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Systematic Review

Fresh Versus Frozen Embryo for the Risk of Pre-Eclampsia: A Systematic Review and Meta-Analysis of Maternal and Neonatal Outcomes

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Abstract

Background: Assisted reproductive technology (ART) is an effective treatment for infertility. However, ART may also be associated with increased pregnancy risks compared with natural conception. Among patients undergoing *in vitro* fertilization and embryo transfer/intracytoplasmic sperm injection (IVF-ET/ICSI), the risks of pregnancy complications and neonatal outcomes may differ between fresh or frozen embryos. This study therefore aimed to investigate differences in pre-eclampsia (PE) and neonatal outcomes between patients who received fresh embryo transfer (fresh ET) and those who received frozen embryo transfer (frozen ET). **Methods:** We conducted a comprehensive and systematic search of electronic databases, including PubMed, Embase, the Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Medical Database, Chinese BioMedical Literature Database (CBM), and China Science and Technology Journal Database (VIP Database), for publications from January 1 2016, to June 30, 2025. This analysis included randomized controlled trials (RCTs) and cohort studies comparing the risk of PE and neonatal outcomes between fresh ET and frozen ET. Two investigators independently performed literature screening, data extraction, and quality assessment. Methodological quality was evaluated using the Cochrane RoB 2.0 tool for RCTs and the Newcastle-Ottawa Scale (NOS) for cohort studies. Statistical analysis was performed using RevMan 5.4 and Stata 16 software. Pooled odds ratios (OR) with 95% CIs were calculated, and heterogeneity was assessed using the I^2 statistic. Subgroup and sensitivity analyses were performed to investigate sources of heterogeneity. Funnel plots were constructed, and the Egger test assessed the likelihood of publication bias. **Results:** This meta-analysis included a total of 14 studies, comprising 3 RCTs and 11 retrospective cohort studies, encompassing 242,879 patients. Frozen ET was associated with significantly higher risks of PE (OR = 1.36, 95% CI: 1.21–1.53 $p < 0.00001$) and cesarean section (OR = 1.27, 95% CI: 1.00–1.60, $p = 0.05$) than fresh ET, but with significantly lower risks of placental abruption (OR = 0.57, 95% CI: 0.33–0.97, $p = 0.04$) and low birth weight (OR = 0.73, 95% CI: 0.65–0.83, $p < 0.00001$). No statistically significant differences in the incidence of preterm birth (OR = 0.92 95% CI: 0.80–1.06, $p = 0.26$) or stillbirth (OR = 0.47, 95% CI: 0.20–1.14, $p = 0.10$) were observed between the two groups. **Conclusions:** These findings indicate that frozen ET significantly increases the risk of PE. However, the long-term effects of frozen ET on overall pregnancy success and neonatal health require further investigation. In clinical practice, interventions tailored to each patient should be actively implemented to minimize the risk of PE. Clinicians should consider a comprehensive assessment of patient characteristics and potential risks when they develop ART protocols, ensuring optimal treatment outcomes. **Registration:** The study has been registered on https://www.crd.york.ac.uk/PROSPERO/ (registration number: CRD420251172725; registration link: https://www.crd.york.ac.uk/PROSPERO/view/CRD420251172725).

Keywords: fresh embryo transfer (fresh ET); frozen embryo transfer (frozen ET); pre-eclampsia (PE); assisted reproductive technology (ART); meta-analysis; preterm birth; low birth weight; stillbirth; cesarean delivery rate; placental abruption

1. Introduction

Increasing numbers of female patients now conceive through assisted reproductive technology (ART) due to infertility [1,2]. The decision to perform fresh or frozen embryo transfer (ET) during ART is personalized according to the patient's specific clinical profile, for example, people who have a high risk of ovarian hyperstimulation syndrome (OHSS) [3]. Fresh ET refers to the placement of embryos into the uterus 3–5 days after oocyte retrieval, without prior cryopreservation [4]. While this approach shortens the time to pregnancy and reduces treatment duration, it is associated with a higher risk of ovarian hyperstimulation syndrome [3]. In contrast, frozen ET involves the cryopreservation of embryos following *in vitro* fertilization

(IVF). Once optimal endometrial receptivity and hormonal conditions are achieved, the embryos are thawed for transfer in a later cycle [4]. This strategy significantly lowers the risk of OHSS and offers greater flexibility in scheduling, allowing for thorough endometrial preparation and physiological synchronization. [5]. Several studies have reported that frozen ET is associated with higher rates of pregnancy and live births compared to fresh ET [6,7,8]. Compared to fresh ET, frozen ET is associated with lower newborn weight, Cesarean delivery, and gestational hypertension [9,10,11,12,13].

