eligible studies were prospective ($n = 12$) or retrospective ($n = 25$). This, however, did not change the direction or the magnitude of the effect observed regarding the

Table I Characteristics of the 38 eligible studies included in the systematic review.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Ashrafi *et al.*, 2014, Iran, Eur J Obstet Gynecol Reprod Biol	Retrospective cross-sectional/ September 2011–October 2012	95/215	No	Women with singleton pregnancies conceived following ART or spontaneous-ly/PCOS, age > 40 years, family history of diabetes in first-degree relatives, pre-pregnancy diabetes, glucose intolerance treated with hypoglycemic agent, history of GDM, history of stillbirth, recurrent miscarriage, history of macrosomia, parity >3, Cushing syndrome, congenital adrenal hyperplasia, hypothyroidism	No	≥2 of the 100-g OGTT glucose levels exceeded: fasting, >5.3 mmol/l (>95 mg/dl); 1 h, >10.0 mmol/l (>180 mg/dl); 2 h > 8.6 mmol/l (>155 mg/dl); and 3 h, >7.8 mmol/l (>140 mg/dl) (American Diabetes Association)	Not reported	Long agonist and antagonist protocols	Not reported	IVF/ICSI	Fresh	Not reported	Progesterone	Yes/yes

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Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Barros Delgadillo *et al.*, 2006, Mexico, Ginecol Obstet Mex	Retrospective cross-sectional/ October 1999–November 2004	26/52	Yes (by maternal age and the number of fetus)	Control group was selected from the institu-tional registry/ pregnancies resolved before Week 26, diabetes mellitus, systemic chronic arterial hypertension, nephropathies, heart disease and diseases of collagen	Unclear	≥2 altered values of the glucose tolerance curve of 180 min and by sieve of 50 g of glucose (>180 mg/dl/h).	rFSH (300–450 IU)	Leuprolide/ long	≥3 follicles ≥18 mm and E2 ≥ 500 pg/ml	IVF	Fresh	Day 3	Progesterone vag. or I.M. gel and oral estradiol	Yes/no
Beyer *et al*, 2016, Germany, Middle East Fertility Society Journal	Retrospective cross-sectional/ 13-year period	467/ 6417	No	ART and delivery at the university Center/ Cryocon-servation of 2PN oocytes resulting from IVM cycles and/or assisted hatching; delivery <24w, multiple pregnancies and incomplete data.	Unclear	Not reported	rFSH	Cetrorelix or Decapeptyl (long)	≥3 follicles ≥17 mm with corresponding E2 serum levels	IVF/ICSI	Fresh/frozen	Not reported	Transdermal estradiol with transvaginal progesterone	Yes/no

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Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Cai *et al*, 2017, Singapore, Hum Reprod	Prospective cross-sectional/ June 2009–September 2010	76/ 1013	No	Aged ≥18 years at 11–14 weeks of gestation/ Type 1 diabetes mellitus or were receiving chemo-therapy or psychotropic drugs.	Yes	75 g OGTT after 8–10 h of overnight fasting at 26–28 weeks' gestation. GDM: ≥7.0 mmol/L for fasting and/or ≥7.8 mmol/L for 2-h postprandial plasma glucose levels (WHO criteria, 1999, 2013)	Not reported	Not reported	Not reported	Undefined	Undefined	Not reported	Not reported	Yes/yes
Caserta *et al*., 2008, Italy, Acta Obstetricia et Gyneco-logica	Prospective cross-sectional/ February 2004–October 2006	358/ 304	Yes (parity, age, height, weight, ethnic origin, smoking and no history of infertility)	Male cause of infertili-ty/chronic medical disorders, OHSS, female causes of infertility	Unclear	Not reported	rFSH (225 IU)	Decapeptyl (long)	≥3 follicles reached 17 mm	ICSI	Fresh	Day 2	Progesterone vag	Yes/no

(Continued)

Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Chaveeva *et al*, 2011, UK, Fetal Diagnosis and Therapy	Prospective cross -sectional/ January 2000–December 2001	634/ 40 261	No	11–13 + 6 weeks of gestation/ pregnancies conceived by IUI, those with fetal aneuploidies or major defects	Unclear	Fasting plasma glucose level is at least 6 mmol/l or the plasma glucose level 2 h after the oral admi-nistration of 75 g glucose is ≥7.8 mmol/l	Not reported	Not reported	Not reported	IVF	Undefined	Not reported	Not reported	Yes/no
Dayan *et al*., 2018, Canada, Hum Reprod	Retro-spective cross-sectional/ January 2013–January 2014	1596/11281	No	A live or stillborn infant weighing ≥500 g at ≥20 weeks' gestation/-women ≤18 years or with missing maternal age, those with multiple gestations, elective terminations or ectopic or molar pregnancies, and if another form of ART was used	Yes	No: BORN birth registry (codes: D0013 & M0531) and CIHI-DAD (codes: O24.5 to O24.8)	Not reported	Not reported	Not reported	IVF/ICSI	Fresh/ frozen	Not reported	Not reported	Yes/yes

(Continued)

Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
De Geyter *et al.*, 2006, Switzerland, Hum Reprod	Prospective cross -sectional/ August 1996–March 2004	261/ 443	No	Pregnancies from infertile couples during the study period	Unclear	Not reported	uhMG or rFSH	Triptorelin acetate/ long or Ganirelix	Not reported	IVF/ICSI	Fresh/frozen	Day 2	Both estradiol valerate and vaginal micronized progesterone	Yes/no
Farhi *et al.*, 2013, Israel, Reprod Biomed Online	Prospective cross -sectional/ June 2006–December 2008	509/ 587	No	6–12 weeks of gestation demonstrating one gesta-tional sac with a fetal heart pulse	Yes	No: The definition of GDM for diagnosis was based solely on patients' report	Not reported	Not reported	Not reported	IVF/ICSI	Fresh/frozen	Not reported	Not reported	Yes/yes
Frankenthal *et al.*, 2018, Israel, Obes Res Clin Pract	Prospective cross -sectional/ June 2006–December 2008	504/ 554	No	6–12 weeks of gestation	Yes	No: The definition of GDM for diagnosis was based solely on patients' report	Not reported	Not reported	Not reported	Undefined	Undefined	Not reported	Not reported	Yes/yes
Harlev *et al.*, 2018, Israel, Int J Gynaecol Obstet	Retro-spective cross-sectional/ January 1991–December 2013	229/ 7929	No	Women aged at least 40 years/ conceived following oocyte donation, were surrogate mothers, or if they had multifetal pregnancies; aged >45 years	Yes	OGTT >200 or an OGTT of 100gr with 2 abnormal values in a non-previously diagnosed patient as diabetic	Not reported	Not reported	Not reported	IVF/ICSI	Undefined	Not reported	Not reported	Yes/yes

