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ΤΜΗΜΑ ΜΑΙΕΥΤΙΚΗΣ

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ΤΙΤΛΟΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

Επίδραση του σακχαρώδη διαβήτη τύπου 1 ή 2 σε υπογόνιμες γυναίκες που υποβάλλονται σε τεχνικές υποβοηθούμενης αναπαραγωγής: Συστηματική ανασκόπηση

Assisted reproduction technologies outcomes in women with infertility and diabetes mellitus type 1 or 2: Systematic review

Όνομα μεταπτυχιακού φοιτητή: Χρήστος Φ. Ζυμπερδίκας
Ιδιότητα : Ειδικευόμενος Ιατρός Μαιευτικής-Γυναικολογίας
Α' Μαιευτική-Γυναικολογική Κλινική ΑΠΘ
Α.Μ. : 20170427

Τριμελής Εξεταστική Επιτροπή:

Καθηγητής κος Δημήτριος Γ. Γουλής - Επιβλέπων

Καθηγητής κος Γρηγόριος Γκριμπίζης

Καθηγητής κος Γεώργιος Μαστοράκος

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Contents

ABSTRACT

BACKGROUND

Objective: To assess pregnancy, maternal and neonatal outcomes in women with or without diabetes mellitus (DM) undergoing assisted reproduction technologies (ART).

METHODS

Eligibility criteria: Prospective or retrospective controlled trials reporting on women with or without DM undergoing ART treatment.

Information sources: Twelve electronic databases were systematically searched up to December 2019, complemented by additional manual searches.

Risk of bias: The risk of bias assessment was performed by the Cochrane's Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool.

Synthesis of results: Each primary outcome was extracted and pooled as mother- and infant-related. In the case of a sufficient number of studies, risk ratios and the corresponding 95% confidence intervals were calculated and implemented in a random-effect model to account for presumed existing heterogeneity.

RESULTS

Included studies: Two studies were included in the present systematic review, reporting on both mother and neonate-related parameters after ART treatment.

Description of the effects: Preterm birth, placenta previa and excessive bleeding during pregnancy were detected more often in pregnancies with DM conceived by ART-protocols than pregnancies without DM. On the other hand, there is no difference in the possibility of placenta abruptio between these two groups. Regarding the neonatal outcomes, large-for-

gestational-age (LGA) embryos and neonatal intensive care unit (NICU) admission were more commonly reported for women with DM. However, marginal results were found regarding neonatal or infant mortality.

DISCUSSION

Strengths and limitations: The present review was conducted and reported in accordance with existing guidelines and the respective methodology was strictly followed in every stage of the study. However, only two studies were included, which were found to present methodological limitations and reported only a few maternal and neonatal outcomes.

Interpretation: Based on the current literature, DM in pregnancies conceived by ART is associated with specific maternal and neonatal complications.

OTHER

Funding: No funding

Registration: Registered in PROSPERO (Registration number: 143187)

Keywords: Diabetes mellitus, pregnancy outcome, neonatal complications, ART, assisted reproductive techniques.

Περίληψη

Σκοπός

Να εκτιμηθούν τα αποτελέσματα της κύησης, οι μητρικές και νεογνικές επιπλοκές σε γυναίκες με Σακχαρώδη Διαβήτη Τύπου 1 ή 2 σε γυναίκες που υποβάλλονται σε τεχνικές υποβοηθούμενης αναπαραγωγής.

Μέθοδος

Κριτήρια καταλληλότητας: Προοπτικές ή αναδρομικές μελέτες σχετικά με γυναίκες με ή χωρίς Σακχαρώδη Διαβήτη που υποβάλλονται σε τεχνικές υποβοηθούμενης αναπαραγωγής.

Πηγές πληροφοριών: Δώδεκα ηλεκτρονικές βάσεις δεδομένων ελέγχθηκαν συστηματικά ως το Δεκέμβριο του 2019, με επιπρόσθετες χειροκίνητες αναζητήσεις.