Current research indicates that women who conceive throughIVF, intracytoplasmic sperm injection (ICSI), or egg donation cycles have a significantly higher risk of PE compared to women who conceive naturally or through intrauterine insemination [14]. During normal pregnancy, cells of the cytotrophoblast (CTB) differentiate into villous trophoblast and extravillous trophoblast (EVT). The EVT continues to differentiate into trophoblastic columns that connect the maternal and fetal tissues. At the distal end of these columns, the stromal trophoblast infiltrates the endometrial stroma up to one-third of the myometrium, while the intravascular extravillous trophoblast enters the lumen of the spiral arteries, causing arterial dilation and transforming them into low-resistance, high-capacity vessels. This ensures adequate blood and nutrient supply to the fetus, maintains normal maternal-fetal exchange, and supports fetal development [15]. PE is a multisystem disease involving multiple pathogenic pathways and mechanisms. The major pathogenic features include vascular endothelial damage, inadequate remodeling of uterine spiral arteries, and maternal immune hyperactivation [16]. The diagnosis of PE is based on new-onset hypertension after 20 weeks of gestation, combined with at least one of the following complications: proteinuria, thrombocytopenia, impaired hepatic or renal function, pulmonary edema, central nervous system abnormalities, or visual disturbances. PE is one of the most severe complications of pregnancy and a major cause of morbidity and mortality in pregnant women and during the perinatal period [16]. It affects an estimated 4 million women globally each year and is responsible for >70,000 maternal deaths and half a million fetal/infant deaths annually [16,17]. Women who previously had PE, as well as their delivered babies, are more likely to have long-term chronic illnesses [18]. Moreover, these women have reduced life expectancy and are predisposed to developing cardiovascular and cerebrovascular diseases, as well as diabetes. Their offspring have an increased risk of preterm birth, perinatal mortality, and neurodevelopmental delays, as well as long-term cardiometabolic diseases later in life [16,19].

The endometrial environment is modified prior to embryo transfer. However, when the endometrial environment is not well adjusted, the endometrial receptivity may be poor, which may lead to abnormal placental attachment. Disruption of this homeostasis can lead to various pregnancy disorders, such as fetal growth restriction and PE [20]. Although published meta-analyses have evaluated the impact of frozen ET on pregnancy outcomes, most were focused on live and preterm birth rates rather than PE risk [4]. Recent observational studies and randomized controlled trials (RCTs) have reported different results for pregnancy outcomes. Some studies suggested that frozen ET may reduce the occurrence of pregnancy-related complications such as PE by improving endometrial receptivity and lowering the risk of OHSS. Other studies have shown that frozen ET increases placenta-related complications. Insufficient luteal function during artificial cycles leads to impaired placental development and abnormal epigenetic regulation, thereby increasing the risk of PE [7,21,22,23]. The number of frozen ET cycles performed in Europe is steadily increasing, currently exceeding 190,000 cycles per year [24]. Frozen ET is widely used in ART to prevent OHSS and to increase pregnancy rates by optimizing the endometrium. However, the mechanisms by which it may cause PE are still unclear. By integrating data from the current literature, this study evaluated the association between frozen ET and PE.

2. Methods

This study is registered with PROSPERO (CRD420251172725) and follows PRISMA guidelines. We systematically searched the following databases: PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang Medical Database, CBM, and VIP Database. The search strategy employed was: ((“frozen embryo transfer” OR FET OR “vitrified embryo transfer”)AND (“fresh embryo transfer” OR “fresh ET”))AND (PE OR preeclampsia OR pre-eclampsia OR “gestational hypertension”)NOT (mice OR rat OR mouse OR rats). The search period was from January 1 2016, to June 30 2025. The literature screening was performed in two stages. First, titles and abstracts were reviewed to identify records eligible for full-text retrieval. Next, the selected full-text articles were evaluated against predetermined inclusion criteria. Two reviewers conducted both stages independently. Any disagreements were resolved by discussion with a third reviewer.