(Continued)

Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Isaksson *et al.*, 2002, Finland, Hum Reprod	Retrospective cross-sectional/ January 1993–March 1999	69/ 345	Yes (maternal age, parity, year of birth, mother's residence, number of children at birth)	Pregnancies ending in birth/ Triplet pregnancies and those ending in spontaneous abortion	Unclear	Not reported	hMG	Buserelin long	≥3 mature follicles ≥18 mm	IVF/ICSI	Undefined	Day 2	Progesterone vag	Yes/no
Katalinic *et al.*, 2004, Germany, Fertil Steril	Prospective cross -sectional/ ART: August 1998–August 2000 Control: January 1993–December 2001	2687/ 7938	No	Pregnancies, conceived after an ICSI procedure and the transfer of fresh embryos before the 16th week of gestation. Control cohort was taken from the Congenital Malformation Monitoring-Centre Saxony-Anhalt/ those who could not be contacted after inclusion, congenital malformation	Yes	No: EUROCAT (code: O24)	Not reported	Not reported	Not reported	ICSI	Fresh	Not reported	Not reported	Yes/yes

(Continued)

Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Knoester *et al.*, 2008, The Nether-lands, Fertil Steril	Prospective cross -sectional/ June 1996–December 1999	87/85	Yes (socioeco-nomic status, gender and birth date)	Singletons conceived by ICSI. Regular preschools and primary schools with zip codes that indicated social class distributions similar to the ICSI cohort assisted in the recruitment of naturally conceived singletons/ Oocyte or sperm donation, cryopreservation of the embryo and selective embryo reduction with medical indication	Unclear	No: Glucose intolerance of variable degree with onset or first recognition during pregnancy	Not reported	Not reported	Not reported	ICSI	Fresh	Not reported	Not reported	Yes/yes

(Continued)

Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Koivurova *et al.*, 2002, Finland, Hum Reprod	Retrospective cross-sectional / 1990–1995	153/580	Yes (sex of the child, year of birth, area, maternal age, parity, social class and fetal plurality)	All IVF live births and stillbirths after completion of week 22 of gestation or with a birth weight of ≥500 g derived from registers at the IVF outpatient clinic in the University Hospital and the Infertility Clinic of the Family Federation of Finland/ not reported	Yes	Altered glucose metabolism requiring dietary or insulin treatment. GDM was detected by a 2 h OGTT (Finnish Diabetes Association and international recommenda-tions)	hMG	Buserelin or Nafarelin long	Not reported	IVF/ICSI	Fresh	Day 2	Progesterone or chorionic gonadotropin for 14 days	Yes/yes
Lee *et al.*, 2018, USA, Fertil Steril	Prospective cross-sectional/ not reported	34/74	Yes (maternal age, race, ethnicity and fetal sex)	All pregnancies at late first trimester at the time of chorionic villus sampling (CVS) and followed until delivery.	Unclear	No: Standard ACOG criteria (ICD-10-CM: O24.415)	Not reported	Not reported	Not reported	Undefined	Fresh/frozen	Not reported	Not reported	Yes/yes

(Continued)

Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Luke *et al.*, 2017, USA, AJOG	Retrospective cross-sectional/ July 2004–December 2010	10 149/ 459 623	No	All live births of ≥22 weeks' gestation and ≥350 g birth weight to Massachusetts resident women	Yes	No: ICD-9 code: 648.8 (abnormal glucose tolerance of mother, antepartum condition, or complication)	Not reported	A range of protocols were used (aromatase inhibitors, minimal stimulation, agonist, agonist flare, antagonist)	Not reported	IVF/ICSI	Fresh/frozen	Not reported	Not reported	Yes/yes
Machtinger *et al.*, 2015, USA, RBMOnline	Retro-spective cross-sectional/ January 2007–December 2011	464/ 1171	No	All women with either spontaneous or IVF singleton pregnancies followed at the outpatient clinics of the hospital during study period/ Pregnancies from Day 5 transfers, multiple pregnancies, pregnancies with vanishing twins, cryopreserved cycles, oocyte donors and gestational carrier cycles	Yes	No: Glucose intolerance with onset or first recognition during pregnancy	Not reported	Not reported	Not reported	IVF/ICSI	Fresh	Day 3	Not reported	Yes/no

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Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Maman *et al.*, 1998, Israel, Fertil Steril	Retrospective cross-sectional/ 1989–1994	169/ 496	Yes (maternal age, gestational age and parity)	Pregnancies that led to a live birth (≥25 weeks' gestation or ≥500 g birth weight)	Unclear	Abnormal fasting blood glucose level or abnormal OGTT result between 24 and 28 weeks of gestation/ sequential pregnancies	Not reported	Not reported	Not reported	Undefined	Undefined	Not reported	Not reported	Yes/yes
Nagata *et al.*, 2019, Japan, BMC Pregnancy and Childbirth	Prospective cross -sectional/ January 2011- March	2993/ 88 873	No	All live births of ≥22 weeks' gestation	Yes	OGTT with 75 g sugar, diagnostic criteria: blood glucose values of (i) ≥92 mg/dl in a fasted state; (ii) ≥180 mg/dl after 1 h; or (iii) ≥153 mg/dL after 2 h	Not reported	Not reported	Not reported	IVF/ICSI	Fresh/frozen	Not reported	Not reported	Yes/yes

