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ASSISTED REPRODUCTION TECHNOLOGIES

Risk of adverse perinatal outcomes after oocyte donation: a systematic review and meta-analysis

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Abstract

Research question In women with singleton pregnancies conceived after assisted reproductive technologies, does the in vitro fertilization with oocyte donation (IVF-OD) affect the perinatal and maternal outcomes compared to autologous in vitro fertilization (IVF-AO)?

Design Systematic review and meta-analysis of studies comparing perinatal and maternal outcomes in singleton pregnancies resulting from IVF-OD versus IVF-AO. An electronic literature search in Pubmed, MEDLINE, and Cochrane database was performed. The main outcome measures were hypertensive disorders in pregnancy, preeclampsia, severe preeclampsia, pregnancy-induced hypertension, preterm birth, early preterm birth, low birth weight, and very low birth weight.

Results Twenty-three studies were included. IVF-OD is associated with a higher risk of hypertensive disorders in pregnancy (OR 2.63, 2.17–3.18), preeclampsia (OR 2.64; 2.29–3.04), severe preeclampsia (OR 3.22; 2.30–4.49), pregnancy-induced hypertension (OR 2.16; 1.79–2.62), preterm birth (OR 1.57; 1.33–1.86), early preterm birth (OR 1.80; 1.51–2.15), low birth weight (OR 1.25, 1.20–1.30), very low birth weight (OR 1.37, 1.22–1.54), gestational diabetes (OR 1.27; 1.03–1.56), and cesarean section (OR 2.28; 2.14–2.42). There was no significant difference in the risk of preterm birth or low birth weight when adjusted for preeclampsia.

Conclusions IVF-OD patients should be considered an independent risk factor for some adverse perinatal outcomes, mainly hypertensive disorders in pregnancy, preeclampsia, and severe preeclampsia. Immunological and hormonal aspects may be involved in these results, and further research focusing in the etiopathogenesis of these pathologies are needed.

Keywords In vitro fertilization · Oocyte donation · Preeclampsia · Preterm birth · Low birth weight

Introduction

An increasing number of women of advanced reproductive age are seeking out assisted reproductive treatments (ART) [1, 2]. Around the world in 2011, 24% of autologous in vitro fertilization (IVF-AO) were performed by women over 40, with a success rate of 5%. During the last European report in 2014, a live birth rate of 8% was reported [3, 4]. For women 45 years of age or older, the success rate is less than 1% [5].

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Women with low ovarian reserves, generally associated with premature ovarian failure, also have a low success rate of between 5 and 7% in IVF-AO [6, 7]. It is estimated that 1% of women suffer from this condition, and oocyte donation (OD) is one option for these women that has shown acceptable results [8–10].

According to the American Society of Reproductive Medicine, ASRM, when the probability of live birth is less than 5% in IVF-AO, the prognosis is considered to be poor, and they must seek other alternatives [11]. Under this scenario, OD offers a more successful treatment option. In Europe during 2014, the live birth rate by aspiration cycle in IVF-OD was 56% [4]. These rates primarily depend on the age of the donor, regardless of the recipient's age [12].

Due to the above, an increasing number of treatments are performed around the world with IVF-OD, reporting 62,598 cycles during 2011 [13]. In Europe, the number of IVF-OD cycles is around 30,000 cycles per year, and nearly half of these are done in Spain, which offers a number of different IVF-OD programs and liberal legal regulations [4, 12]. In this report, 64% of OD recipients were 40 years of age or older, which supposes that most of these pregnancies are exposed to additional obstetric and perinatal complications, considering that pregnancy at an advanced reproductive age is a known risk factor for pathologies during pregnancy [14].

Despite age, infertility per se [15] and ART [16], independent risk factors are considered for adverse perinatal results. It is suggested that endocrine and endometrial changes induced by controlled ovarian stimulation (COS) could be associated with these results [17–19].

A number of systematic studies and reviews have suggested that IVF-OD may constitute an independent risk factor for poor obstetric and perinatal results, when compared to both spontaneous pregnancies and pregnancies by IVF-AO [20–23].

Several reports show a consistent association between IVF-OD patients and the development of gestational hypertension (GHT) in its different manifestations [24, 25]; however, with other conditions such as preterm birth (PB), low birth weight (LBW), gestational diabetes (GD), c-sections, and placenta anomalies such as placenta previa or placental abruption, some reports show no differences [26–30].

Due to discrepancies and ambiguity in the related literature, the researchers decided to perform a systematic literature review and synthesize the results of studies that compare the perinatal results of pregnancies obtained by IVF-OD versus IVF-AO.

Material and methods

Given that this was a systematic review and meta-analysis and did not involve any intervention in humans, the present study was exempt from Institutional Review Board approval. We utilized the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement to report the results [31]. We registered this study in the International Prospective Register of Systematic Reviews (PROSPERO) with the ID CRD42019124002.

Search strategy

We conducted a systematic review and meta-analysis of observational studies published in English, comparing perinatal outcomes in singleton pregnancies after IVF-AO and IVF-OD. An electronic search was performed in the following databases: Pubmed, MEDLINE, and The Cochrane database, from 1982 through January 2019. We also searched the references of the relevant articles. The search combined terms and descriptors related to variants for the interventions and population study: IVF with or without intracytoplasmic sperm injection (ICSI) and fresh or frozen embryo transfer. The search strategy was modified to fit with the syntaxes used in each database consulted.

Data extraction

In a first screening, two independent authors (J.M, M.C) assessed all of the abstracts retrieved from the search, and then they obtained the full manuscripts of citations that fit the inclusion criteria. They judged study eligibility, assessed quality, and extracted data solving discrepancies by agreement. Both authors critically analyzed the summarized results and referred to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to evaluate the quality of evidence for each outcome [32].

Eligibility criteria

Inclusion criteria

The review included studies that reported perinatal outcomes in pregnancies obtained by IVF-OD or IVF-AO. We included only studies that reported singleton pregnancies and that separately reported fresh embryo transfers (ET) and frozen embryo transfer (FET) for both IVF-AO and IVF-OD.

Since there is evidence that some perinatal outcomes, such as gestational age at birth and birth weight, differ between fresh ET and FET [17, 18, 33], we carried out two sub-analysis for each outcome, analyzing pregnancies after fresh ET and FET separately. The selection criteria are described in Table 1.

Exclusion criteria

The analysis was limited to singleton pregnancies, excluding those studies that reported singleton and multiple pregnancies together. We excluded studies that studied perinatal outcomes in IVF-OD pregnancies, but did not include a control group to compare, or the comparison group were spontaneous

Table 1 PICOs—population, intervention, comparison, and outcomes of interest

Population	Women undergoing ART with a singleton pregnancy
Intervention	IVF after oocyte donation (OD)
Comparator	IVF with autologous oocytes (AO)
Primary outcomes	● Hypertensive disorders of pregnancy ○ Preeclampsia ○ Severe preeclampsia ○ Pregnancy induced hypertension ● Preterm birth ○ Early preterm birth ● Low birth weight ○ Very low birth weight
Secondary outcomes	● Small for gestational age ● Large for gestational age ● Cesarean section ● Gestational diabetes ● Premature rupture of membranes (PROM) ● Placenta previa ● Placental abruption ● Postpartum hemorrhage
Studies	Cohorts, case-control

pregnancies. In addition, studies that included double gamete donation were excluded.

Outcome measures

Main outcomes: hypertensive disorders in pregnancy (HDP), preeclampsia and severe preeclampsia, pregnancy-induced hypertension (PIH), preterm birth (PTB), early preterm birth, low birth weight (LBW), very low birth weight (VLBW). HDP was defined as blood pressure of ≥ 140/90 mmHg on two or more occasions, at least 6 h apart, and more than 20 weeks of gestation. Preeclampsia was defined as blood pressure of ≥ 140/90 mmHg on two or more occasions, at least 6 h apart, with proteinuria of ≥ 0.3 g/day and more than 20 weeks of gestation. Both definitions were consistent with the definition established by the International Society for the Study of Hypertension in Pregnancy (ISSHP) [34]. Severe preeclampsia was identified in the included studies, according to ICD-10 codes obtained from the maternal hospital discharge data. PIH was defined as a blood pressure of ≥ 140/90 mmHg on two or more occasions, at least 6 h apart, without proteinuria and more than 20 weeks of gestation [35]. PTB and early PTB were defined as a live birth before 37 weeks and 32 weeks respectively. LBW and VLBW were defined as birth weight below 2500 g and 1500 g respectively.

Secondary outcomes: small for gestational age (SGA), defined in two ways: birth weight under 2 standard deviations [30] or below the 10th percentile [17]; large for gestational age (LGA), defined as birth weight above the 90th percentile; gestational diabetes, which was defined according to the criteria of the American College of Obstetricians and Gynecologists. In addition, cesarean section, premature rupture of membranes (PROM), placenta previa, placental abruption, and postpartum hemorrhage were included, and their definitions adhered to The International Committee Monitoring Assisted Reproductive Technologies/World Health Organization glossary [35].

Risk of bias assessment

We followed the guidance suggested by the Newcastle-Ottawa Scales (NOS) for assessing the quality of included studies [36]. The studies were evaluated on selection process, comparability of cohorts, and outcomes ascertainment. Table 2 shows the quality assessment and risk of bias of the included studies.

Analysis

To determine the pooled effect of each variable, we used a Mantel-Haenszel model and applied the fixed-effects model. The odds ratio (OR) for dichotomous data accompanied by the 95% confidence intervals (CIs) were calculated. Statistical significance was set at a P values < .05. We evaluated the degree of variation across studies attributable to heterogeneity with the I^2 statistic. When the heterogeneity was greater than 50% ($I^2 > 50\%$), we applied the random-effects model [53]. We conducted meta-analysis using Review Manager Software [54].

Results

The search yielded 2172 articles but 2137 were excluded at title/abstract screening. The remaining 35 studies were considered eligible by one or both reviewers. Twenty-three of these met inclusion criteria [19, 27–30, 39, 41, 43, 46, 48, 50, 51]. A flow diagram shows in detail the selection of studies for inclusion in the Fig. 1.

Description of included studies

There were 23 studies assessing maternal outcomes in singletons after IVF-OD versus IVF-AO meeting the inclusion criteria [19, 27–30, 39, 41, 43, 46, 48, 50, 51] .The characteristics of the included studies are provided in Table 2.

Synthesis of results

The characteristics of the 23 studies, involving 58,597 IVF-OD cycles and 351,766 IVF-AO cycles, are summarized in Table 3. All of the studies had NOS scores > 7 were considered to be high quality.