2.1 Criteria for Inclusion or Exclusion

This study enrolled patients who underwent Frozen ET or fresh ET during IVF-ET/ICSI. The outcome measures included neonatal outcomes (low birth weight, preterm birth rate, stillbirth rate) and maternal outcomes (PE incidence, mode of delivery, placental abruption). Exclusion criteria included (1) literature that could not extract statistical data (e.g., systematic reviews, conference abstracts); (2) studies that did not meet the study criteria (e.g., non-human experiments or lack of control groups); (3) reports with incomplete outcome data or statistical de-

Table 1. Characteristics of included studies.

Study	Duration of trial	Design	Outcomes
Zhang et al. (2018) [25]	2013 to 2015	RCT	PE, preterm birth
Chen et al. (2016) [8]	2013 to 2015	RCT	PE, preterm birth
Maheshwari et al. (2022) [26]	2016 to 2019	RCT	PE, preterm birth, low birth weight, cesarean section
Johnson et al. (2019) [27]	2000 to 2015	Retrospective cohort study	PE, preterm birth, placental abruption, cesarean section
Lei et al. (2019) [28]	2013 to 2015	Retrospective cohort study	PE, preterm birth, placental abruption
H Petersen et al. (2023) [29]	1994 to 2014	Retrospective cohort study	PE, cesarean section
Zargar et al. (2021) [30]	2019 to 2021	Retrospective cohort study	PE, preterm bith, stillbirth, low birth weight
Zhang et al. (2024) [31]	2018 to 2021	Retrospective cohort study	PE, preterm birth, placental abruption, low birth weight, cesarean section
Tarlatzi et al. (2021) [3]	1990 to 2013	Retrospective cohort study	PE, reterm birth, stillbirth, low birth weight
Collée et al. (2023) [32]	2020 to 2022	Retrospective cohort stuy	PE, preterm birth, stillbirth
Yu et al. (2024) [33]	2017 to 2021	Retrospective ohort study	PE, preterm birth, stillbirth, placental abruption
Niu et al. (2023) [34]	2012 to 2020	Retrospective cohort study	PE, preterm birth, low birth weight
Blazquez et al. (2018) [35]	2013 to 2016	Retrospective cohort study	PE, cesarean section
Epelboin et al. (2023) [22]	2013 to 2017	Retrospective cohort study	PE

RCT, randomized controlled trial; PE, pre-eclampsia.

fects; (4) literature lacking necessary records (e.g., incomplete sample information) or duplicate publications.

2.2 Data Extraction and Analysis

Data extraction was independently performed by two investigators. Any discrepancies were resolved through discussion or arbitration with a third investigator. Extracted data included authors, publication year, country, study design (e.g., RCT, cohort study), number of participants in the fresh ET group, and the frozen ET group. Outcome measures consisted of the primary outcome: PE; secondary outcomes: mode of delivery, incidence of placental abruption, low birth weight, preterm birth rate, and stillbirth rate. The characteristics of included studies are summarized in Tables 1 (Ref. [3,8,22,25,26,27,28,29,30,31,32,33,34,35]), 2 (Ref. [3,8,22,25,26,27,28,29,30,31,32,33,34,35]).

Data analysis was performed using Review Manager (RevMan version 5.4.1; The Cochrane Collaboration, Copenhagen, Denmark). Dichotomous variables are presented as OR with corresponding 95% CI. The I^2 statistic was employed to assess heterogeneity. According to the Cochrane Handbook for Systematic Reviews of Interventions, an I^2 value of 0 indicates no observed heterogeneity, I^2 values from 50–75% represent moderate heterogeneity, and I^2 values >75% indicate high heterogeneity. The fixed-effects model is preferred as the default, with the random-effects model adopted when I^2 >50%. To examine the robustness of the results, findings from a fixed-effect model are also provided as a sensitivity analysis. For the meta-analysis of a certain outcome that includes 10 or more studies, the publication bias was assessed by visually inspecting the symmetry of the funnel plot, supplemented with the Egger test.