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Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Ochsen-kuhnet *al*, 2003, Germany, Arch Gynecol Obstet	Retrospective cross-sectional/ 1991–1996	163/ 322	Yes (maternal age, gestational age and parity)	Gestational age of at least 24 completed weeks and/or children with >499 g birth weight	Yes	No: Screening test with 50 g Glucose and a 100 g OGTT	Not reported	Not reported	Not reported	Undefined	Undefined	Not reported	Not reported	Yes/yes
Qin *et al*, 2016, China, Reprod Sci.	Prospective cross -sectional/ March 2013–February 2016	1260/ 2480	No	Women who provided informed consent, belonged to singleton pregnancies, participated in the follow-up process and had a complete case report form/ deliveries of women <15 years and >60 years, twin, triplet, and quadruplet) pregnancies, egg donation	Unclear	Not reported	Not reported	Not reported	Not reported	IVF/ICSI	Undefined	Not reported	Not reported	Yes/no

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Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Reubinoff *et al.*, 1997, Israel, Fertil Steril	Retro-spective cross-sectional/ 1983–1993	260/ 260	Yes (maternal age, parity, ethnic origin, location and date of delivery)	Pregnancies leading to live births (>25 weeks' gestation or > 500 g birth weight)	Yes	No: Two abnormal values in OGTT	CC + hMG or hMG alone	GnRH analogue (long luteal or follicular)	Leading follicle reached 17–20 mm and serum E2 levels >500 pg/ml	IVF	Fresh/frozen	Not reported	Progesterone I.M.	Yes/yes
Sazonova *et al.*, 2011, Sweden, Hum Reprod	Retro-spective cross-sectional/ 2002–2006	20 236/ 571 914	No	Data from 16 IVF clinics were cross-linked with the Swedish Medical Birth Registry and compared with all children born after spontaneous conception during the same time period	Yes	No: ICD-10 codes	rFSH or hMG	Agonist or antagonist protocols	Not reported	IVF/ICSI	Fresh/frozen	Not reported	Not reported	Yes/yes

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Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Schieve *et al.*, 2007, USA, Matern Child Health J	Retro-spective cross-sectional/ 1997–1998	1400/ 1400	Yes (birth month and year, maternal age, parity, race/ ethnicity)	Restriction to singletons AND exclusion if: maternal age <20, education <high school, mother not married, public/no health insurance for prenatal care, public/no health insurance for labour and delivery; no or inadequate prenatal care or third trimester initiation of prenatal care, and data on race/ ethnicity missing	Unclear	Not reported	Not reported	Not reported	Not reported	IVF/ICSI	Fresh/frozen	Not reported	Not reported	Yes/no

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Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Sebastiani *et al.*, 2009, Spain, An Pediatr (Barc).	Retro-spective cross-sectional/ January 1999–December 2005	176/185	No	Data collected from all pregnancies that were conceived in the study period/ Hereditary disease, children of alcoholic mothers, drug addicts and children of mothers who have used drugs with potential teratogenic effect during pregnancy	Unclear	Not reported	Not reported	Not reported	Not reported	IVF/ICSI	Undefined	Not reported	Not reported	Yes/no
Silberstein *et al.*, 2014, Israel, J Matern Fetal Neonatal Med	Retro-spective cross-sectional/ 1988–2006	1294/ 171 513	No	All women who conceived and delivered singletons at the Soroka University Medical Center in the study period	Unclear	Not reported	Not reported	Not reported	Not reported	IVF	Undefined	Not reported	Not reported	Yes/no

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Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Stojnic *et al.*, 2013, Serbia, Clin Exp Obstet Gynecol	Prospective cross-sectional/ January 2006–January 2010	634/634	Yes (maternal age, parity, education, and BMI)	All pregnancies with duration of >26 weeks/ pregnancies resulting from an oocyte donation, cryopreserved cycles or conceived as twin but continued as singleton	Yes	If at least two values of plasma glucose concen-trations are ≥5.28, 10.0, 8.61 or 7.78 mmol/l for fasting, 1-, 2- and 3-h post-glucose load glucose values, after performing a 100 g OGTT (American Diabetes Association, WHO, 1999)	rFSH or hMG	GnRH agonist long	When at least of half of the dominant follicles reached 18 mm in average diameter	IVF/ICSI	Fresh	Day 2 or 3	Micronized oral/vaginal progesterone 600 mg per day or muscular progesterone 250 mg on every second day	Yes/yes
Suzuki *et al.*, 2007, Japan, Reprod Med Biol	Retrospective cross-sectional/ 2002–2006	89/849	No	Elderly primiparous women (aged ≥35 years)/ Women who underwent GIFT, IUI and OI.	No	A 75-g, 2-h OGTT Plasma glucose level meeting two of the following criteria: ≥100 mg/dl while fasting, ≥180 mg/dl after 1 h or ≥150 mg/dl after 2 h (Japan Society of Obstetrics & Gynecology, 1995)	Not reported	Not reported	Not reported	IVF/ICSI	Fresh	Not reported	Not reported	Yes/yes

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Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Szymusik *et al.*, 2019, Poland, Arch Med Sci	Retro-spective cross-sectional/ 2004–2014	336/ 308	Yes (maternal age and parity)	Pregnancies who delivered >22 weeks of gestation/ history of preterm birth, gestational hypertensive disorders or placental pathologies in the previous pregnancy, oocyte donation, frozen/ thawed ET and major fetal anomalies	Unclear	OGTT of 75 g ≥92 (fasting), ≥180 (1 h) and ≥153 mg/dl (2 h)	Not reported	Not reported	Not reported	IVF/ICSI	Fresh	Not reported	Not reported	Yes/yes
Tomic *et al.*, 2011, Croatia, Arch Gynecol Obstet	Prospective cross-sectional/ 2006–2009	283/ 283	Yes (ethnic origin, maternal age, gravidity, smoking, BMI, weight gain in pregnancy, site and time of delivery)	Primiparous women ≥35 years of age with a birth weight at least 500 g	Unclear	Not reported	rFSH or hMG	GnRH agonist long	≥2 follicles reached 16–17 mm in diameter	Undefined	Fresh	Day 3–5	Progesterone vag gel or capsule	Yes/no