Table 2 Description of included studies in the meta-analysis

Study ID	Area/duration	Design of the study	N IVF-OD	N IVF-AO	Outcomes	Quality of studies (NOS)
Soderstrom 1998 [20]	Finland 1991–1996	Retrospective cohort study	41	68	Pregnancy induced hypertension	8/9
Wiggins 2005 [37]	USA 1999–2004	Retrospective case-control	50	50	Pregnancy induced hypertension	8/9
Krieg 2008 [38]	USA 2001–2005	Retrospective cohort study	38	87	Preterm birth Small for gestational age Preeclampsia Cesarean section Gestational diabetes	7/9
Zegers-Hochschild 2010 [39]	Chile 1995–2005	Retrospective cohort study	2424	15110	Preterm birth Low birth weight	8/9
Klatsky 2010 [40]	USA 1998–2005	Retrospective cohort study	77	81	Preterm birth Early preterm birth Low birth weight Hypertensive disorder of pregnancy Preeclampsia	9/9
Gibbons 2011 [41]	USA 2004–2006	Retrospective cohort study	10176	49252	Low birth weight Very low birth weight	8/9
Stoop 2012 [27]	Belgium 1999–2008	Retrospective cohort study	147	147	Preterm birth Low birth weight Very low birth weight Hypertensive disorder of pregnancy Pregnancy induced hypertension Preeclampsia Gestational diabetes Placenta previa Premature rupture of membranes	9/9
Malchau 2013 [21]	Denmark 1995–2010	Retrospective cohort study	215	15526	Preterm birth Early preterm birth Low birth weight Small for gestational age Hypertensive disorder of pregnancy Preeclampsia Cesarean section	8/9
Cobo 2014 [42]	Spain 2007–2014	Retrospective cohort study	1380	420	Pregnancy induced hypertension	8/9
Marino 2014 [43]	Australia 1982–2002	Retrospective cohort study	69	2338	Preterm birth Early preterm birth Low birth weight Very low birth weight Small for gestational age Large for gestational age	8/9
Van Dorp 2014 [44]	Netherland 1992–2009	Retrospective case-control	110	311	Small for gestational age Hypertensive disorder of pregnancy Preeclampsia Pregnancy induced hypertension Gestational diabetes Placental abruptionPlacenta previa Postpartum hemorrhage	9/9
Levron 2014 [45]	Israel 2005–2011	Retrospective cohort study	139	126	Hypertensive disorder of pregnancy Preeclampsia Pregnancy induced hypertension	8/9
Baker 2015 [46]	USA 2004–2010	Retrospective cohort study	12862	55846	Preterm birth Low birth weight	8/9
Letur 2016 [47]	France 2005–2012	Cross-sectional cohort study	169	284	Hypertensive disorder of pregnancy Preeclampsia Pregnancy induced hypertension	8/9
Jeve 2016 [28]	UK 2007–2014	Retrospective cohort study	45	45	Preterm birth Hypertensive disorder of pregnancy Cesarean section	8/9

Table 2 (continued)

Study ID	Area/duration	Design of the study	N IVF-OD	N IVF-AO	Outcomes	Quality of studies (NOS)
Nedjet 2016 [48]	Sweden 2003–2012	Retrospective cohort study	388	26696	Preterm birth Early preterm birth Low birth weight Very low birth weight Small for gestational age Large for gestational age Hypertensive disorder of pregnancy Pregnancy induced hypertension Preeclampsia Gestational diabetes Placental abruption Placenta previa Premature rupture of membranes Cesarean section Postpartum hemorrhage	9/9
Tarlatzi 2016 [29]	Belgium 1991–2013	Retrospective cohort study	144	144	Preterm birth Low birth weight Small for gestational age Hypertensive disorder of pregnancy Pregnancy induced hypertension Preeclampsia Gestational diabetes Cesarean section	9/9
Dude 2016 [49]	USA 2008–2010	Retrospective cohort study	8852	55126	Preterm birthLow birth weight	9/9
Kamath 2017 [50]	UK 1991–2011	Retrospective cohort study	4248	95844	Preterm birth Early preterm birth Low birth weight Very low birth weight	9/9
Sites 2017 [51]	USA 2005–2010	Retrospective cohort study	912	8505	Preterm birth Hypertensive disorder of pregnancy Preeclampsia Severe preeclampsia	9/9
Vidal 2017 [19]	Spain 2008–2012	Retrospective cohort study	7544	6718	Preterm birth Early preterm birth Low birth weight Very low birth weight Small for gestational age Cesarean section rate	8/9
Yu 2018 [52]	USA 2009–2013	Retrospective cohort study	8447	18653	Preterm birth Low birth weight Small for gestational age	8/9
Rodriguez-Wallberg 2019 [30]	Sweden 2007–2014	Prospective cohort study	259	515	Preterm birth Early preterm birth Low birth weight Very low birth weight Small for gestational age Large for gestational age Hypertensive disorder of pregnancy Pregnancy induced hypertension Preeclampsia Severe preeclampsia Gestational diabetes Placental abruption Placenta previa Premature rupture of membranes Cesarean section Postpartum hemorrhage	9/9

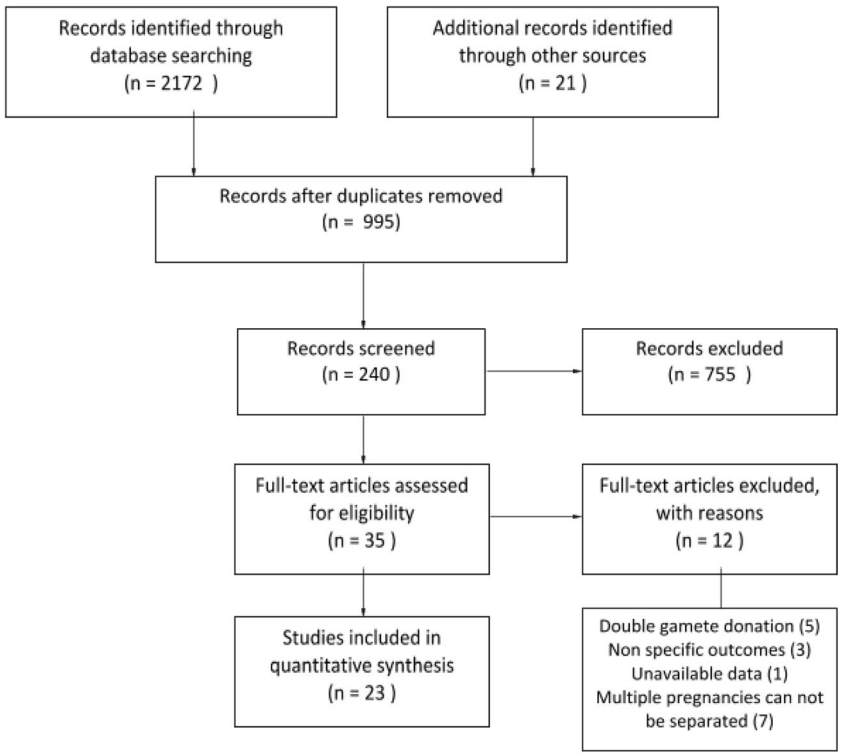

Fig. 1 Preferred outcome items for systematic reviews and meta-analysis flow diagram detailing selection of studies for inclusion

Main outcomes

Hypertensive disorders in pregnancy

Eight studies reported early HDP including 11,049 patients, 2466 in the IVF-OD group and 52,254 patients in the IVF-AO group. The overall OR for HDP was 2.63 (95% CI 2.17–3.18; I2 = 53%; Fig. 2a). The quality of evidence was moderate according to GRADE (Table 3).

An increase in HDP in IVF-OD group was observed for patients after fresh ET (four studies; $n = 1203$ patients) compared to IVF-AO (OR = 2.62; 95% CI 1.93–3.55; I2 = 30%; moderate quality of evidence; Fig. 2b). An increase in HDP was also observed for patients IVF-OD after FET (one studies; $n = 243$ patients) compared to IVF-AO after FET (OR = 3.34; 95% CI 1.52–7.36; moderate quality of evidence; Fig. 2c).

Preeclampsia

Eleven studies reported preeclampsia including 47,729 patients, 2459 in the IVF-OD group, and 52,296 patients in the IVF-AO group. The overall OR for preeclampsia was 2.64 (95% CI 2.29–3.04; I2 = 41%; Fig. 3a). The quality of evidence was moderate according to GRADE (Table 3). A subgroup analysis concerning the fresh ET patients (five studies; $n = 29,499$ patients) indicated that IVF-OD increased preeclampsia with an OR of 3.17 (95% CI 2.67–3.75; I2 = 15%; moderate quality of evidence; Fig. 3b). The risk of preeclampsia was also higher in pregnancies resulting from IVF-OD after FET than from IVF-AO after FET (three studies; $n = 8358$ patients; OR = 1.75; 95% CI 1.23–2.49; I2 = 30%; moderate quality of evidence; Fig. 3c).

Severe preeclampsia

Two studies were included in the analysis. Overall, they evaluated 10,191 deliveries (1171 after IVF-OD and 9020 after IVF-AO). The OR was of 3.22 (95%CI 2.30–4.49; I2 = 45%) when comparing pregnancies after IVF-OD to IVF-AO. The quality of evidence was moderate according to GRADE (Fig. 4a). IVF-OD after fresh ET was associated with an increased risk of severe preeclampsia (two studies; $n = 8627$ patients) compared with IVF-AO after fresh ET (OR = 3.36; 95% CI 2.30–4.93; I2 = 0%; moderate quality of evidence; Fig. 4b). An increase in severe preeclampsia was also observed for patients IVF-OD after FET (two studies; $n = 1564$ patients) compared to IVF-AO after FET (OR = 2.83; 95% CI 1.45–5.52; I2 = 18%; moderate quality of evidence; Fig. 4c).

Pregnancy-induced hypertension

Ten studies reported PIH including 13,277 patients, 2688 in the IVF-OD group, and 28,635 patients in the IVF-AO group. The overall OR for PIH was 2.16 (95% CI 1.79–2.62; I2 = 7%; Fig. 5a). The quality of evidence was moderate according to GRADE (Table 3).