Κίνδυνος προκατάληψης: Ο κίνδυνος προκατάληψης πραγματοποιήθηκε με βάση το Cochrane's Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) εγχειρίδιο.

Σύνθεση των αποτελεσμάτων: Κάθε πρωταρχικό αποτέλεσμα κατηγοριοποιήθηκε ως σχετιζόμενο με τη μητέρα ή το νεογνό. Σε περίπτωση που υπήρχαν πάνω από μία μελέτες για το ίδιο αποτέλεσμα, παρουσιάστηκαν σχετικός κίνδυνος από κάθε μία και τα αντίστοιχα διαστήματα εμπιστοσύνης με σκοπό να παρουσιαστεί πιθανή υπάρχουσα ετερογένεια μεταξύ των μελετών.

Αποτελέσματα

Συμπεριλαμβανόμενες μελέτες: Δύο μελέτες συμπεριελήφθησαν στην παρούσα συστηματική ανασκόπηση, οι οποίες σχετίζονται τόσο με μητρικές όσο και με νεογνικές

επιπτώσεις του προϋπάρχοντος Σακχαρώδους Διαβήτη μετά από εφαρμογή τεχνικών Υποβοηθούμενης Αναπαραγωγής.

Περιγραφή των αποτελεσμάτων: Ο πρόωρος τοκετός, η χαμηλή πρόσφυση του πλακούντα και η υπερβολική αιμορραγία κατά τη διάρκεια της εγκυμοσύνης ήταν οι επιπλοκές που καταγράφηκαν συχνότερα στις εγκυμοσύνες με προϋπάρχοντα Σακχαρώδη Διαβήτη που υποβλήθηκαν σε τεχνικές Υποβοηθούμενης Αναπαραγωγής. Αντίθετα, δε φάνηκε αξιοσημείωτη διαφορά στην πιθανότητα εμφάνισης αποκόλλησης του πλακούντα. Σχετικά με τις επιπλοκές που αφορούν το νεογνό, παρατηρήθηκε αυξημένη συχνότητα εμφάνισης Μεγάλων για την ηλικία της κύησης νεογνών και εισαγωγής των νεογνών στη Μονάδα Εντατικής Νοσηλείας Νεογνών (ΜΕΝΝ). Ωστόσο, αμφιλεγόμενα ήταν τα αποτελέσματα σχετικά με τη νεογνική θνησιμότητα.

Συζήτηση

Δυνατότητες και περιορισμοί: Η παρούσα ανασκόπηση πραγματοποιήθηκε και συντάχθηκε με βάση τις υπάρχουσες κατευθυντήριες οδηγίες και η κατάλληλη μεθοδολογία χρησιμοποιήθηκε σε κάθε στάδιο της μελέτης. Ωστόσο, δύο μελέτες συμπεριλήφθηκαν με βάση τους υπάρχοντες περιορισμούς.

Ερμηνεία αποτελεσμάτων: Με βάση την υπάρχουσα βιβλιογραφία, ο Σακχαρώδης Διαβήτης σε κυήσεις που λαμβάνουν χώρα μετά από τεχνικές Υποβοηθούμενης Αναπαραγωγής σχετίζεται με ορισμένες μητρικές και νεογνικές επιπλοκές.

Χρηματοδότηση: Καμία.

Αριθμός Εγγραφής στο PROSPERO: 143187.

Λέξεις κλειδιά: Σακχαρώδης Διαβήτης, αποτέλεσμα κύησης, νεογνικές επιπλοκές, τεχνικές υποβοηθούμενης αναπαραγωγής.

Introduction

Rationale

Infertility is generally defined as a couple's inability to conceive after one year of regular, unprotected intercourse (Cunningham et al., 2017). Assisted reproduction technologies (ART), such as intrauterine insemination (IUI), *in vitro* fertilization (IVF), and intra-cytoplasmic sperm injection (ICSI), have been applied for the management of male and female infertility (Jenabi et al., 2020).