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Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Valenzuela-Alcaraz *et al.*, 2016, Spain, J Matern Fetal Neonatal Med	Retro-spective cross-sectional/ 2004–2010	223/ 460	No	Only pregnancies that were treated, followed-up and delivered at the Infertility and Assisted Reproduction Unit, Hospital Clinic	Unclear	Not reported	FSH	GnRH agonist	Not reported	IVF/ICSI	Undefined	Not reported	Not reported	Yes/no
Verlaenen *et al.*, 1995, Belgium, Obstet Gynecol	Retro-spective cross-sectional/ January 1988–June 1994	140/ 140	Yes (parity, maternal age, height, weight, no fertility history)	Singleton pregnancies of >20 weeks' gestation/ early pregnancy loss (<20w), embryo reduction, women referred later than 20w' gestation due to complications	Unclear	Not reported	Not reported	Not reported	Not reported	IVF	Undefined	Not reported	Not reported	Yes/no

(Continued)

Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Xu *et al.*, 2014, Australia, BMC Pregnancy and Childbirth	Retro-spective cross-sectional/ January 2007–December 2009	12 105/ 381 345	No	Singleton births during the study period/ records that did not state ART status or gestational age	Unclear	Not reported	Not reported	Not reported	Not reported	IVF/ICSI	Undefined	Not reported	Not reported	Yes/no
Xu *et al.*, 2015, China, Zhongguo Dang Dai Er Ke Za Zhi	Retro-spective cross-sectional/ October 2010–October 2012	94/ 164	No	Newborns admitted to the hospital after delivery	Unclear	Not reported	Not reported	Not reported	Not reported	IVF/ICSI	Undefined	Not reported	Not reported	Yes/no
Yang *et al.*, 2019, China, Gynecol Endocrinol	Retro-spective cross-sectional/ January 2015–January 2018	1663/ 3326	Yesv (maternal age, BMI, parity and gravidity)	Deliveries at ≥24 weeks of gestation/ uterine malformation, adenomyosis, uterine myoma, submucous myoma, obesity or low weight, severe intrauterine adhesions, chronic hypertension, and diabetes	Yes	2-h 75 g OGTT between 24 and 28 weeks of gestation, if ≥1 of the three plasma glucose concen-trations equalled or exceeded the following values: fasting glucose 5.1 mmol/L, 1-h level 10.0 mmol/L and 2-h level 8.5 mmol/L	Not reported	Not reported	Not reported	IVF/ICSI	Frozen	Not reported	Not reported	Yes/no

(Continued)

Table I Continued.

Study, country of origin, journal or meeting	Type of study/ Study period	Patients ART/SC	Matching	Inclusion/ exclusion criteria	PCOS patients included	Clear definition of GDM	Gonado-tropin type (dose) in patients undergoing ART	GnRH analogue/ protocol in patients undergoing ART	Criteria for hCG adminis-tration in patients undergoing ART	Fertilization method in patients undergoing ART	Fresh/ Frozen ET in patients undergoing ART	Day of ET in patients undergoing ART	Luteal phase support/ endome-trial preparation in patients undergoing ART	Authors contacted/ replied
Zadori *et al.*, 2003, Hungary, J Assist Reprod Genet	Retro-spective cross-sectional/ January 1995–February 2002	185/ 185	Yes (maternal age, parity, gravidity and previous obstetric outcome)	Deliveries at the Department of Obstetrics and Gyne-cology, University of Szeged in the study period	Unclear	Not reported	Not reported	Not reported	Not reported	Undefined	Undefined	Not reported	Not reported	Yes/no
Zhu *et al.*, 2016, China, Sci Rep	Retro-spective cross-sectional/ 2006–2014	1659/ 5193	Yes (maternal age and birth year)	Pregnancies conceived during the study period	Unclear	Not reported	Not reported	Not reported	Not reported	IVF/ICSI	Undefined	Not reported	Not reported	Yes/no

GDM: gestational diabetes mellitus; OGTT: oral glucose tolerance test; rFSH: recombinant FSH, CC: clomiphene citrate; E2: estradiol, CC; Clomiphene citrate, ACOG: SC: spontaneous conception, ET: embryo transfer, PCOS: polycystic ovary syndrome, PN: pronuclei, WHO: World Health Organization, OHSS: ovarian hyperstimulation syndrome