2.3 Subgroup and Sensitivity Analyses

Subgroup analyses based on design stratification were conducted to assess heterogeneity and its impact on study outcomes. Due to the limited number of studies involving artificial cycle frozen ET and patients with polycystic ovary syndrome, no further subgroup analyses were performed to avoid misleading conclusions.

2.4 Quality Assessment

Quality assessment was independently conducted by two investigators. Discrepancies were resolved through discussion or arbitration by a third investigator. RCTs were evaluated using the Cochrane Risk of Bias Tool (RoB 2.0) across five domains, with the risk categorized as “Low”, “High”, or “Some Concerns” (Table 3, Ref. [8,25,26]). The overall “grade” is determined by a three-tier assessment of bias risk. This included (1) All five domains are rated “low risk”. (2) One or more domains are rated “some concern”, with no domain rated “high risk”. (3) Any domain is rated “high risk”; or when multiple domains are rated “some concern”, the overall assessment concludes that the reliability of the results is severely compromised. (Note: Although the latter scenario exists, standard practice typically deems a single “high-risk” domain sufficient for classification). The five bias domains included bias arising from the randomization process (3 core assessments), bias due to deviations from intended interventions (3 core assessments), bias due to missing outcome data (3 core assessments), bias in measurement of the outcome (2 core assessments), and bias in selection of the reported result (2 core assessments). Cohort studies were assessed with the Newcastle-Ottawa Scale (NOS). The NOS scoring system has distinct versions for cohort studies and case-control studies. Its evaluation encompasses three dimensions: subject selection (maximum 4 stars), comparability of groups (maximum 2 stars), and

Table 2. Enumerated totals of outcomes and events for studies of frozen ET and fresh ET.

Study (Year)	Outcome	Frozen ET (n/N)	Fresh ET (n/N)	Study-specific OR (95% confidence interval)
Zhang et al. (2018) [25]	PE	5/250	3/212	1.42 [0.34, 6.02]
	Placental abruption	NR	NR	
	Preterm birth	18/250	16/212	0.95 [0.47, 1.91]
	Low birth weight	NR	NR	
	Stillbirth	NR	NR	
	Cesarean section	NR	NR	
Chen et al. (2016) [8]	PE	19/434	6/427	3.21 [1.27, 8.12]
	Placental abruption	NR	NR	
	Preterm birth	81/434	68/427	1.21 [0.85, 1.73]
	Low birth weight	NR	NR	
	Stillbirth	NR	NR	
	Cesarean section	NR	NR	
Maheshwari et al.(2022) [26]	PE	5/307	1/309	5.10 [0.59, 43.90]
	Placental abruption	NR	NR	
	Preterm birth	9/307	12/309	0.75 [0.31, 1.80]
	Low birth weight	7/307	13/309	0.53 [0.21, 1.35]
	Stillbirth	NR	NR	
	Cesarean section	35/307	36/309	0.98 [0.60, 1.60]
Johnson et al. (2019) [27]	PE	27/271	153/1861	1.24 [0.80, 1.90]
	Placental abruption	8/271	61/1861	0.90 [0.42, 1.90]
	Preterm birth	72/271	594/1861	0.77 [0.58, 1.03]
	Low birth weight	NR	NR	
	Stillbirth	NR	NR	
	Cesarean section	164/271	1081/1861	1.11 [0.85, 1.43]
Lei et al. (2019) [28]	PE	29/673	72/1583	0.95 [0.61, 1.47]
	Placental abruption	3/673	26/1583	0.27 [0.08, 0.89]
	Preterm birth	275/673	597/1583	1.14 [0.95, 1.37]
	Low birth weight	NR	NR	
	Stillbirth	NR	NR	
	Cesarean section	NR	NR	
H Petersen et al. (2023) [29]	PE	991/18037	3371/78300	1.29 [1.20, 1.39]
	Placental abruption	NR	NR	
	Preterm birth	NR	NR	
	Low birth weight	NR	NR	
	Stillbirth	NR	NR	
	Cesarean section	5133/18037	19910/78300	1.17 [1.13, 1.21]
Zargar et al. (2021) [30]	PE	26/356	24/313	0.95 [0.53, 1.69]
	Placental abruption	NR	NR	
	Preterm birth	14/356	26/313	0.45 [0.23, 0.88]
	Low birth weight	20/356	33/313	0.51 [0.28, 0.90]
	Stillbirth	6/356	15/313	0.34 [0.13, 0.89]
	Cesarean section	NR	NR	
Zhang et al. (2024) [31]	PE	132/1745	65/1458	1.75 [1.29, 2.38]
	Placental abruption	14/1745	33/1458	0.35 [0.19, 0.66]
	Preterm birth	158/1745	153/1458	0.85 [0.67, 1.07]
	Low birth weight	107/1745	113/1458	0.78 [0.59, 1.02]
	Stillbirth	NR	NR	
	Cesarean section	1327/1745	937/1458	1.77 [1.51, 2.06]