Diabetes mellitus (DM) is one of the most common, non-infectious, progressive, and chronic diseases, constituting a health burden worldwide (Yenice et al., 2020). It is a heterogeneous metabolic disorder, characterized by elevated blood glucose concentrations secondary to either resistance to the action of insulin or insufficient insulin secretion, or both. The most common classification includes type 1 (T1DM), type 2 (T2DM), and gestational diabetes (GDM) (Solis-Herrera et al., 2018). Patients with DM are at high risk for chronic complications, such as nephropathy, retinopathy, and peripheral vascular disease; thus, adequate control of intermediate risk factors (e.g., glucose, total cholesterol, blood pressure) is essential in reducing the risk for potential complications (Tefera et al., 2020). In addition, women with T1DM are more likely to have delayed menarche, menstrual dysfunction and, possibly, earlier menopause (Wellons et al., 2018).

Although the association between DM and pregnancy complications is established (high risk for *in utero* neurodevelopment (Avci et al., 2020), increased fetal distress, single umbilical artery (SUA) (Ebbing et al., 2020), fetal macrosomia, decreased contraction amplitude and duration in utero (Al-Qahtani et al., 2011), preterm prelabour rupture of membranes

(PPRoM) (El-Achi et al., 2020), instrumental vaginal delivery, non-elective Caesarean section], there is a controversy regarding the possible association between pre-existing DM (T1DM or T2DM) and ART outcome. DM in women that undergo ART has been associated with pregnancy-induced hypertension (PIH) and preeclampsia (Kouhkan et al., 2018, Wei et al., 2008), antepartum hemorrhage (Kouhkan et al., 2018), cesarean section (Luke et al., 2016, Kouhkan et al., 2018), preterm birth (Wei et al., 2008, Kouhkan et al., 2018, Xu et al., 2014), placenta previa and placenta abruption (Wei et al., 2008, Luke et al., 2019), birth defects (Luke et al., 2016) and vanishing twin pregnancies (Márton et al., 2016). On the other hand, some studies show no such association (Razem et al., 2019, Wei et al., 2008).

Objective

The aim of the present study is to systematically review the existing evidence regarding the association between the existence of DM (T1DM or T2DM) and ART outcomes (pregnancy and live birth rate).

Materials and Methods

Protocol and registration

The protocol of the present review was conducted *a priori* according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Greene, 2011). The review is reported according to the PRISMA statement (Liberati et al., 2009) and the corresponding extension for abstracts (Beller et al., 2013). The protocol was registered in the PROSPERO database (registration number: 143187).

Information sources and search

Twelve electronic databases were systematically searched up to December 2019 (Table No 8). MESH terms and pertinent keywords were used with a structure conducted to fit each database. No restrictions were applied in matters of publication language, status or year of publication. Moreover, the reference lists of pertinent reviews as well as of the eligible studies were manually assessed. Grey literature was explored through relative registers and databases. The search was performed independently by two authors (CFZ and VFZ).

Eligibility criteria and study selection

The eligibility criteria were pre-determined (Table No 1). A study was considered eligible, if it included at least one group of women with T1DM or T2DM following an ART protocol ("experimental" group), and all of the inclusion and none of the exclusion criteria were fulfilled. Following duplicates removal, all remaining articles were sequentially searched on the basis of title, abstract and full-text using pre-determined pilot forms prepared by the second author (VFZ). The study selection was performed by two review authors (CFZ, VFZ), while any disagreements were solved after consulting the last author (DGG).

Data collection process and data items

Data extraction was performed by two authors (CFZ, VFZ) in piloted collection forms that were constructed *a priori*. In an effort to examine the possible influence of the various ART protocols on the outcomes, all pertinent variables regarding the health of the infant and the mother were considered as primary outcomes. The respective data were classified as infant- and mother-related. Moreover, several parameters were *a priori* determined to examined their possible influence on the treatment outcomes through subgroup analyses.