An increase in PIH in IVF-OD group was observed for patients after fresh ET (four studies; $n = 9209$ patients)

Table 3 Summary of findings table displaying the results of primary outcomes and sub-analysis comparing IVF-OD with IVF-AO in fresh and frozen ET

Outcome	Absolute effect risk difference per 1000 FET versus fresh ET (95%CI)	Odds ratio (95%CI)	Number of studies	Participants	Quality of evidence (grade)
Primary outcomes					
Hypertensive disorder in pregnancy—overall	97 more per 1000 (78 more to 116 more)	2.63 (2.17, 3.18)	8	11,049	⊕⊕⊕○ Moderate
Hypertensive disorder in pregnancy—IVF-OD fresh ET vs IVF-AO fresh ET	96 more per 1000 (66 more to 127 more)	2.62 (1.53, 3.55)	4	1203	⊕⊕⊕○ Moderate
Hypertensive disorder in pregnancy—IVF-OD FET vs IVF-AO FET	121 more per 1000 (42 more to 200 more)	3.34 (1.52, 7.36)	1	243	⊕⊕⊕○ Moderate
Preeclampsia—overall	97 more per 1000 (83 more to 111 more)	2.64 (2.29, 3.04)	11	47,729	⊕⊕⊕○ Moderate
Preeclampsia—IVF-OD fresh ET vs IVF-AO fresh ET	115 more per 1000 (98 more to 132 more)	3.17 (2.67, 3,75)	5	29,499	⊕⊕⊕○ Moderate
Preeclampsia—IVF-OD FET vs IVF-AO FET	56 more per 1000 (21 more to 91 more)	1.75 (1.23, 2.49)	3	8358	⊕⊕⊕○ Moderate
Severe preeclampsia—overall	117 more per 1000 (83 more to 150 more)	3.22 (2.30, 4.49)	2	10,191	⊕⊕⊕○ Moderate
Severe preeclampsia—IVF-OD fresh ET vs IVF-AO fresh ET	121 more per 1000 (83 more to 159 more)	3.36 (2.30, 4.93)	2	8627	⊕⊕⊕○ Moderate
Severe preeclampsia—IVF-OD FET vs IVF-AO FET	104 more per 1000 (37 more to 171 more)	2.83 (1.45, 5.52)	2	1564	⊕⊕⊕○ Moderate
Pregnancy-induced hypertension—overall	77 more per 1000 (58 more to 96 more)	2.16 (1.79, 2.62)	10	13,277	⊕⊕⊕○ Moderate
Pregnancy induced hypertension—IVF-OD fresh ET vs IVF-AO fresh ET	49 more per 1000 (23 more to 76 more)	1.64 (1.26, 2.13)	4	9209	⊕⊕⊕○ Moderate
Pregnancy induced hypertension—IVF-OD FET vs IVF-AO FET	80 more per 1000 (36 more to 124 more)	2.22 (1.43, 3.46)	2	1564	⊕⊕⊕○ Moderate
Preterm birth—overall IVF-OD vs IVF-AO	45 more per 1000 (28 more to 62 more)	1.57 (1.33, 1.86)	14	267,614	⊕⊕○○ Low
Preterm birth—IVF-OD fresh ET vs IVF-AO fresh ET	37 more per 1000 (18 more to 55 more)	1.44 (1.20, 1.74)	11	229,377	⊕⊕○○ Low
Preterm birth—IVF-OD FET vs IVF-AO FET	67 more per 1000 (32 more to 102 more)	1.96 (1.38, 2.78)	5	37,935	⊕⊕○○ Low
Preterm birth adjusted for preeclampsia—IVF-OD vs IVF-AO	29 more per 1000 (1 fewer to 59 more)	1.34 (0.99, 1.81)	2	16,515	⊕⊕○○ Low
Early preterm birth—overall	59 more per 1000 (41 more to 77 more)	1.80 (1.51, 2.15)	6	153,533	⊕⊕○○ Low
Early preterm birth—IVF-OD fresh ET vs IVF-AO fresh ET	52 more per 1000 (9 more to 95 more)	1.26 (1.11, 1.43)	5	134,460	⊕⊕○○ Low
Early preterm birth—IVF-OD FET vs IVF-AO FET	107 more per 1000 (50 more to 165 more)	2.93 (1.65, 5.20)	3	9514	⊕⊕○○ Low
Low birth weight—overall	22 more per 1000 (18 more to 26 more)	1.25 (1.20, 1.30)	12	257,928	⊕⊕○○ Low
Low birth weight—IVF-OD fresh ET vs IVF-AO fresh ET	22 more per 1000 (12 more to 32 more)	1.25 (1.13, 1.38)	10	220,645	⊕⊕○○ Low
Low birth weight—IVF-OD FET vs IVF-AO FET	60 more per 1000 (37 more to 83 more)	1.83 (1.45, 2.30)	4	36,614	⊕⊕○○ Low
Low birth weight adjusted for preeclampsia—*IVF-OD vs IVF-AO*	19 more per 1000 (17 fewer to 56 more)	1.21 (0.84, 1.75)	2	16,515	⊕⊕○○ Low
Very low birth weight—overall	32 more per 1000 (20 more to 43 more)	1.37 (1.22, 1.54)	7	200,773	⊕⊕○○ Low
Very low birth weight —IVF-OD fresh ET vs IVF-AO fresh ET	31 more per 1000 (20 more to 42 more)	1.36 (1.23, 1.52)	7	194,089	⊕⊕○○ Low
Very low birth weight —IVF-OD FET vs IVF-AO FET	113 more per 1000 (51 more to 175 more)	3.08 (1.66, 5.73)	3	9514	⊕⊕○○ Low

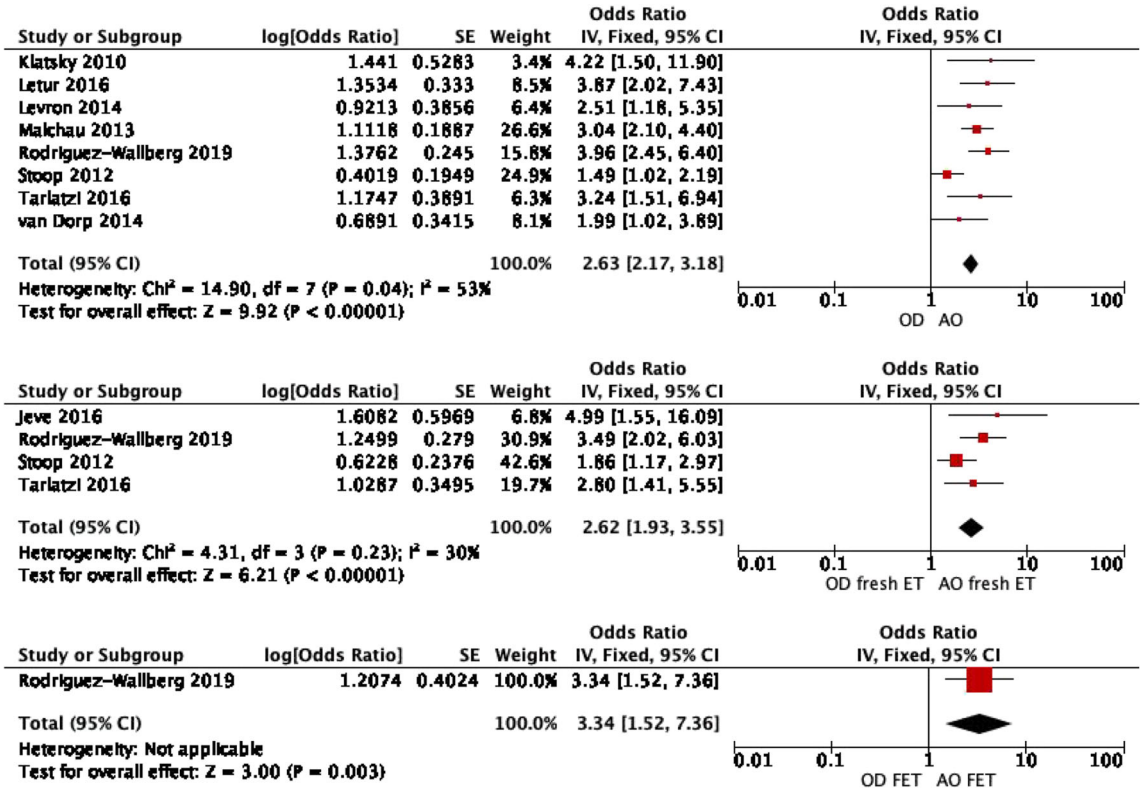

Fig. 2 Forest plots comparing hypertensive disorder in pregnancy after **a** IVF-OD vs IVF-AO, **b** IVF-OD fresh ET vs IVF-AO fresh ET, and **c** IVF-OD FET vs IVF-AO FET

compared to IVF-AO (OR = 1.64; 95% CI 1.26–2.13; I2 = 41%; moderate quality of evidence; Fig. 5b). The risk of PIH was also higher in pregnancies resulting from IVF-OD after FET than from IVF-AO after FET (two studies; $n = 1564$ patients; OR = 2.22; 95% CI 1.43–3.46; I2 = 0%; moderate quality of evidence; Fig. 5c).

Preterm birth

Sixteen studies reported PTB including 267,614 patients, 46,671 in the IVF-OD group, and 301,381 patients in the IVF-AO group. The overall OR for preterm birth was 1.57 (95% CI 1.33–1.86; I2 = 88%; Fig. 6a). The quality of evidence was low according to GRADE (Table 3).

A subgroup analysis concerning the fresh ET patients (11 studies; $n = 229,377$ patients) indicated that IVF-OD increased PTB with an OR of 1.44 (95% CI 1.20–1.74; I2 = 95%; low quality of evidence; Fig. 6b). IVF-OD was also associated with an increased PTB compared with IVF-AO when FET (five studies; $n = 37,935$ patients) was performed. (OR = 1.96; 95% CI 1.38–2.78; I2 = 73%; low quality of evidence; Fig. 6c). We also performed sub-analysis considering those pregnancies that did not develop preeclampsia as this could have been the preceding cause for intervention and PTB. Two studies adjusted for preeclampsia and the analysis revealed no significant difference between IVF-OD and IVF-AO groups considering PTB (aOR = 1.34; 95% CI 0.99–1.81; I2 = 0%; low quality of evidence; Fig. 6d).

Early preterm birth

Six studies reported early PTB including 153,533 patients, 12,800 in the IVF-OD group, and 147,718 patients in the IVF-AO group. The overall OR for early PTB was 1.80 (95% CI 1.51–2.15; I2 = 12%; Fig. 7a). The quality of evidence was low according to GRADE (Table 3).

An increase in early PTB in IVF-OD group was observed for patients after fresh ET (five studies; $n = 134,460$ patients) compared to IVF-AO (OR = 1.68; 95% CI 1.10–2.59; I2 = 77%; low quality of evidence; Fig. 7b). The risk of early PTB was also higher in pregnancies resulting from IVF-OD after FET than from IVF-AO after FET (three studies; $n = 9514$ patients; OR = 2.93; 95% CI 1.65–5.20; I2 = 0%; low quality of evidence; Fig. 7c).