Table 2. Continued.

Study (Year)	Outcome	Frozen ET (n/N)	Fresh ET (n/N)	Study-specific OR (95% confidence interval)
Tarlatzi et al. (2021) [3]	PE	24/746	69/2885	1.36 [0.85, 2.17]
	Placental abruption	NR	NR	
	Preterm birth	54/746	332/2885	0.60 [0.44, 0.81]
	Low birth weight	33/746	222/2885	0.56 [0.38, 0.81]
	Stillbirth	2/746	55/2885	0.14 [0.03, 0.57]
	Cesarean section	NR	NR	
Collée et al. (2023) [32]	PE	10/150	7/117	1.12 [0.41, 3.04]
	Placental abruption	NR	NR	
	Preterm birth	24/150	13/117	1.52 [0.74, 3.14]
	Low birth weight	NR	NR	
	Stillbirth	3/150	2/117	1.17 [0.19, 7.14]
	Cesarean section	NR	NR	
Yu et al. (2024) [33]	PE	387/18322	376/25796	1.46 [1.26, 1.68]
	Placental abruption	49/18322	86/25796	0.80 [0.56, 1.14]
	Preterm birth	226/18322	295/25796	1.08 [0.91, 1.29]
	Low birth weight	NR	NR	
	Stillbirth	14/18322	23/25796	0.86 [0.44, 1.67]
	Cesarean section	NR	NR	
Blazquez et al.(2018) [35]	PE	7/80	29/353	1.07 [0.45, 2.54]
	Placental abruption	NR	NR	
	Preterm birth	NR	NR	
	Low birth weight	NR	NR	
	Stillbirth	NR	NR	
	Cesarean section	55/80	224/353	1.27 [0.75, 2.13]
Niu et al. (2023) [34]	PE	74/8691	96/11178	0.99 [0.73, 1.34]
	Placental abruption	NR		
	Preterm birth	485/8691	640/11178	0.97 [0.86, 1.10]
	Low birth weight	235/8691	375/11178	0.80 [0.68, 0.94]
	Stillbirth	NR		
	Cesarean section	NR		
Epelboin et al.(2023) [22]	PE	760/19873	1162/48152	1.61 [1.47, 1.76]
	Placental abruption	NR	NR	
	Preterm birth	NR	NR	
	Low birth weight	NR	NR	
	Stillbirth	NR	NR	
	Cesarean section	NR	NR	

NR, not reported; Fresh ET, fresh embryo transfer; frozen ET, frozen embryo transfer; OR, odds ratio.

outcome/exposure measurement (maximum 3 stars), with a total score of 9 stars. Higher star ratings indicate superior study quality. This assessment was conducted independently by two researchers. All disagreements were resolved through consensus, with arbitration by a third researcher when necessary. Studies scoring ≥7 stars (maximum 9) were deemed to be high quality (Table 4, Ref. [3,22,27,28,29,30,31,32,33,34,35]).

3. Results

3.1 Study Selection

This systematic review analyzed data from 14 studies identified through a comprehensive and explicit search of databases and relevant journals. Initially, 548 records were identified after exhaustive manual and database searches. Following screening of titles and abstracts, 45 records were screened, of which 29 were excluded based on title and abstract. The remaining 16 records underwent full-text assessment. Of these, 2 were excluded (1 cross-sectional study and 1 due to unavailable complete data), and 14 studies met the inclusion criteria and were included in the meta-analysis. The process of study selection and inclusion is shown in Fig. 1.