Risk of bias in individual studies

The risk of bias was *a priori* assessed by the Risk Of Bias In Non-randomized Studies of Interventions tool (ROBINS-I) (Sterne et al., 2016). The latter includes seven domains: 1. bias due to confounding, 2. bias in the selection of participants into the study, 3. bias in classification of interventions, 4. bias due to deviations from intended interventions, 5. bias due to missing data, 6. bias in the measurement of outcomes, and 7. bias in the selection of the reported result. Each domain was rated as “low-risk”, “moderate-risk”, “serious risk”, “critical risk” or “no information”. The overall risk of bias for each study was rated as “low-risk” (all domains being “low-risk”), “moderate risk” (at least one domain being “moderate risk” and the remaining being “low risk”), “serious risk” (at least one domain being “serious risk”, but no domain being “critical risk”), “critical risk” (at least one domain being “critical risk”), and “no information” (at least one domain being “no information”, but no domain being “serious risk” or “critical risk”). The risk of bias was assessed independently by two authors (CFZ and VFZ).

Risk of bias across studies

If >10 studies could be included in the meta-analysis, reporting biases (publication bias and/or "small study effects") were *a priori* planned to be assessed through visual inspection of contour-enhanced funnel plots (Peters et al., 2008), Begg's rank correlation test (Begg et al., 1994), and Egger's weighted regression test (Egger et al., 1997). Furthermore, the Duval and Tweedie's trim-and-fill procedure (Duval and Tweedie, 2000) was performed, in case the previous tests implied the existence of publication bias.

The overall quality of the evidence for each primary outcome was examined according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (Guyatt et al., 2013), based on the following interpretations: "high-quality": very confident that the true effect lies close to that of the estimated, "moderate-quality": moderately confident that the true effect lies close to the estimated, but there is a possibility that it is substantially different, "low-quality": the true effect may be substantially different from the estimated, and "very low-quality": the true effect is likely to be substantially different from the estimated.

Summary measures and synthesis of results

The extracted data were considered appropriate for pooling, if matched control groups of women with T1DM or T2DM, who had conceived naturally, would be included, reporting on the same outcomes as the groups of women, who underwent ART procedures.

For each outcome, risk ratios (RRs) and the respective 95% confidence intervals (CIs) were calculated. In case at least five studies reported on the same outcome, a random-effects model was implemented as the primary method to estimate the pooled data, since high heterogeneity

was expected among the studies, due to the variation in settings and patient characteristics. Calculation of the τ^2 and the I^2 statistic was used to assess the extent and impact of between-study heterogeneity, respectively.

Additional analyses

Potential sources of heterogeneity searched via pre-determined mixed-effects subgroup analyses and random-effects meta-regression. The latter was performed exclusively for meta-analyses, including at least five trials.

Results

Study selection

From the initially retrieved 9789 records, after removal of the duplicates, 9536 articles remained for further evaluation. Following the sequential removal of articles on the basis of title and abstract, eighteen full text articles were assessed. From the latter, sixteen were excluded for various reasons, leaving two articles in the present systematic review.

Study characteristics and risk of bias within studies

The characteristics of the eligible trials are briefly presented in Table 1. The present review included only two retrospective studies performed in various settings, implementing several ART protocols. Moreover, the latter reported both on obstetric as well as perinatal complications. Due to the limited number of included studies and the heterogeneity of the reported outcomes, no meta-analysis was possible to be performed. Nevertheless, these two retrospective studies presented a moderate risk of bias (Table 7).

Results of individual studies and synthesis of results

A) Obstetric complications

The most common pregnancy complication detected was preterm birth. In details, adjusted odds ratio (AOR) for preterm birth was similar in two researches (2.74, 95% CI 1.61–4.67) (Xu et al., BMC 2014) and 2.34 (95% CI 2.23–2.45) (Luke et al., ARG 2019). Moreover, placenta praevia was more often observed in the diabetic group with AOR: 0.8 (95% Cl 0.48–1.33) (Luke et al., ARG 2019). Furthermore, excessive bleeding during pregnancy was also noted to be more frequent in pregnancies conceived by ART with pre-existing DM (Luke et al., ARG 2019).