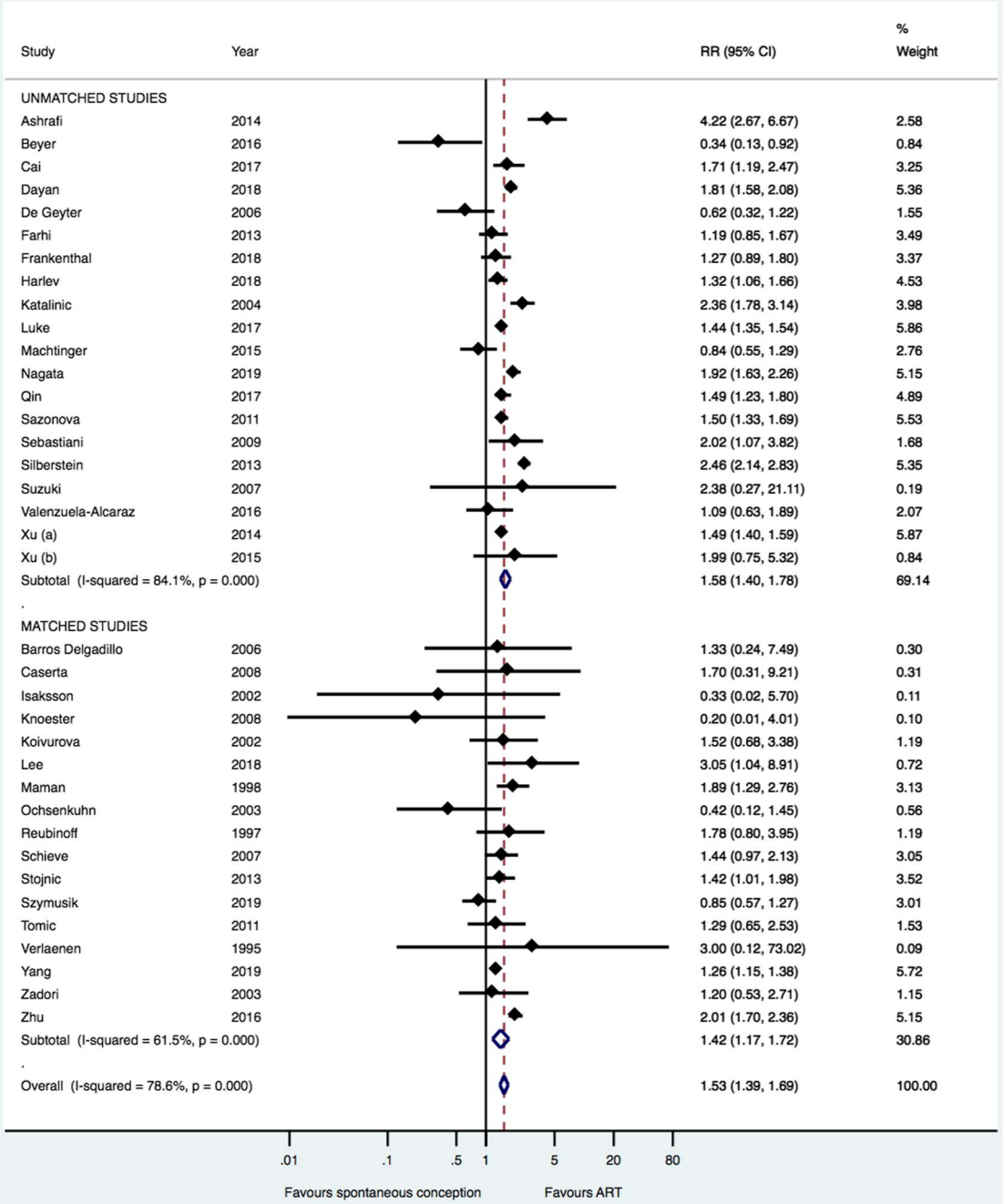

Figure 2 Gestational diabetes mellitus after ART versus after spontaneous conception in matched and unmatched studies. RR: risk ratio.

type of conception and the presence of GDM (prospective studies: RR 1.52, 95% CI 1.27–1.83, I^2 62.2%, 112 954 women—retrospective studies: RR 1.53, 95% CI 1.36–1.72, I^2 82.5%, 1 780 645 women) (Supplementary Fig. S1). Meta-regression analysis confirmed that the type of study (prospective versus retrospective) did not have a significant effect on the association between type of conception and GDM (coefficient: 0.99, 95% CI 0.74–1.35, $P = 0.99$).

Type of ET. Subgroup analysis was performed according to whether pregnancies after ART were achieved exclusively either by fresh or by frozen ET ($n = 17$). Compared to women achieving pregnancy spontaneously, a higher risk of GDM was observed in women achieving singleton pregnancy after fresh ET ($n = 14$) (RR 1.38, 95% CI 1.03–1.85, I^2 75.4%, 605 740 women). This association was not present when women achieving pregnancy spontaneously were compared with those

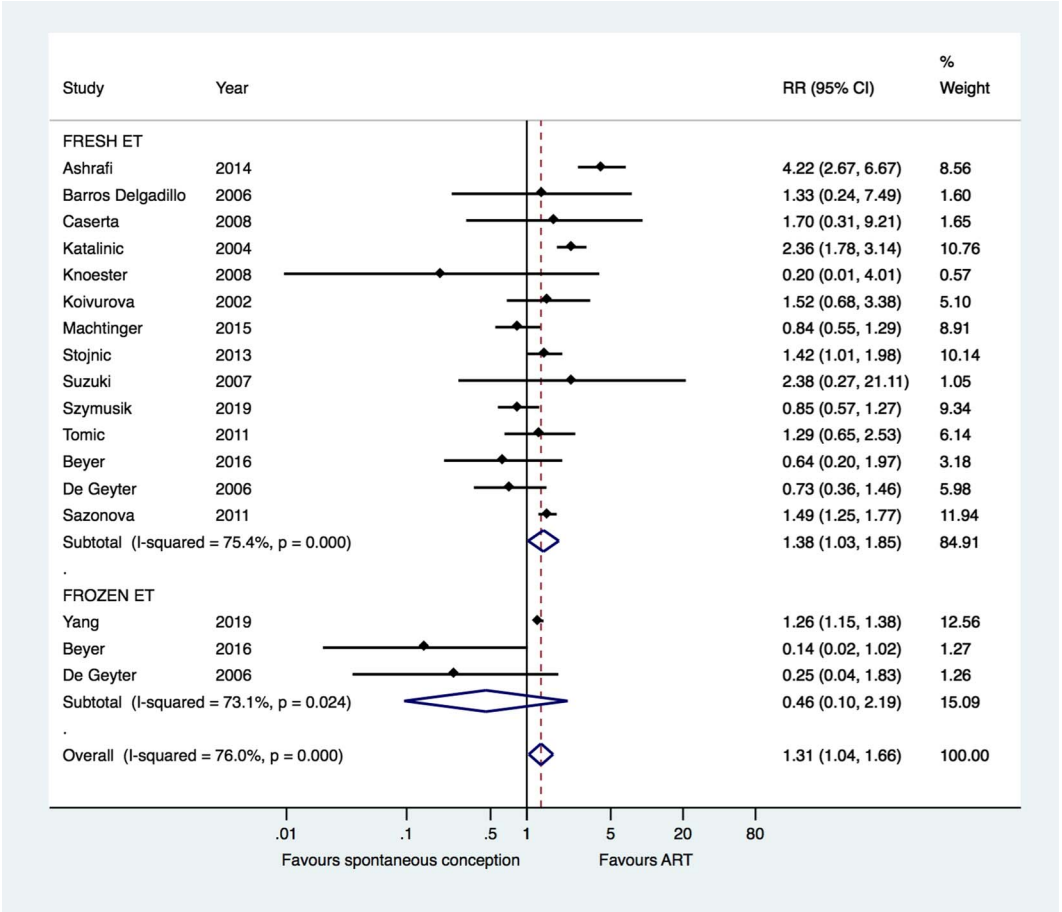

Figure 3 Gestational diabetes mellitus after ART versus after spontaneous conception according to type of embryo transfer. ET: embryo transfer.

achieving singleton pregnancy after frozen ET ($n = 3$) (RR 0.46, 95% CI 0.10–2.19; I^2 73.1%, 12 186 women) (Fig. 3). Meta-regression analysis did not detect a significant effect of type of ET (fresh versus frozen) on the association between type of conception and GDM (coefficient: 0.53, 95% CI 0.19–1.44, $P = 0.19$).