The risk of bias in the RCT group was assessed using Cochrane RoB 2.0, as shown in Table 3. All three studies were classified as having a moderate risk of bias. The

Table 3. Risk of bias assessments of RCTs using the Cochrane RoB 2.0 tool.

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the reported result	Grade
Maheshwari et al. 2022 [26]	low	Some concerns	low	Some concerns	Low	Some concerns
Chen et al. 2016 [8]	low	Some concerns	low	Some concerns	Low	Some concerns
Zhang et al. 2018 [25]	low	Low	low	Low	Low	Low

Table 4. Risk of bias assessments of cohort studies using the Newcastle-Ottawa scale (NOS).

Study	Selection (4 ★)	Comparability (2 ★)	Outcome (3 ★)	Total score
Yu et al. (2024) [33]	★★★★	★★	★	7
Zhang et al. (2024) [31]	★★★★	★★	★★	8
Epelboin et al. (2023) [22]	★★★★	★★	★	7
Johnson et al. (2019) [27]	★★★★	★★	★	7
Lei et al. (2019) [28]	★★★★	★★	★★★	9
Zargar et al. (2021) [30]	★★★★	★	★★	7
Tarlatzi et al. (2021) [3]	★★★★	★★	★★★	9
Blazquez et al. (2018) [35]	★★★★	★★	★★	8
Collée et al. (2023) [32]	★★★★	★	★★★	8
H Petersen et al. (2023) [29]	★★★★	★	★★	7
Niu et al. (2023) [34]	★★★★	★★	★★	8

quality of the 11 cohort studies were evaluated using the Newcastle-Ottawa Scale (NOS), as presented in Table 4. four studies scored 8 points, five studies scored 7 points and Two studies scored 9. We assessed publication bias using funnel plots and detected asymmetry with Egger's test. The non- significant *p*-value indicates symmetry, suggesting no apparent publication bias in our meta-analysis.

3.2 Summary of Main Outcomes

Frozen ET was associated with significantly increased risks of PE (OR = 1.36, 95% CI: 1.21–1.53) and cesarean section (OR = 1.27, 95% CI: 1.00–1.60) compared with fresh ET, and significantly reduced risksal abruption (OR = 0.57, 95% CI: 0.33–0.97) and low birth weight (OR = 0.73, 95% CI: 0.65–0.83). No statistically significant differences in the incidence rates of preterm birth and stillbirth were observed between the two groups. Egger's test revealed no publication bias for the PE and preterm birth outcomes (PE: p = 0.845; preterm birth: p = 0.370). This meta-analysis about PE, Preterm birth, placental abruption, cesarean section, stillbirth and low birth weight are unlikely to be significantly affected by publication bias (see **Supplementary Figs. 1,2,3,4,5,6**).

3.2.1 Comparison Between Frozen ET and Fresh ET for the Incidence of PE

This analysis included a total of 14 studies, including 3 RCTs. The pooled analysis showed that frozen ET was associated with a significantly higher risk of PE compared to fresh ET (OR = 1.36, 95% CI: 1.21–1.53, $p < 0.00001$). The overall heterogeneity was moderate (I^2 = 58%, p = 0.004). In subgroup analysis of the three RCTs, the results showed a higher risk of PE in the frozen ET group compared to the fresh ET group (OR = 2.75, 95% CI: 1.32–5.72, $p = 0.007$), with low heterogeneity ($I^2 = 0\%$, $p = 0.54$). Subgroup analysis of the 11 non-RCT (NRCT) studies also showed a higher risk of PE in the frozen ET group (OR = 1.34, 95% CI: 1.19–1.51, $p < 0.00001$). The moderate heterogeneity ($I^2 = 62\%$, $p = 0.0043$) suggests the study design may have impacted the effect estimation, as shown in Fig. 2.