On the other hand, no significant differences were reported regarding the frequency of placenta abruptio between pregnancies with pre-existing Diabetes Mellitus conceived by ART and pregnancies without pre-existing DM conceived by ART (Luke et al., ARG 2019).

B) Neonatal complications

As far as the neonatal outcome is concerned, large-for-gestational age (LGA) embryo was the complication most frequently detected in diabetic pregnant women (Luke et al., ARG 2019). Moreover, pre-existing DM was associated with the increased possibility of NICU admission of neonatal (Luke et al., ARG 2019).

On the other hand, there are controversial results as far as the effect of the presence of pre-existing DM in pregnancies conceived by ART on neonatal and infant death. While there is an opinion that pre-existing DM is not associated with the pregnancy outcome and embryo loss (Wei et al., FS 2008), there is evidence that support the association of pre-existing DM with neonatal death (AOR 1.17, 95% Cl 0.88–1.56) and infant death (AOR 1.28, 95% Cl 1.02–1.60) (Luke et al., ARG 2019).

Finally, due to insufficient pertinent data, the originally planned subgroup analyses for the identification of the potential influence of several factors on the treatment outcomes could not be performed.

Risk of bias across studies and additional analyses

Due to the inadequate number of available studies, the examination for reporting biases (including publication bias and/or “small study effects”) was not possible to be performed as

initially planned. Similarly, the *a priori* determined additional analyses were not possible to be performed.

Discussion

The present review summarized the existing literature regarding the influence of pre-existing diabetes mellitus on the effectiveness of ART-treated infertile women. According to the respective findings, pre-existing DM, when ART-protocols are used, seems to be associated with several maternal and infantile complications.

In general, pre-existing diabetes mellitus is one among several pathological conditions which are associated with infertility disorders treated by ART (Schieve et al., MCHJ 2007). Also, pre-existing diabetes mellitus is reported to be associated with an increased risk for both maternal and fetal morbidity and mortality (Jauniaux et al., RBO 2013). Moreover, pre-existing DM was associated with the increased possibility of birth defects (OR 1.50, 95% Cl 1.00-2.25) (Luke et al., RM 2016).

Based on findings through the existing literature, the use of ART protocols is by itself an important factor of preterm delivery (Sazonova et al., HR 2011, Helmerhorst et al., BMJ 2004, Frangez et al., EJOGRB 2014). Moreover, according to the results of the present research, pre-existing diabetes mellitus is a condition that proliferates the possibility of preterm delivery in pregnancies conceived by ART (Xu et al., BMC 2014, Luke et al., ARG 2019), without however pointing out the exact mechanism that is responsible for this complication. On the other hand, there is one research that indicates no connection between pre-existing DM and preterm birth among the pregnancies that were included in this research (Frangez et al., EJOGRB 2014).

The possibility of an association between pre-existing diabetes mellitus in pregnancies conceived by ART and pre-eclampsia was also investigated. There is a strong association between pre-existing DM and preeclampsia in spontaneous pregnancies, supported by the current literature. Some pathological tracts appear in both conditions. These include endothelial dysfunction, imbalance of angiogenic factors, increased oxidative stress and dyslipidemia (Poon et al., Int J Gynaecol Obstet. 2019). However, there appeared no evidence to support a possible stronger association between pre-existing DM and preeclampsia in pregnancies conceived by ART. There was only one study to point out that Pregnancy Induced Hypertension (PIH) and preeclampsia were reported in two and three cases respectively in pregnancies conceived by ART with pre-existing DM (Wei et al., FS 2008).