Low birth weight

Twelve studies were included in the analysis. Overall, they evaluated 257,928 deliveries (55,852 after IVF-OD and 286,150 after IVF-AO). The OR was of 1.25 (95%CI 1.20–1.30; I2 = 0%) when comparing pregnancies after IVF-OD to IVF-AO. The quality of evidence was low according to

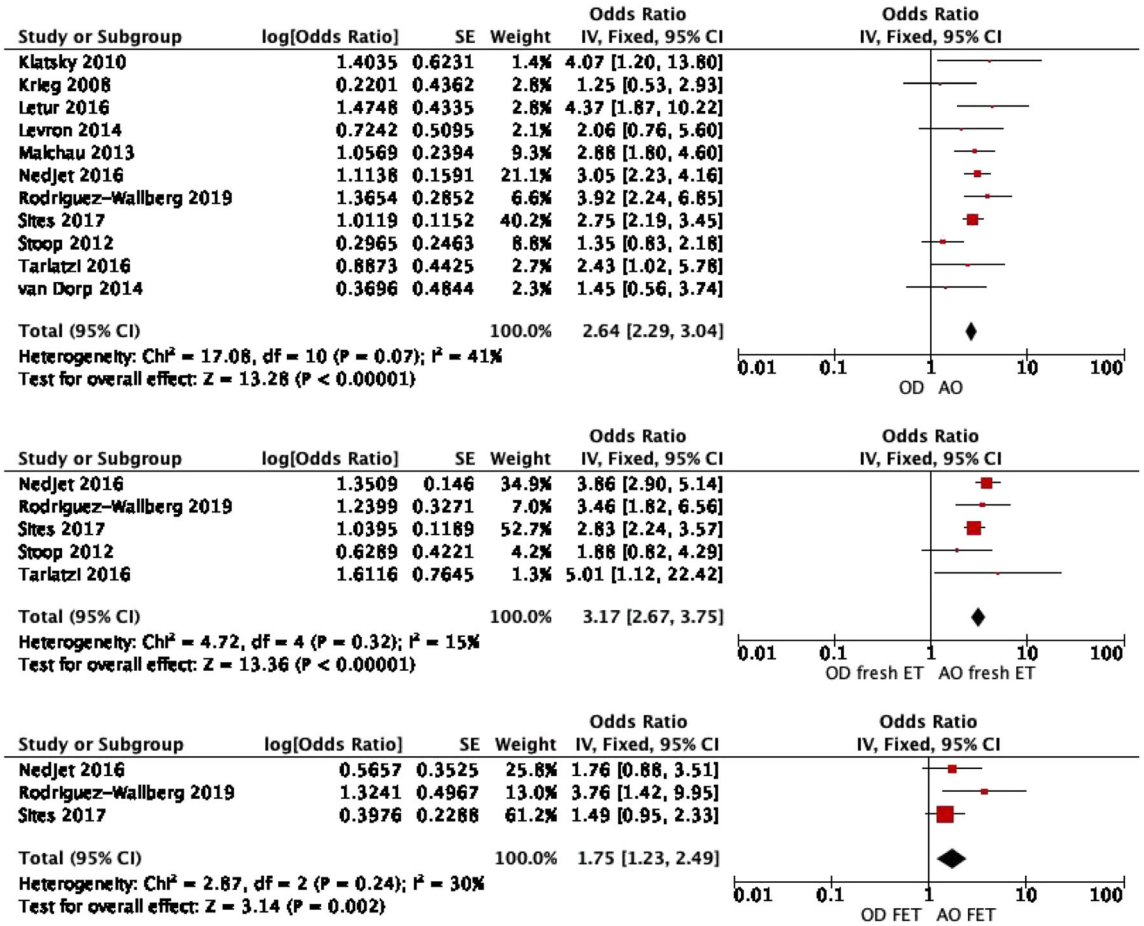

Fig. 3 Forest plots comparing preeclampsia in pregnancy after **a** IVF-OD vs IVF-AO, **b** IVF-OD fresh ET vs IVF-AO fresh ET, and **c** IVF-OD FET vs IVF-AO FET

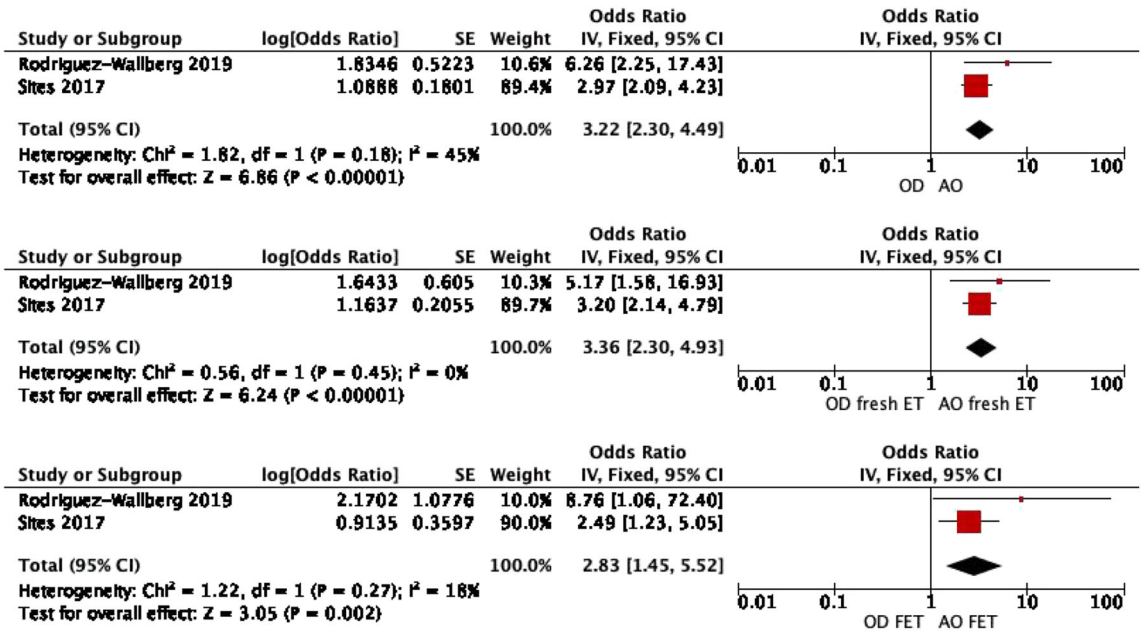

Fig. 4 Forest plots comparing severe preeclampsia after **a** IVF-OD vs IVF-AO, **b** IVF-OD fresh ET vs IVF-AO fresh ET, and **c** IVF-OD FET vs IVF-AO FET

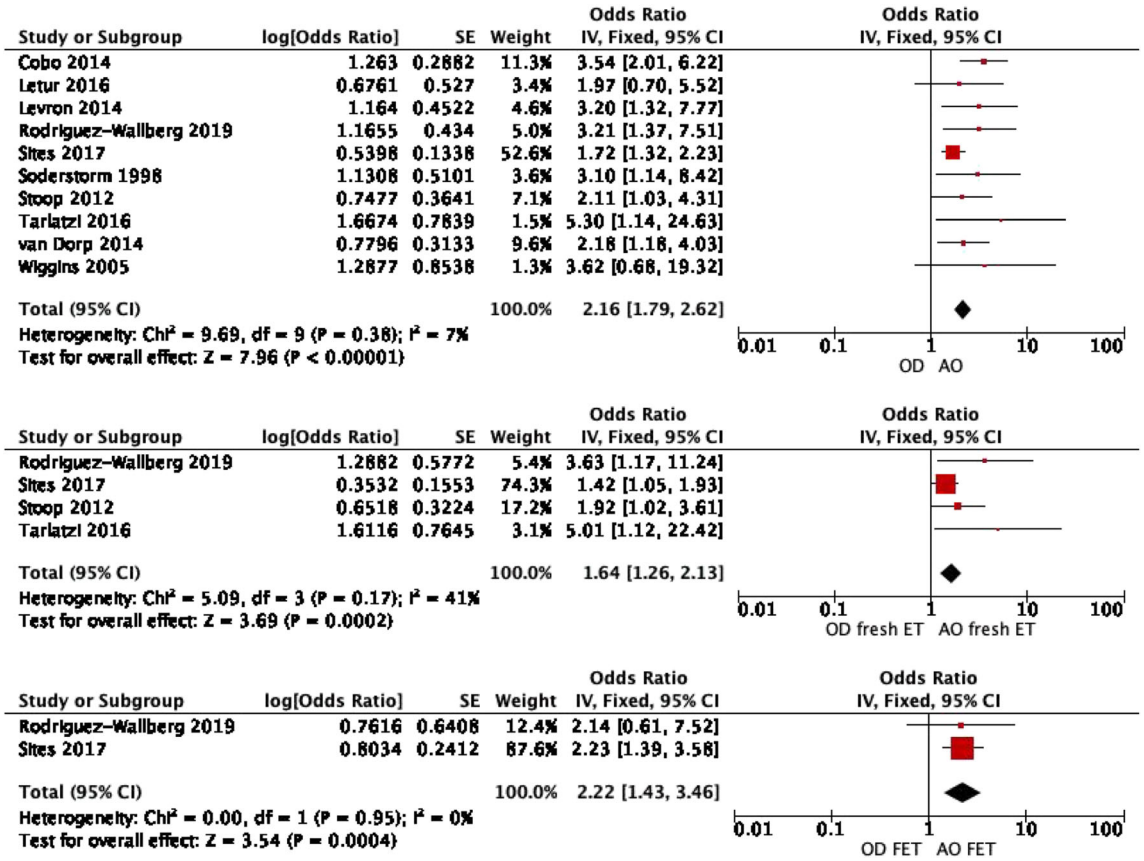

Fig. 5 Forest-plots comparing pregnancy induced hypertension after **a** IVF-OD vs IVF-AO, **b** IVF-OD fresh ET vs IVF-AO fresh ET, and **c** IVF-OD FET vs IVF-AO FET

GRADE (Fig. 8a). IVF-OD after fresh ET was associated with an increased risk of LBW (ten studies; $n = 220{,}645$ patients) compared with IVF-AO after fresh ET (OR = 1.25; 95% CI 1.13–1.38; I2 = 79%; low quality of evidence; Fig. 8b). An increase in LBW was also observed for patients IVF-OD after FET (four studies; $n = 36{,}614$ patients) compared to IVF-AO after FET (OR = 1.83; 95% CI 1.45–2.30; I2 = 0%; low quality of evidence; Fig. 8c).

We also performed sub-analysis considering those pregnancies that did not develop preeclampsia as this could have been the preceding cause for intervention and LBW. Two studies adjusted for preeclampsia and the analysis revealed no significant difference between IVF-OD and IVF-AO groups considering LBW (aOR = 1.21; 95% CI 0.84–1.75; I2 = 0%; low quality of evidence; Fig. 8d).

Very low birth weight

Seven studies reported VLBW including 200,773 patients, 22,831 in the IVF-OD group, and 181,510 patients in the IVF-AO group. The overall OR for VLBW was 1.37 (95% CI 1.22–1.54; I2 = 44%; Fig. 9a). The quality of evidence was low according to GRADE (Table 3).

A subgroup analysis concerning the fresh ET patients (seven studies; $n = 194{,}089$ patients) indicated that IVF-OD increased VLBW with an OR of 1.36 (95% CI 1.23–1.52; I2 = 23%; low quality of evidence; Fig. 9b). IVF-OD was also associated with an increased VLBW compared with IVF-AO when FET (three studies; $n = 9514$ patients) was performed. (OR = 3.08; 95% CI 1.66–5.73; I2 = 0%; low quality of evidence; Fig. 9c).