Method of fertilization. Subgroup analysis was performed according to whether pregnancies were achieved exclusively after IVF or ICSI ($n = 13$). Compared to women achieving pregnancy spontaneously, a higher risk of GDM was observed in women achieving singleton pregnancy by IVF ($n = 7$) (RR 1.95, 95% CI 1.56–2.44, I^2 43.1%, 265 253 women). This association was not present when women achieving singleton pregnancy spontaneously were compared with those achieving singleton pregnancy by ICSI ($n = 6$) (RR 1.42, 95% CI 0.94–2.15, I^2 73.5%, 103 402 women) (Fig. 4). Meta-regression analysis did not detect a significant effect of method of fertilization (IVF versus ICSI) on the association between type of conception and GDM (coefficient: 0.80, 95% CI 0.45–1.41, $P = 0.40$).

Inclusion of patients with PCOS. Subgroup analysis was performed according to whether studies included patients with PCOS ($n = 15$), excluded specifically patients with PCOS ($n = 2$) or this information was unclear ($n = 20$). This, however, did not change the significance or the direction of the effect observed regarding the type of conception and the presence of GDM (patients with PCOS excluded: RR 4.12, 95% CI 2.63–6.45, I^2 0%, – patients with PCOS included: RR 1.49, 95% CI 1.33–1.66, I^2 75.0%, – unclear information: RR 1.46, 95% CI 1.22–1.75, I^2 77.7%) (Fig. 5). Meta-regression analysis detected a significant effect ($P < 0.03$) of the population analysed on the association between type of conception and the presence of GDM. More specifically, the RR of GDM after ART compared to SC was significantly higher in studies that specifically excluded patients with PCOS compared to those which included patients with PCOS ($P < 0.01$) or to those in which this information was unclear ($P < 0.01$).

Quality assessment by NOS. Subgroup analysis was performed according to whether eligible studies were classified as of 'good quality' ($n = 24$) or as of 'poor quality' ($n = 13$). This, however, did not change the direction or the magnitude of the effect observed regarding the type of conception and the presence of GDM ('good quality' studies: RR 1.53, 95% CI 1.35–1.74, I^2 74.8%, 709 503 women—'poor quality' studies: RR 1.50, 95% CI 1.26–1.79, I^2 83.9%, 1 184 096 women) (Supplementary Fig. S2).

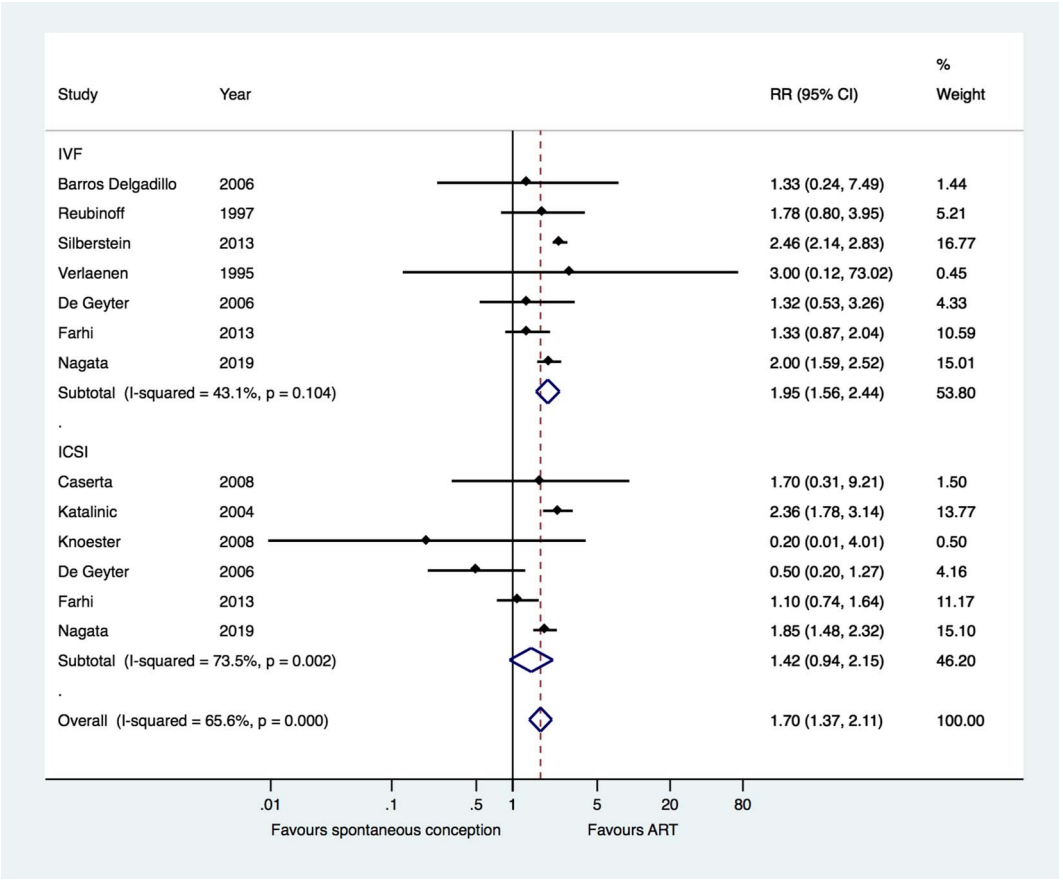

Figure 4 Gestational diabetes mellitus after ART versus after spontaneous conception according to method of fertilization.