Based on our research, placenta previa and placenta abruption are two complications that could be associated with pre-existing DM in pregnancies conceived by ART. There is one research to support the opinion that these complications of the placenta are associated with the different morphology and gene expression that have been reported in such pregnancies, especially IVF placentas (Luke et al., ARG 2019).

Cesarean section is also increased in pregnancies conceived with ART. There is a study that sustains the opinion that cesarean section is increased in pregnancies conceived by ART than spontaneous pregnancies (Shilpi et al., HRU 2012), especially in singleton than twin pregnancies (Helmerhorst et al., BMJ 2004). According to *Luke et al.,* Pre-existing DM may slightly increase the risk for cesarean section in pregnancies conceived by ART comparing to pregnancies conceived by ART without the presence of pre-existing DM. It is well

established that Primary Caesarean was detected in pregnancies conceived by ART with pre-existing DM with OR of 1.22 (95% Cl 1.00-1.50) (Luke et al., RM 2016).

As far as the risk for Large for Gestational Age Embryos is concerned, it is well supported by the current literature that there is an association between pre-existing diabetes and LGA embryos. *McGrath et al.* suggest that there are several mechanisms, such as hyperglycemia or excessive weight gain, that can lead to LGA embryos, possibly by overnutrition of the fetus, hyperinsulinemia and increase of adipokine levels (McGrath et al., BC 2018). Finally, there is evidence that supports the association between LGA and ART protocols, especially the use of frozen embryo transfer (FET) (Luke et al., JRM 2016).

Conclusions

Pre-existing DM is connected with some important complications that are related both to maternal and neonatal conditions. DM is a chronic disease, which can be easily detected and effectively managed. The proper management of DM before the beginning of ART-protocols and during pregnancy should minimize the possibility of the appearance of these complications and contribute to achieve the desired result of a pregnancy, which is the birth of healthy infants.

However, there are still several aspects that remain to be further investigated by future well-designed studies. In detail, there are several maternal- and ART-related factors that should be assessed for their influence on the treatment outcomes. Moreover, various ART protocols should be compared for their relative efficacy. Finally, several factors regarding the infant and embryo status and the possible complications should be recorded and reported in detail.

Conflict of interest. The authors have no conflict of interest to disclose.

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Tables

Table 1. Eligibility criteria used for study inclusion in the present review.

Criterion	Inclusion	Exclusion
Population	Female of any age, nationality, with DM type 1 or 2	Male patients Female patients of any age, with other systematic disease than DM1 or DM2
Intervention	ART protocol followed	Natural conception
Comparison	Female patients without DM that underwent ART treatment	Female patients with DM Female patients undergoing other types of reproductive techniques than ART
Outcomes	Pregnancy rate Live birth rate	Obstetric, maternal or neonatal complications
Study design	Randomized (controlled) trials Prospective (controlled) trials Retrospective (controlled) trials Cohort studies	Case reports/reports of cases Books/conferences abstracts Unsupported opinion of expert Narrative reviews Systematic reviews Meta-analyses Editorials Letters to the Editor/Author Ongoing trials without reporting outcomes

	Case-control studies
	Studies with inappropriate control group

DM: diabetes mellitus.

Table 2. ROBINS-I tool (Stage I) - At protocol stage.

Specify the review question	
Participants	Female of any age, nationality, with diabetes mellitus (DM) type 1 or 2
Experimental intervention	ART protocol (any type)
Comparator	Women with similar characteristics without following ART protocol
Outcomes	Pregnancy rate - Live birth rate Obstetric, maternal or neonatal complications

Table 3. ROBINS-I tool (Stage II) - For each study.

Specify a target randomized trial specific to the study	
Design	Cluster randomized
Participants	Female of reproduction age, of any nationality, with DM type 1 or 2, without any other pathological medical condition
Experimental intervention	ART protocol (any type)
Comparator	Women with similar characteristics (age, nationality, previous medical history) without following ART protocol

DM: diabetes mellitus.

Table 4. Outcome specifications.