Secondary outcomes

Small for gestational age

Five studies, including 120,100 patients, provided information on SGA. IVF-OD was associated with a diminished risk of SGA compared with IVF-AO (OR = 0.83; 95% CI 0.78–0.89; I2 = 28%; low quality of evidence; Supplementary Fig. S1a). The subgroup analysis in patients with fresh ET (three studies; $n = 32{,}606$ patients) revealed no significant differences between the groups as regards SGA (OR = 1.19; 95% CI 0.64–2.25; I2 = 84%; low quality of evidence; Supplementary Fig. S1b). However, after FET, there was an increased risk of SGA in pregnancies resulting from IVF-OD compared to IVF-AO (four studies; $n = 36{,}614$ patients; OR =

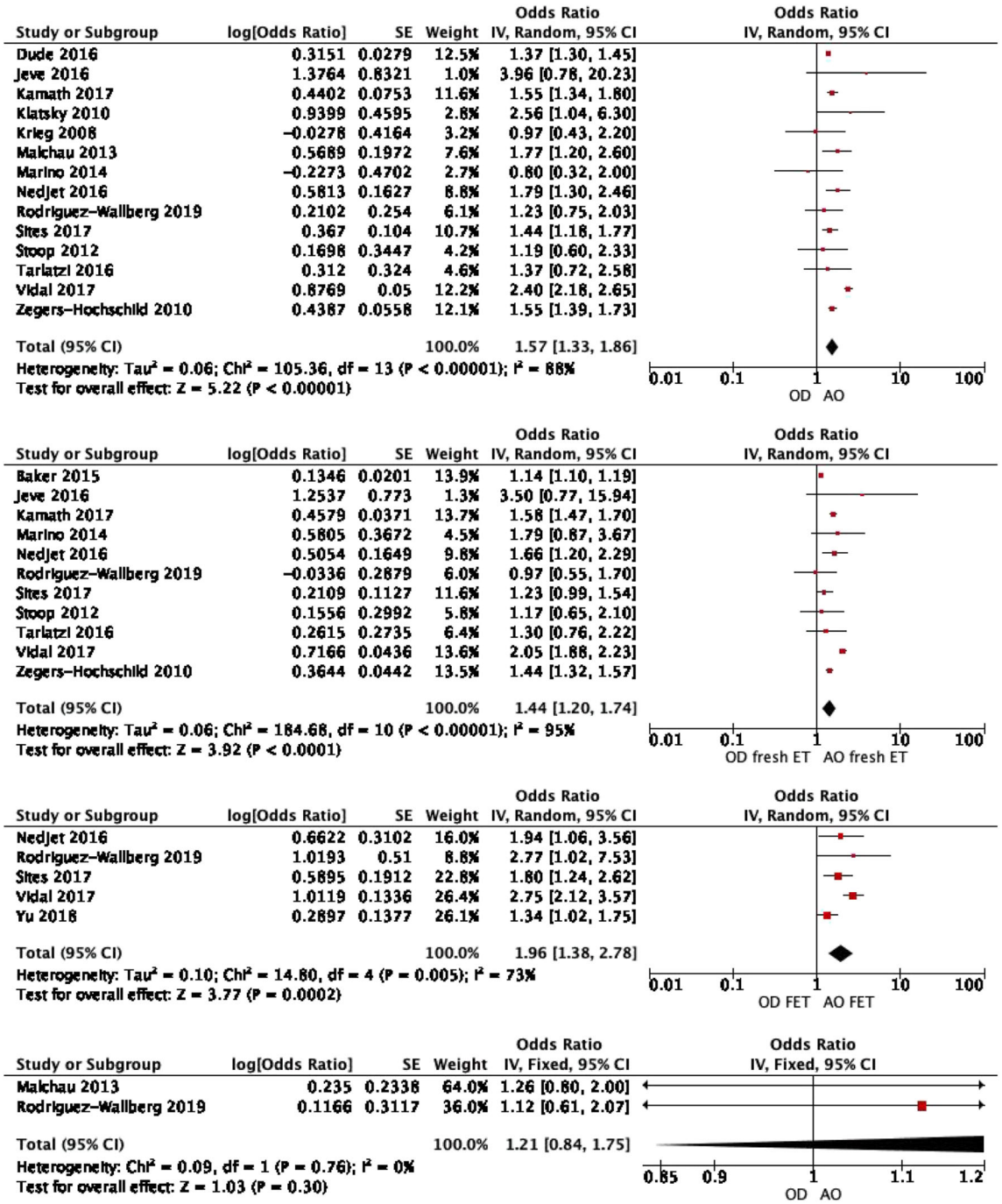

Fig. 6 Forest-plots comparing preterm birth after **a** IVF-OD vs IVF-AO, **b** IVF-OD fresh ET vs IVF-AO fresh ET, **c** IVF-OD FET vs IVF-AO FET, and **d** IVF-OD vs IVF-AO adjusted for preeclampsia

1.61; 95% CI 1.21–2.15; I2 = 0%; low quality of evidence; Supplementary Fig. S1c).

Large for gestational age

Three studies, which included 30,262 patients, provided data on LGA (Table 4). No differences were observed between the IVF-OD group and the IVF-AO group (OR = 0.89; 95% CI 0.57–1.40; I2 = 28%; low quality of evidence; Supplementary Fig. S2a). Neither were differences noted between the FET groups and between the fresh ET groups (low quality of evidence; Supplementary Fig. S2b, S2c).

Cesarean section

An increase in cesarean section in IVF-OD group was observed (seven studies; $n = 54{,}044$ patients) compared to IVF-AO (OR = 2.28; 95% CI 2.14–2.42; I2 = 23%;

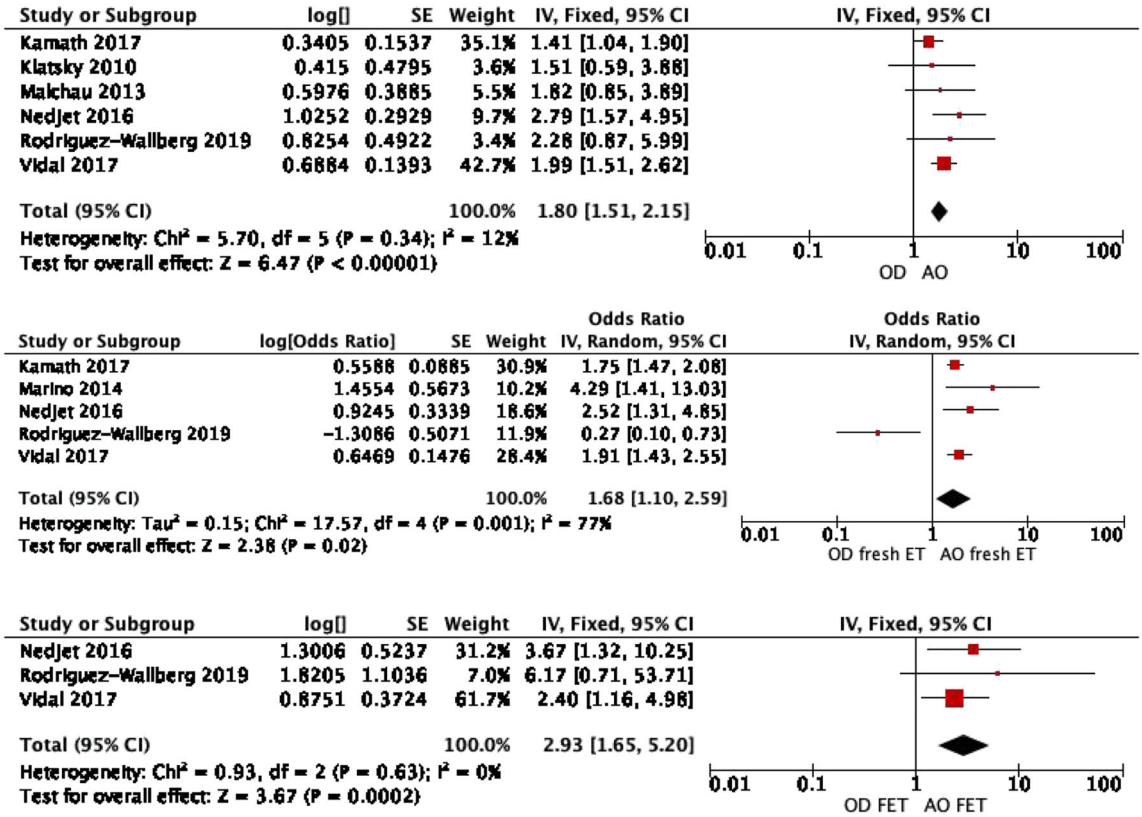

Fig. 7 Forest-plots comparing early preterm birth after **a** IVF-OD vs IVF-AO, **b** IVF-OD fresh ET vs IVF-AO fresh ET, and **c** IVF-OD FET vs IVF-AO FET

low quality of evidence; Supplementary Fig. S3a). The risk of cesarean section was also increased in pregnancies resulting from IVF-OD after fresh ET (three studies; n = 9514 patients; OR = 1.62; 95% CI: 1.39–1.89; I2 = 76%; low quality of evidence; Supplementary Fig. S3b) and IVF-OD after FET five studies; n = 32,743 patients; OR = 1.76; 95% CI 1.54–2.01; I2 = 0%; low quality of evidence; Supplementary Fig. S3c).

Gestational diabetes

Seven studies, including 38,289 patients, provided information on gestational diabetes. IVF-OD was associated with an increased risk of gestational diabetes compared with IVF-AO (OR = 1.27; 95% CI 1.03–1.56; I2 = 0%; low quality of evidence; Supplementary Fig. S4a). After fresh ET, there was an increased risk of gestational diabetes in pregnancies resulting from IVF-OD compared to IVF-AO (five studies; n = 29,499 patients; OR = 1.28; 95% CI 1.01–1.61; I2 = 0%; low quality of evidence; Supplementary Fig. S4b). However, the subgroup analysis in patients with FET (three studies; n = 8358 patients) revealed no significant differences between the groups (OR = 1.12; 95% CI 0.72–1.76; I2 = 0%; low quality of evidence; Supplementary Fig. S4c).

Premature rupture of membranes

Three studies, which included 28,152 patients, provided data on PROM (Table 4). No differences were observed between the IVF-OD group and the IVF-AO group (OR = 1.29; 95% CI 0.85–1.96; I2 = 19%; low quality of evidence; Supplementary Fig. S5a). Neither were differences noted between the FET groups and between the fresh ET groups (low quality of evidence; Supplementary Fig. S7b, S7c).

Placenta previa

Four studies, which included 28,405 patients, provided data on placenta previa (Table 4). No differences were observed between the IVF-OD group and the IVF-AO group (OR = 0.63; 95% CI 0.33–1.20; I2 = 0%; low quality of evidence; Supplementary Fig. S6a). Neither were differences noted between the FET groups and between the fresh ET groups (low quality of evidence; Supplementary Fig. S6b, S6c).