Discussion

Main findings

This systematic review and meta-analysis, including 1 934 494 pregnant women and 163 302 women with GDM, showed an increased risk of GDM in women achieving singleton pregnancy by ART compared with those achieving singleton pregnancy spontaneously. This higher risk was observed after IVF but not after ICSI, and after fresh but not after frozen ET. Nevertheless, meta-regression analyses did not detect any significant effect of method of fertilization or type of ET on the association between GDM and type of conception.

Strengths

To accurately evaluate the association between ART and risk of GDM, studies including exclusively women with PCOS and multiple pregnancies were excluded, since they are considered as strong risk factors for the development of GDM (Qin *et al*., 2015, Yu *et al*., 2016). To the best of our knowledge, this is the largest systematic review and meta-analysis focusing on the association between ART and risk of GDM in singleton pregnancies. The present meta-analysis is sufficiently large to provide precise risk estimates. Moreover, it allowed us to perform subgroup analyses, aiming to evaluate the impact of fertilization method and type of ET on the risk of GDM.

Limitations

The definition of GDM was not reported or was unclear in several studies, while a high degree of heterogeneity in its definition was present among those studies that offered such data. Thus, no meaningful subgroup analysis was feasible. Moreover, although the quality of most of the studies was characterised as 'good' by NOS, the retrospective design in the majority of the included studies, as well as the fact that most of the studies were unmatched, are potential sources of bias. Nevertheless, the higher risk of GDM in women achieving singleton pregnancy after ART as compared to those achieving pregnancy after SC did not change in subgroup analyses, evaluating whether pooled studies were prospective/retrospective or matched/unmatched.

Comparison with the literature

Two previous meta-analyses evaluated the association between ART and risk of GDM in singleton pregnancies (Jackson *et al*., 2004, Pandey *et al*., 2012). Both meta-analyses showed a higher risk for GDM, although with a limited number of studies [Jackson *et al*., 2004: odds ratio (OR) 2.00, 95% CI 1.36–2.99, $n = 4$, 2291 women; Pandey *et al*., 2012: RR 1.48, 95% CI 1.33–1.66, $n = 6$, 587 790 women]. In the present meta-analysis, the overall sample size increased from 587 790 to 1 934 494 women compared with the meta-analysis by Pandey *et al*. (2012).

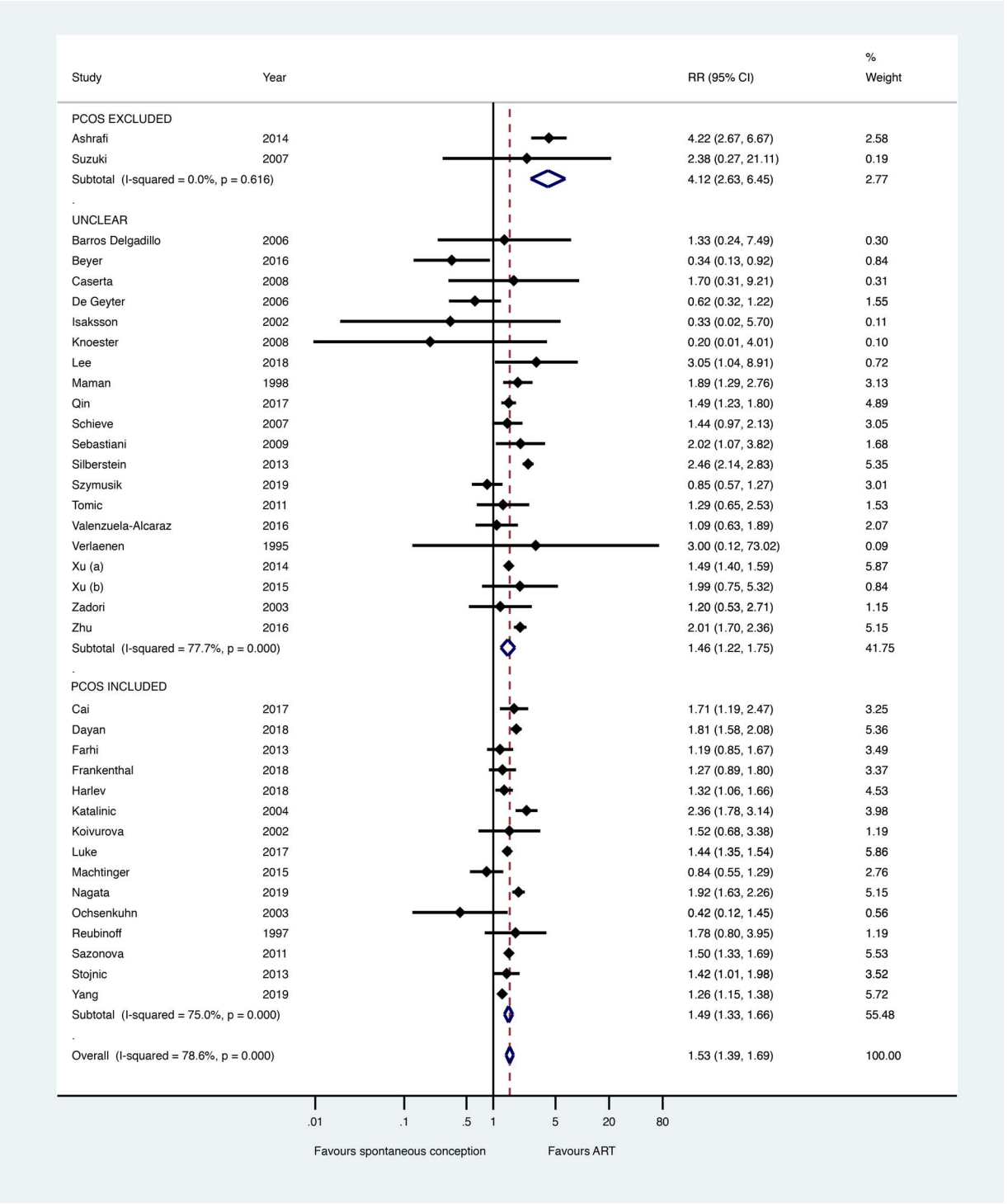

Figure 5 Gestational diabetes mellitus after ART versus after spontaneous conception in studies including patients with PCOS or not, or whether this information was unclear. PCOS: polycystic ovary syndrome