Placental complications (O1)	Harm
Birth weight (O2)	Harm
Preterm birth (O3)	Harm
NICU admission (O4)	Harm
Neonatal death (O5)	Harm
Infant death (O6)	Harm

Table 5. Numerical result being assessed.

Placental complications (O1)	OR
Birth weight (O2)	OR
Preterm birth (O3)	OR
NICU admission (O4)	OR
Neonatal death (O5)	OR
Infant death (O6)	OR

Table 6. Confounding domains listed in the review protocol.

Confounding domain	**Measured variable(s)**	**Is there evidence that controlling for this variable was unnecessary?***	**Is the confounding domain measured validly and reliably by this variable (or these variables)?**
Maternal Background	Pre-pregnancy BMI	No	Yes
	Smoking during pregnancy	No	Yes
	Hypertension	No	Yes
	Diabetes mellitus	No	Yes
	Epilepsy	No	No
	Age	No	Yes
	Country	No	Yes
	Race/ethnicity	No	Yes
	Education	No	Yes
	Socio-economic background	No	Yes
ART protocol parameters	Male factor	No	Yes
	Endometriosis	No	Yes
	Ovulation disorders	No	Yes
	Tubal factors	No	Yes
	Uterine factors	No	Yes
	Oocyte source	No	Yes
	semen sources	No	Yes
	Use of ICSI and	No	Yes

	assisted hatching		
	Number of embryos transferred	No	Yes
	Number of fetal heartbeats at the six-week ultrasound	Yes	No
	Embryo state (fresh or thawed)	No	Yes
Complications during pregnancy	Hypertensive disorders in pregnancy	No	Yes
	Gestational diabetes	No	Yes
	Antepartum hemorrhage	No	Yes

ICSI: intra-cytoplasmic sperm injection.

Table 7. Risk of bias assessment.

	Luke et al., 2019						Xu et al., 2004
Signaling questions	***Response options (O1)***	***Response options (O2)***	***Response options (O3)***	***Response options (O4)***	***Response options (O5)***	***Response options (O6)***	***Response options (O3)***
Bias due to confounding							
Risk of bias judgment	Low	Low	Low	Low	Low	Low	Low
Bias in selection of participants into the study							
Risk of bias judgment	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Bias in classification of interventions							
Risk of bias judgment	Low	Low	Low	Low	Low	Low	Low
Bias due to deviations from intended interventions							
Risk of bias judgment	Low	Low	Low	Low	Low	Low	Low
Bias due to missing data							
Risk of bias judgment	Low	Low	Low	Low	Low	Low	Low

Bias in measurement of outcomes							
Risk of bias judgment	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Bias in selection of the reported result							
Risk of bias judgment	Low	Low	Low	Low	Low	Low	Low
Overall bias							
Risk of bias judgment	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

Table 8. Electronic databases searched, search strategies used and corresponding results.

Electronic database	Search strategy used	Limits	Hits
Databases of published trials			
MEDLINE Searched via PubMed on September 2019 http://www.ncbi.nlm.nih.gov/pubmed	((((non-insulin depen* diabet*) OR (non insulin depend* diabet*) OR (diabet* mellit*) OR (diabet* type 2) OR (diabet* type II) OR (diabet* type-2) OR (diabet* type-II)) AND (pregnan* OR impregn* OR obg* OR embryo* OR gestat* OR fetus* OR gynaecol* OR gynecol*) AND ((assist* reprod* techn*) OR (assist* reproduc*) OR fertil* OR infertil* OR (reprod* medic*) OR (reprod* care*) OR (reprod* health*))))	*No limitations*	**2543**
Scopus Searched on December 28, 2019 http://www.scopus.com/	((((non-insulin depen* diabet*) OR (non insulin depend* diabet*) OR (diabet* mellit*) OR (diabet* type 2) OR (diabet* type II) OR (diabet* type-2) OR (diabet* type-II)) AND (pregnan* OR impregn* OR obg* OR embryo* OR gestat* OR fetus* OR gynaecol* OR gynecol*) AND ((assist* reprod* techn*) OR (assist* reproduc*) OR fertil* OR infertil* OR (reprod* medic*) OR (reprod* care*) OR (reprod* health*))))	*Limit to: EXACT KEYWORD: "Pregnancy complications"*	**4523**
ScienceDirect	(Assisted Reproductive Techniques) AND (diabetes OR endocrinology)	*Limit to:*	