Placental abruption

Four studies, which included 28,405 patients, provided data on placental abruption (Table 4). No differences were observed between the IVF-OD group and the IVF-AO group

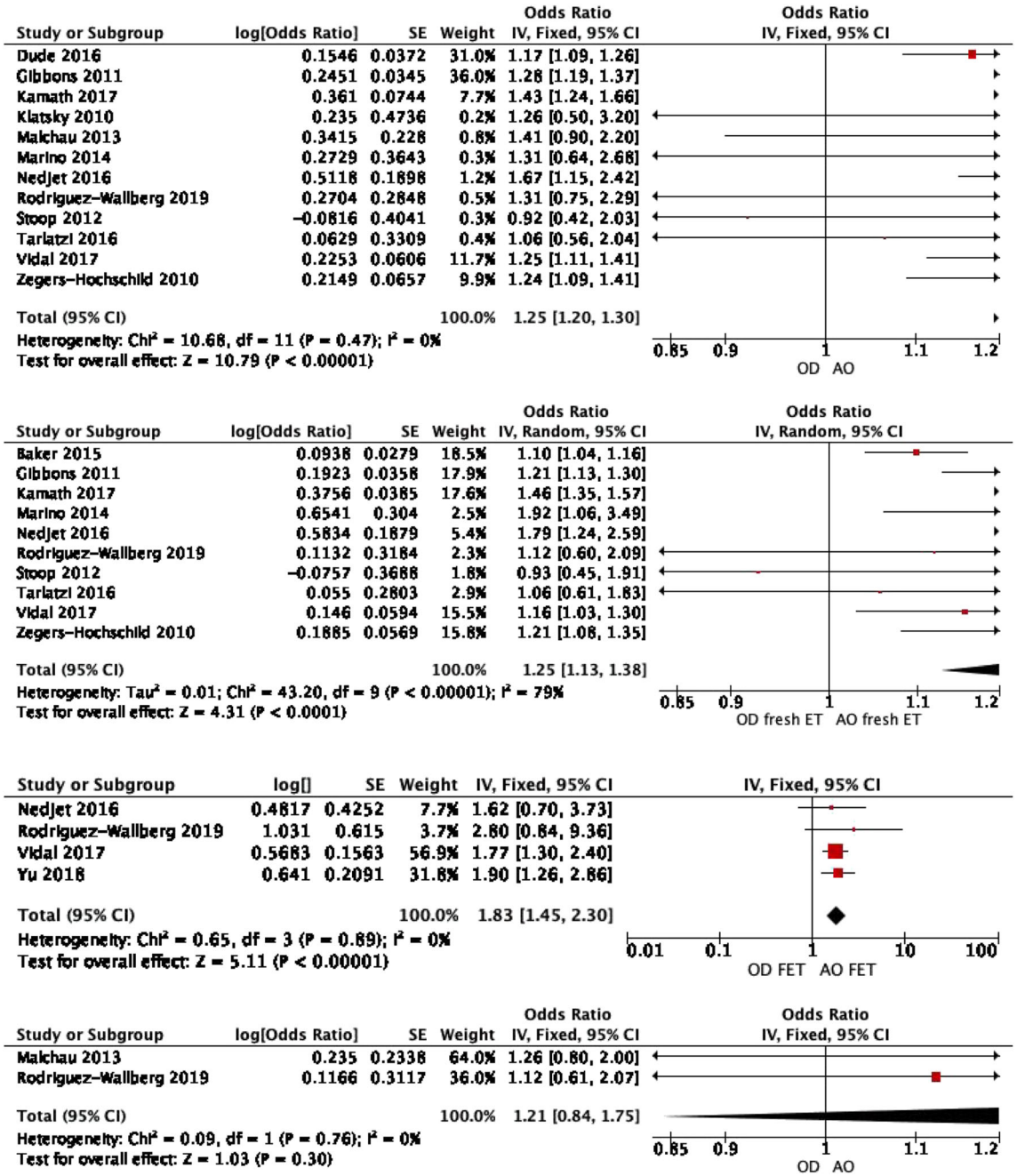

Fig. 8 Forest-plots comparing low birth weight after **a** IVF-OD vs IVF-AO, **b** IVF-OD fresh ET vs IVF-AO fresh ET, **c** IVF-OD FET vs IVF-AO FET, and **d** IVF-OD vs IVF-AO adjusted for preeclampsia

(OR = 1.15; 95% CI 0.52–2.53; I2 = 0%; low quality of evidence; Supplementary Fig. S7a). Neither were differences noted between the FET groups and between the fresh ET groups (low quality of evidence; Supplementary Fig. S7b, S7c).

Postpartum hemorrhage

Three studies, including 28,111 patients, provided information on PPH. IVF-OD was associated with an increased risk of PPH compared with IVF-AO (OR = 1.96; 95% CI 1.20–3.20; I2 = 73%; low quality of evidence; Supplementary Fig. S8a). The subgroup analysis in patients with fresh ET (two studies; $n = 20{,}821$ patients) revealed no significant differences between the groups as regards PPH (OR = 1.90; 95% CI 0.77–472; I2 = 90%; low quality of evidence; Supplementary Fig. S8b). However, after FET, there was an increased risk of PPH in pregnancies resulting from IVF-OD compared to IVF-AO (two studies; $n = 7037$ patients; OR = 1.76; 95% CI 1.33–2.34; I2 = 37%; low quality of evidence; Supplementary Fig. S8c).

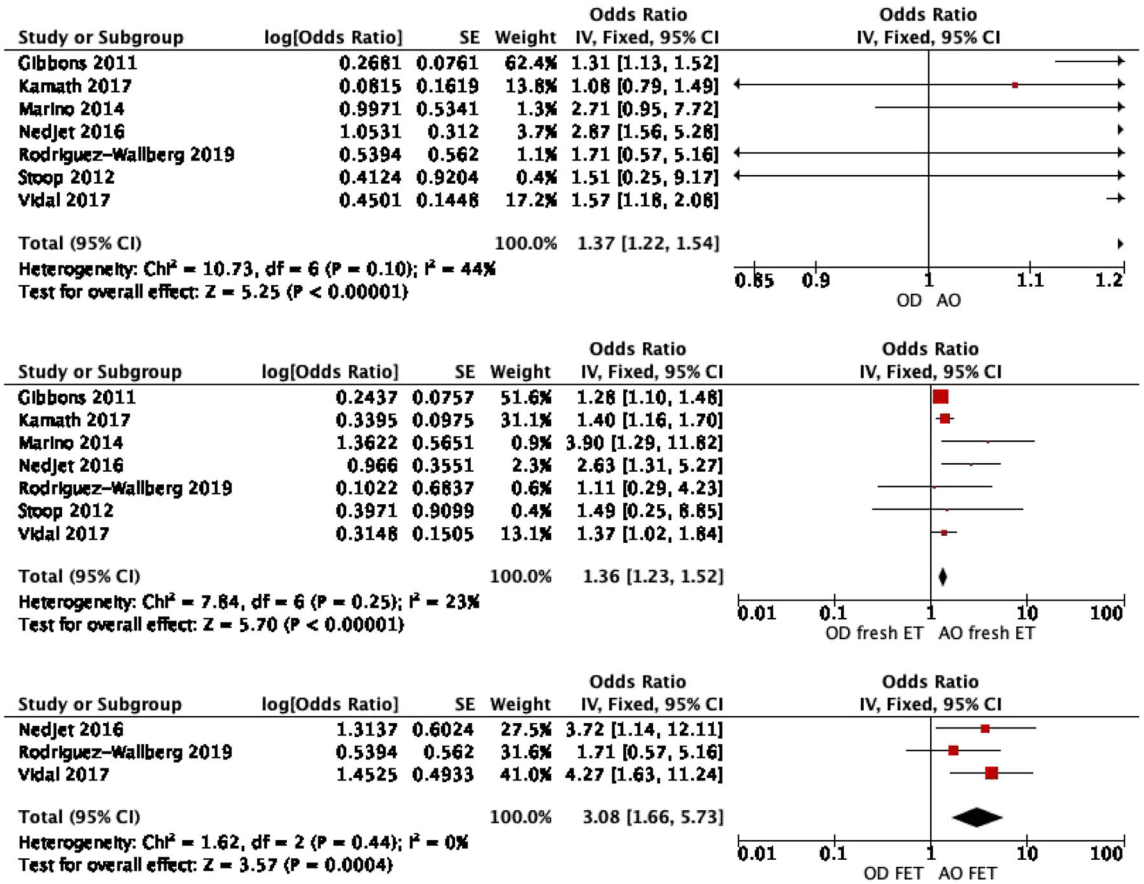

Fig. 9 Forest-plots comparing very low birth weight after **a** IVF-OD vs IVF-AO, **b** IVF-OD fresh ET vs IVF-AO fresh ET, and **c** IVF-OD FET vs IVF-AO FET

Discussion

Main results

This systematic review includes 58,597 pregnancies obtained by IVF-OD and 351,766 by IVF-AO. Pregnancies obtained by IVF-OD are associated with adverse perinatal results that range in magnitude. A higher risk of hypertensive disorders in pregnancy is seen in all of its manifestations (pregnancy-induced hypertension (PIH), preeclampsia, and severe preeclampsia), in addition to PTB, early PTB, LBW, and VLBW, in comparison to pregnancies obtained by IVF-AO. For all these outcomes, the differences remain similar when analyzing patients who underwent IVF-OD with fresh ET and FET separately. However, when adjusting for preeclampsia, no differences were observed in terms of PTB and LBW.

In the IVF-OD group were also observed a higher risk in terms of gestational diabetes, cesarean section, and postpartum hemorrhage. On the other hand, no differences were found when evaluating the risk of SGA, LGA, placenta previa, placental abruption, and PROM.

Strengths

Many of the previous reviews include multiple birth results, without separating these from single birth results, although it is known that the former are associated with a higher mortality rate. This review excludes all studies that reported results without differentiating multiple and single pregnancies. Additionally, some previous reviews [17, 18, 33], while arguing that the use of frozen embryo transfer is associated with a higher birth weight, LGA (large for gestational age), and cesarean section rate, suggest isolating this factor in order evaluate results without its influence.

The number of single births included in the current systematic review was much higher in comparison to previous reviews, as it includes the results of recent studies with a high number of patients not included in previous systematic reviews [19, 30, 50].

The studies included have used appropriate study designs that matched for potential confounders such as maternal age. In cases where this was not possible, the effect of these confounding variables was accounted for with the use of adjusted OR analysis.