Interpretation of the study

The underlying mechanisms regarding the increased risk of GDM in women achieving singleton pregnancy by ART compared with those achieving singleton pregnancy spontaneously remain unclear. Moreover, whether the association observed is explained by the presence of infertility *per se* or the ART procedure performed cannot be evaluated on the basis of the data presented (Wang *et al.*, 2017). A potential explanation for the increased risk of GDM after ART might be the use of progesterone for luteal phase support in all ART cycles as well as during the first trimester of pregnancy (Rebarber *et al.*, 2007, Ashrafi

et al., 2014). Progesterone is known to increase insulin resistance (Branisteanu and Mathieu, 2003), which can lead to GDM.

Although a higher risk of GDM was observed after fresh but not after frozen ET, meta-regression analysis failed to detect a potential effect of the type of ET (fresh versus frozen) on the GDM risk. This might be due to the fact that the number of datasets pooled, comparing pregnancies after frozen ET versus pregnancies after SC, was limited ($n = 3$), in contrast to that comparing pregnancies after fresh ET versus pregnancies after SC ($n = 14$). Alternatively, the higher risk of GDM only after fresh ET might be due to the known adverse effects of ovarian stimulation on endometrial receptivity (Kolibianakis *et al*., 2002, Van Vaerenbergh *et al*., 2009). Endometrial quality is reported to be associated with the incidence of GDM in singleton pregnancies, since a higher probability of GDM is shown to be present after frozen ET in a hormonal replacement cycle compared with frozen ET in a natural cycle (adjusted OR 0.52, 95% CI 0.39–0.69) (Saito *et al*., 2019).

The higher risk of GDM, observed only after fresh ET, might be attributed to differences in the quality of placentation between fresh cycles and frozen-thawed cycles (Kansal Kalra *et al*., 2011), explained by differences in the hormonal peri-implantation environment in these two clinical scenarios. It has been suggested that supraphysiologic steroid hormone levels during the fresh stimulated cycles may lead to abnormal endometrial angiogenesis and abnormal placentation (Maheshwari *et al*., 2018). Altered placental gene regulation has been associated with GDM, probably through epigenetic mechanisms involvement (Nomura *et al*., 2014, Finer *et al*., 2015, Reichetzeder *et al*., 2016).

Regarding the method of fertilization, although the higher risk of GDM was statistically significant only after IVF but not after ICSI, the direction and magnitude of the effect were similar in both groups, while meta-regression analysis did not detect any significant effect of the fertilization method on the association between GDM and type of conception. Thus, it appears that the method of fertilization does not affect the association between GDM and type of conception.

The higher risk of GDM, observed only after IVF but not after ICSI, might be due to the expected higher proportion of women with female pathology associated not only with infertility, but also with GDM, such as advanced maternal age and obesity. On the contrary, in couples undergoing ICSI the expected main cause leading to infertility is male factor and the anticipated presence of the above risk factors in these couples is lower.

Due to the fact that a higher risk of GDM has been reported among women with PCOS compared to those without PCOS (Palomba *et al*., 2015, Azziz *et al*., 2016, Bahri Khomami *et al*., 2018), the observed association between the type of conception and GDM could be partially attributed to the inclusion of women with PCOS in many of the eligible studies. However, by performing subgroup analysis and meta-regression, the higher risk of GDM after ART compared to SC was still present in studies that specifically excluded PCOS women. In fact, the RR of GDM after ART compared to SC was significantly higher in studies that specifically excluded patients with PCOS compared to those which included them or to those in which this information was unclear. Thus, the effect of the presence of patients with PCOS in many of the eligible studies is probably negligible, which might be attributed to the relatively low proportion of women with PCOS patients in these studies.

Women achieving pregnancy after ART should be monitored for GDM, since the risk is increased compared with SC pregnancies. Early detection as well as appropriate support and care is warranted, aiming to avoid serious complications during pregnancy. Whether this risk is attributed to the underlying infertility status of the couples undergoing ART as compared with those who conceived spontaneously needs to be further elucidated.

Conclusion

In conclusion, the present systematic review and meta-analysis, by analysing 1 893 599 women, showed a higher risk of GDM in women achieving singleton pregnancy by ART compared with those achieving pregnancy spontaneously. This finding highlights the importance of early detection of GDM in women treated by ART, which could lead to timely and effective interventions, prior to ART as well as during early pregnancy.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Acknowledgements

We would like to thank the following authors for providing us with the extra information regarding their published studies: Dr Eitan Lunenfeld, Dr Judy E. Stern, Prof. Barbara Luke, Dr Sari Koivurova, Dr Mahnaz Ashrafi, Dr Chie Nagata, Prof. Alexander Katalinic, Dr Iwona Szymusik, Dr Dolly Farhi, Prof. Christina Bergh, Dr Avi Harlev, Prof. Benjamin Reubinoff, Dr Shunji Suzuki, Dr Cai Shirong, Prof. Peter Hillemanns, Prof. Margareta D. Pisarska, Dr Marjolein Knoester, Prof. Natalie Dayan and Prof. Jelena Stojnic.

Authors' roles

J.K.B.: performed the literature search and contributed towards the data extraction, the analyses and interpretation of the data and the drafting of the manuscript. P.A.: conceived the idea for the study, reviewed the protocol, contributed towards the literature search, interpretation of the data and revised the manuscript for important intellectual content. D.G.G. and G.T.L.: reviewed the protocol and revised the manuscript for important intellectual content. B.C.T. and G.F.G.: revised the manuscript for important intellectual content. E.M.K.: constructed the protocol and contributed towards the data extraction, the analyses and interpretation of the data and the drafting of the manuscript. All authors approved the final version of the manuscript.

Funding

No financial support was received for this study.

Conflict of interest

No conflicts of interest were declared.

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