Searched on August 28, 2019 http://www.sciencedirect.com/science			**503**
Google Scholar Searched on September 25, 2019 https://scholar.google.gr	diabetes "assisted reproductive technique"		**768**
Cochrane Database of Systematic Reviews Searched via The Cochrane Library on September 25, 2019 http://onlinelibrary.wiley.com/cochranelibrary	((((non-insulin depen* diabet*) OR (non insulin depend* diabet*) OR (diabet* mellit*) OR (diabet* type 2) OR (diabet* type II) OR (diabet* type-2) OR (diabet* type-II)) AND (pregnan* OR impregn* OR obg* OR embryo* OR gestat* OR fetus* OR gynaecol* OR gynecol*) AND ((assist* reprod* techn*) OR (assist* reproduc*) OR fertil* OR infertil* OR (reprod* medic*) OR (reprod* care*) OR (reprod* health*))))	*Limit to:*	**316**
Cochrane Central Register of Controlled Trials Searched via The Cochrane Library on September 25, 2019 http://onlinelibrary.wiley.com/cochra	((((non-insulin depen* diabet*) OR (non insulin depend* diabet*) OR (diabet* mellit*) OR (diabet* type 2) OR (diabet* type II) OR (diabet* type-2) OR (diabet* type-II)) AND (pregnan* OR impregn* OR obg* OR embryo* OR gestat* OR fetus* OR gynaecol* OR gynecol*) AND ((assist* reprod* techn*) OR (assist* reproduc*) OR fertil* OR infertil* OR (reprod*	*Limit to:*	**199**

nelibrary	medic*) OR (reprod* care*) OR (reprod* health*))))		
Ovid database Searched via HEAL-Link on September 25, 2019 http://ovidsp.ovid.com	(diabet* OR endocrin*) AND (pregnan* OR impregn* OR obg* OR embryo* OR gestat* OR fetus* OR gynaecol* OR gynecol*) AND (assist* reprod* techn*)	*Limit to: Search in Title, Abstract and Author Keywords.*	**110**
VHL Search Portal Searched on September 25, 2019 (Databases included: LILACS, BBO-Dentistry, IBECS, BINACIS, MedCarib) http://pesquisa.bvsalud.org/portal/	(diabet* OR endocrin*) AND (pregnan* OR impregn* OR obg* OR embryo* OR gestat* OR fetus* OR gynaecol* OR gynecol*) AND (assist* reprod* techn*)	*Limit to:*	**89**
Evidence-Based Medicine Searched on September 25, 2019 http://ebm.bmj.com/search	Abstract OR Title (diabet* OR endocrinol*) AND Abstract OR Full Text OR Title (assist* reprod* techn*)	*Limit to:*	
Nature Databases and Gateways Searched on September 25, 2019	Assisted Reproductive Techniques, diabetes	*Limit to: in Full Text*	**292**

http://www.nature.com/			
African Journals Online Searched on September 25, 2019 http://www.ajol.info/	Assisted reproductive techniques	*Limit to:*	**3**
Databases of dissertations, theses and conference proceedings			
German National Library of Medicine (ZB MED) Searched via MEDPILOT on August 28, 2019 https://www.livivo.de/app	(diabet* OR endocrin*) AND (pregnan* OR impregn* OR obg* OR embryo* OR gestat* OR fetus* OR gynaecol* OR gynecol*) AND (assist* reprod* techn*) (aristerh sthlh)	*Limit to:* *"Cataloque Medicine Health"*	**160**
Sum			**9789**