Table 4 Summary of findings table for the secondary outcomes and sub-analysis comparing IVF-OD with IVF-AO in fresh and frozen ET

Outcome	Absolute effect risk difference per 1000 FET versus fresh ET (95%CI)	Odds ratio (95%CI)	Number of studies	Participants	Quality of evidence (grade)
Secondary outcomes					
Small for gestational age—overall IVF-OD vs IVF-AO	18 fewer per 1000 (25 fewer to 11 fewer)	0.83 (0.76, 0.89)	8	120,100	⊕⊕○○ Low
Small for gestational age—IVF-OD fresh ET vs IVF-AO fresh ET	18 more per 1000 (45 fewer to 81 more)	1.19 (0.64, 2.25)	3	32,606	⊕⊕○○ Low
Small for gestational age—IVF-OD FET vs IVF-AO FET	48 more per 1000 (19 more to 77 more)	1.61 (1.21, 2.15)	4	36,614	⊕⊕○○ Low
Large for gestational age—overall	29 fewer per 1000 (162 fewer to 103 more)	0.89 (0.57, 1.40)	3	30,262	⊕⊕○○ Low
Large for gestational age—IVF-OD fresh ET vs IVF-AO fresh ET	52 more per 1000 (9 more to 95 more)	0.75 (0.20, 2.81)	2	20,821	⊕⊕○○ Low
Large for gestational age—IVF-OD FET vs IVF-AO FET	12 more per 1000 (56 fewer to 81 more)	1.13 (0.57, 2.25)	2	7037	⊕⊕○○ Low
Cesarean section—overall	82 more per 1000 (76 more to 88 more)	2.28 (2.14, 2.42)	7	54,044	⊕⊕○○ Low
Cesarean section—IVF-OD fresh ET vs IVF-AO fresh ET	48 more per 1000 (33 more to 63 more)	1.62 (1.39, 1.89)	5	32,743	⊕⊕○○ Low
Cesarean section—IVF-OD FET vs IVF-AO FET	57 more per 1000 (43 more to 70 more)	1.76 (1.54, 2.01)	3	9514	⊕⊕○○ Low
Gestational diabetes—Overall	24 more per 1000 (2 more to 45 more)	1.27 (1.03, 1.56)	7	38,289	⊕⊕○○ Low
Gestational diabetes—IVF-OD fresh ET vs IVF-AO fresh ET	24 more per 1000 (1 more to 47 more)	1.28 (1.01, 1.61)	5	29,499	⊕⊕○○ Low
Gestational diabetes—IVF-OD FET vs IVF-AO FET	12 more per 1000 (33 fewer to 57 more)	1.12 (0.72, 1.76)	3	8358	⊕⊕○○ Low
PROM—overall	26 more per 1000 (16 fewer to 67 more)	1.29 (0.85, 1.96)	3	28,152	⊕⊕○○ Low
PROM—IVF-OD fresh ET vs IVF-AO fresh ET	7 more per 1000 (42 fewer to 56 more)	1.07 (0.66, 1.75)	3	21,115	⊕⊕○○ Low
PROM—IVF-OD FET vs IVF-AO FET	38 more per 1000 (17 fewer to 94 more)	1.47 (0.84, 2.56)	2	7037	⊕⊕○○ Low
Placenta previa—overall	46 fewer per 1000 (110 fewer to 18 more)	0.63 (0.33, 1.20)	4	28,405	⊕⊕○○ Low
Placenta previa—IVF-OD fresh ET vs IVF-AO fresh ET	64 fewer per 1000 (144 fewer to 16 more)	0.53 (0.24, 1.17)	3	21,115	⊕⊕○○ Low
Placenta previa—IVF-OD FET vs IVF-AO FET	14 fewer per 1000 (184 fewer to 157 more)	0.87 (0.16, 4.79)	2	7037	⊕⊕○○ Low
Placental abruption—overall	14 more per 1000 (65 fewer to 93 more)	1.15 (0.52, 2.53)	4	28,405	⊕⊕○○ Low
Placental abruption—IVF-OD fresh ET vs IVF-AO fresh ET	44 fewer per 1000 (145 fewer to 58 more)	0.65 (0.23, 1.78)	2	20,821	⊕⊕○○ Low
Placental abruption—IVF-OD FET vs IVF-AO FET	36 more per 1000 (83 fewer to 155 more)	1.43 (0.43, 4.71)	2	7037	⊕⊕○○ Low
Postpartum hemorrhage—overall	67 more per 1000 (18 more to 116 more)	1.96 (1.20, 3.20)	3	28,111	⊕⊕○○ Low
Postpartum hemorrhage—IVF-OD fresh ET vs IVF-AO fresh ET	64 more per 1000 (26 fewer to 155 more)	1.90 (0.77, 4.72)	2	20,821	⊕⊕○○ Low
Postpartum hemorrhage—IVF-OD FET vs IVF-AO FET	57 more per 1000 (28 more to 85 more)	1.76 (1.33, 2.34)	2	7037	⊕⊕○○ Low

Previous reviews only included retrospective cohort studies, while our review includes a recently published prospective cohort study [30]. These factors significantly increase the validity of our findings.

Moreover, the meta-analysis showed acceptable values through low *I2* values and narrow confidence levels for primary results such as preeclampsia and severe preeclampsia. This suggests that the precision of the meta-analysis is of good quality and that the estimated value is relatively stable. The low statistical heterogeneity observed in some of the variables is one of the main strengths of our meta-analysis.

Limitations

No comparison could be made by adjusting for age during this meta-analysis. However, the studies included in the review have adjusted important confounding variables such as this one. IVF-OD recipients are also highly heterogeneous in terms of prior medical conditions and the cause for infertility. This last variable was unfortunately not adjusted in most of the studies included. Extensive cohort studies with more specific data on OD recipients are required. Oocyte donors also represent a heterogeneous group, which includes healthy young women who donate eggs for altruistic or financial reasons, and the exchange of eggs, where women with different infertility diagnoses donate excess oocytes from their IVF treatment. It is unknown if this factor affects obstetric and neonatal outcomes.

It was not possible to distinguish between the FET protocols used in the analysis. This is important as recent data suggest that adverse perinatal outcomes, e.g., preeclampsia is more common in programmed/artificial FET cycles in the absence of a corpus luteum.

Comparison to other studies

Our review is consistent with the latest reviews published regarding a higher risk of hypertensive disorders in pregnancy, preeclampsia, and severe preeclampsia by IVF-OD patients.

One systematic review [23] reported hypertensive disorders in pregnancy rate of 13.0 to 39.3% in singleton pregnancies after IVF-OD and 1.9 to 23.3% after IVF-AO in comparison to the studies included in our review, which reported a rate of 18 to 33% for IVF-OD and 7 to 14.9% for autologous IVF. That and other reviews found similar results to ours, reporting a higher risk of hypertensive disorders in pregnancy for the IVF-OD group, with OR of 2.30 (CI 95% 1.60–3.32) [23] and OR 3.92 (CI 95% 3.21–4.78) [55].With respect to preeclampsia, in addition to the two studies mentioned above, there are some recent reviews that exclusively study this outcome [24, 25, 40]; however, one of these included multiple pregnancies [25]. In all of these studies, a significantly higher risk of preeclampsia was found in the IVF-OD group with OR 2.11 (CI 95%, 1.42–3.15) [23], OR 2.90 (CI 95% 1.98–4.24) [55], OR 3.12 (CI 95% 2.56–3.85) [25], OR 3.12 (CI 95% 2.56–3.85) [24], and RR 2.62 (CI 95% 2.13–3.21) [56]. Our study found a similar OR, including a larger sample size and obtaining an acceptable heterogeneity of the studies.

There are confounding variables such as multiple pregnancy and advanced maternal age found in most of the studies reviewed. Upon performing a meta-regression, one review found that neither of these two variables contributes to the effect that IVF-OD has on the appearance of preeclampsia [25].

Only one systematic review analyzed the risk of PIH, reporting a higher risk for the IFV-OD group, with OR 3.08 (IC 95% 2.26–4.19). This difference is slightly greater than in our study [55].

We found no other reviews analyzing the risk of severe preeclampsia.

In previous reports, it is concluded that maternal age may be a strong confounder when evaluating the perinatal risks in IVF-OD pregnancies. One study [57] investigated the risk of adverse obstetric outcomes according to different age groups of recipients in IVF-OD. Irrespective of age, IVF-OD patients had higher rates of HDP when compared to the IVF-AO group, showing that advanced maternal age alone, as a factor, cannot account for this difference, as the youngest IVF-OD patients had the highest rate of HDP. A later review concluded that the increased risk of HDP in IVF-OD patients was independent of maternal age and multiple gestations [58]. Two additional meta-analyses had concluded that the increased risk of HDP in IVF-OD pregnancies was independent of maternal age and multiple gestations [23, 59]. These results show that IVF-OD seems to be independently associated with higher rate of HDP and preeclampsia, also in recipient young women, even within IVF-OD programs with a strict single embryo transfer policy.

During the last decade, different observational studies and subsequent systematic reviews have agreed that IVF-OD patients have a significantly higher risk of PTB and LBW than IVF-AO.

A systematic review with meta-analysis compared obstetric and neonatal results in IVF-OD pregnancies, reporting single and multiple births separately [23]. They found that the risks of PTB (OR 1.75, CI 95% 1.39–2.20) and LBW (OR 1.53, CI 95% 1.16–2.01) significantly increased in IVF-OD pregnancies versus IVF-AO. Another systematic review with meta-analysis found a higher risk of PTB in IVF-OD versus IVF-AO (OR 1.34, CI of 95% 1.08 to 1.66), although it has a smaller sample size than our study [55]. Neither of these two reviews reported frozen and fresh embryo transfer data separately.

Given that some recent studies have indicated that children born by IVF with FET have a greater birth weight in comparison to IVF by fresh ET [16–18, 33], the combination of fresh and frozen ET cycles could affect the real estimate of perinatal results. A more recent systematic review with meta-analysis

only included IVF-OD studies, with a separate analysis according to fresh or frozen ET [60]. By excluding IVF pregnancies with frozen embryo transfer, they found significant differences in terms of PTB and LBW as in our study. Additionally, this review was the only one to study early PTB and VLBW subgroups with results similar to ours, discovering that IVF-OD patients have a higher risk of early PTB and VLBW in comparison to pregnancies by IVF-AO. That review has a smaller sample size than ours.

Only two observational studies have studied the possible relationship of preeclampsia and the increased risk of PTB and LBW in IVF-OD patients [21, 30]. Neither of them found significant differences in the risk of PTB or LBW, after adjusting for preeclampsia.

Several of the reports analyzed found no differences in terms of average birth weight corrected for gestational age in IVF-OD versus IVF-AO [21, 27, 39, 59, 61]. In terms of SGA, the results are inconsistent; one review showed differences (OR 1.81, 95% CI 1.26–2.60) [55] and another found no differences (OR 1.14, 95% CI 0.83–1.56) [23]. In our study, which as opposed to previous reviews excluded patients with frozen embryo transfer in the sub-analysis, there were no differences found between the groups for SGA.

A recent review concluded that there was no evidence of a higher risk of gestational diabetes in IVF-OD patients [23]; however, our review shows significant differences. This could be due to the fact that the meta-analysis includes different recent studies which increase the number of cases, although this result must be evaluated with caution, considering possible discrepancies in terms of the definition of this condition by the different studies included.

Our study is consistent with the other reviews regarding the risk for cesarean section [23]. Including new studies, the finding of a higher risk of cesarean section is maintained in IVF-OD patients in comparison to IVF-AO, with a high cesarean section rate for both groups (58.4% and 27.8%).

Interpretation of the results

During the current decade, many observational studies and subsequent systematic reviews have posited that the fact that IVF-AO patients with fresh embryo transfer have a higher risk of PTB, preeclampsia, and LBW in comparison to IVF-AO with frozen embryo transfer could be due in part to COS [16, 17, 19, 33]. Recent studies reported that supraphysiological levels of estradiol after COS in IVF-AO could have a negative effect on the endometrial receptivity and placentation [61–64], and others have suggested a higher risk of PB and LBW if more than 20 oocytes are recovered during IVF-AO [46, 57, 65].

IVF-OD recipients do not require COS; therefore, the concentrations of estradiol and progesterone in them are similar to IVF-AO patients with frozen embryo transfer; and also, more physiological in comparison to IVF-AO patients with fresh embryo transfer. Despite this, different systematic reviews have indicated that IVF-OD patients have a higher risk of hypertensive disorders in pregnancy, preeclampsia, and LBW in comparison to IVF-AO [23–25, 37, 40, 55, 56]. Therefore, COS could constitute confounding variable when comparing perinatal results between IVF-OD and IVF-AO patients with fresh embryo transfer, as IVF-OD patients are not exposed to this altered hormonal medium.

Regardless of the influence of estradiol on initial gestation, it can be seen that the appearance of hypertensive disorders in pregnancy, preeclampsia, and LBW is associated with placentation anomalies. Pregnancy success depends on adequate implantation and placentation, and any problem during this process could lead to changes in the production of vasculogenic and angiogenic factors, which are related to the appearance of hypertensive disorders in pregnancy and major placental syndromes [61, 66, 67]. The term "placental insufficiency" is used to describe the abnormal transport of uteroplacental nutrients, which leads to placental damage and known pregnancy complications such as preeclampsia and intrauterine fetal growth restriction. The severity of placental insufficiency could influence underlying physiopathologies common for many cases of PTB and preeclampsia [49, 61]. IVF-OD is significantly related to an alteration in placental markers, which is associated with a higher risk of anomalous placentation and placental insufficiency [68, 69].

In the majority of FET protocols, the pituitary-ovarian axis is suppressed by estradiol supplementation in the context of a programmed cycle, resulting in the absence of a corpus luteum, which is a major source of reproductive hormones. Although estradiol and progesterone are replaced during a programmed FET in the first trimester, other products of the corpus luteum are not administered. Unknown factors may be related to developing a future abnormal placental function, but there are some factors such as relaxin, whose role is very important for maternal cardiovascular adaptation to pregnancy. Deficient circulatory adaptations during early gestation have been seen in FET and are also linked to adverse pregnancy outcomes, including preeclampsia [70–72]. FET with natural cycle does not have hormonal substitution and allows the more physiological development of a corpus luteum. A current randomized trial where 75% of the FETs were performed in a natural, ovulatory cycle, found no increased risk of preeclampsia compared with those with fresh ET [73]. Another study reported that programmed FET cycles were associated with higher rates of preeclampsia (12.8% versus 3.9%; $P = 0.02$) and preeclampsia with severe features (9.6% versus 0.8%; $P = 0.002$) compared with modified natural FET cycles [70]. Further investigations are needed to compare the maternal and perinatal outcomes of stimulated cycles versus natural modified cycles in FET in order to clarify this matter.

Additionally, normal placentation requires the development of immune tolerance between the fetus and the mother.

It has been suggested that preeclampsia could be the result of an abnormal maternal immune response to new fetal antigens derived from paternity [45]. The higher risk of preeclampsia in IVF-OD pregnancies could be explained by an immunological mechanism, as the fetus is allogenic to the gestational carrier. Therefore, the mother must face a higher degree of antigenic dissimilarity in comparison to spontaneously conceived pregnancies [74–76]. It has been suggested that the increase in risk of preeclampsia in IVF-OD pregnancies is secondary to an immune rejection phenomenon in the placental-endometrial interface [45, 77]. One study on placental biopsies has found significant histological and immunohistological differences between the placenta in IVF-OD and IVF-AO pregnancies, specifically an increase in immunological activation, villitis, chronic deciduitis, ischemic changes, and fibrin deposition, which is similar to the graft versus host disease after solid organ transplant and further supports the immunological hypothesis of preeclampsia [59, 78].

Likewise, it has been suggested that an eventual incompatibility of the human leukocyte antigen (HLA) between oocyte donors and their recipients could promote an immunological imbalance between the mother and fetus, which would increase the risk of placental pathology.

The high rate of complications in OD pregnancies could be a consequence of a high level of HLA incompatibility. A lower prevalence of preeclampsia has been found in IVF-OD pregnancies when the donor was related to the recipient than when not [79]. Considering these immunological mechanisms, in the evaluation of IVF-OD pregnancies, it may be worth it to perform an HLA study of the donor and recipient in order to select haplo-identical combinations that would be more comparable to spontaneously conceived pregnancies [59, 79]. New studies that include uncomplicated IVF-OD pregnancies and pregnancies with preeclampsia are required to determine how the HLA compatibility affects perinatal results.

Preeclampsia and anomalous placentation have also been associated with the interaction between the maternal KIR AA genotype and the fetal HLA-C2. This combination inhibits uterine NK cells, which would lead to inadequate placentation [79]. It is speculated that in the future, the comparison of KIR and HLA-C variants before IVF-OD could be a useful measure for reducing hypertensive disorders [80].

Preterm birth is a syndrome with multiple factors, including infectious causes, iatrogenesis, and spontaneous preterm birth, and the influence that IVF-OD has over these is an interesting topic of research. In our study, there is a high rate of preeclampsia and severe preeclampsia, particularly in the IVF-OD group, and the relationship between severe preeclampsia and iatrogenic PTB is well known [49, 61]. Given this association, there is a question of whether the risk of PTB found in IVF-OD is due to an iatrogenic PTB or another cause. Recent studies support the hypothesis that placental insufficiency contributes to a large proportion of PTBs considered to be "spontaneous" [49, 61]. In our study after adjusting for preeclampsia, no differences between the groups were found in terms of PTB and LBW, supporting that the increased risk for these outcomes in the IVF-OD group may be a consequence of preeclampsia. Future studies that analyze the relationship between IVF-OD, PTB, LBW, and preeclampsia are needed.

Given that SGA is associated with hypertensive disorders in pregnancy, which increases two to three times in IVF-OD pregnancies, it would be expected that SGA rates would also be high, although results are inconsistent. In our study, the analysis shows no differences between the two groups for SGA, and a significant risk of hypertensive disorders in pregnancy and preeclampsia. The use of freezing techniques is associated with a higher birth weight according to recent reports [17, 18, 33], and that is a big difference between previous reviews and ours, as they have not excluded patients with fresh embryo transfers, which could explain these results.

One prospective observational study takes a clinical and histological look at IVF-OD and autologous IVF patients who developed PE, obtaining no cases of SGA in the IVF-OD group with preeclampsia, while nearly 30% of the children born by IVF-AO with preeclampsia were SGA ($P < 0.0001$). This study is limited by its small sample size but suggests that preeclampsia has a different physiopathology in IVF-AO and IVF-OD pregnancies. There are different microscopic findings between the placentas of IVF-OD and IVF-AO pregnancies that could support this theory [81].

Our results show that cesarean sections are performed over twice as often in IVF-OD in comparison to IVF-AO. It is possible that this higher frequency is due to the fact that the IVF-OD group is more vulnerable to pregnancy complications in relation to the results described in this study, particularly hypertensive disorders in pregnancy and preeclampsia.

It should also be noted that such a high cesarean section rate is also associated with other risks, mainly maternal risks such as postpartum hemorrhage, hysterectomy, cardiac arrest, venous thrombosis, and major infection [82].

Prevention

The findings in this study must not be used to discourage the use of IVF-OD, but rather to advise patients on the risks of the procedure.

They must receive pre-conception guidance on the increase of risks during pregnancy and that these risks are regardless of age or multiple pregnancies.

Many IVF-OD recipients are first-time mothers and over the age of 40, who also show pre-existing risk factors for the development of hypertensive disorders [83]. It is vitally important to perform a complete medical evaluation. Moreover, obstetricians must be aware of the increase in pregnancy risks in this particular group of patients and implement adequate monitoring strategies during prenatal, labor, and postnatal care [84].

High-quality reports conclude that the rate of preeclampsia is at least 10% lower when a daily dosage of 60 to 150 mg of aspirin is administered after the first trimester to women with a higher risk of developing this condition [81, 85]. Some guides recommend administering aspirin to women with a higher risk of preeclampsia; however, OD is not included among these [83]. IVF-OD carries nearly three times the risk of preeclampsia in comparison to spontaneous pregnancies, which is higher than other more well-known risk factors; therefore, prophylactic treatment with aspirin at low dosages should be an intervention to consider for future IVF-OD research.

The use of serial ultrasounds to diagnose SGA and fetal growth restriction may be a proper monitoring strategy for this group of patients. Further studies are necessary to demonstrate whether implementation of markers as the mean uterine artery pulsatility index (UtA-PI) and the automated measurement of the soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) ratio may improve the diagnosis and management of PE, especially in high-risk patients. The transfer of a single embryo during IVF-OD cycles should be encouraged in order to minimize the risk of multiple pregnancies, which are associated with a higher perinatal morbidity rate, including PTB and preeclampsia [86]. Oocyte cryopreservation has also been suggested as an alternative to avoid OD later, although data on the success rates and obstetric and perinatal results are limited [87, 88].

Conclusions

Based on current evidence, pregnancy in IVF-OD patients should be considered an independent risk factor for some adverse perinatal results, mainly hypertensive disorders in pregnancy, preeclampsia, severe preeclampsia, and pregnancy-induced hypertension, but also cesarean sections.

Given the increase in the number of pregnancies achieved by IVF-OD and the associated morbidity described in this study, it is highly important to understand the etiopathogenesis of these pathologies. Recent evidence associates the placenta and its inadequate function in IVF-OD patients with these results. The immunological aspects involved, such as HLA compatibility between the donor and recipient, are promising lines of research that could help prevent adverse perinatal results in the future.

Meanwhile, patients must be aware of the risks before undergoing IVF-OD, and pregnancy must be handled in high-risk obstetric centers with individualized monitoring and management strategies to reduce complications.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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