Leave-one-out sensitivity analysis showed that exclusion of any single study did not materially change the pooled effect estimate, with all recalculated odds ratios remaining greater than 1 (range of point estimates: 1.31–1.41). Across all iterations, the 95% confidence interval bounds remained consistently above unity (lower limit 1.16; upper limit 1.58). These findings indicate that no individual study disproportionately influenced the results, sup-

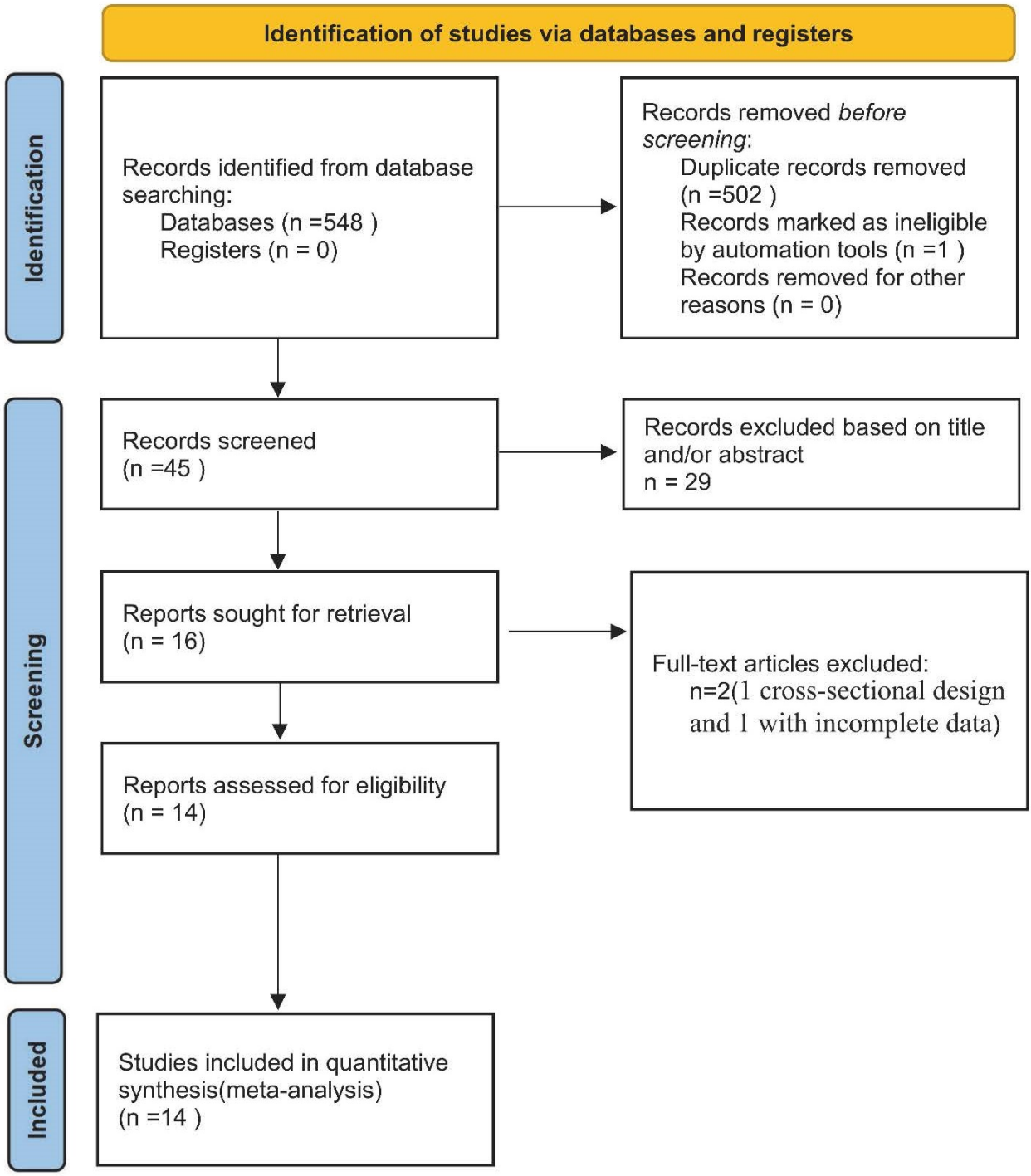

Fig. 1. PRISMA flow diagram for systematic reviews.

porting the robustness of the association between frozen ET and increased risk of pre-eclampsia (see **Supplementary Fig. 7**).

3.2.2 Comparison Between Frozen ET and Fresh ET for the Incidence of Preterm Birth

A total of 11 studies (3 RCTs, 8 NRCTs) were used to compare the incidence of preterm birth between fresh and frozen ET groups. A random-effects model was used for the pooled analysis. The overall results showed no significant difference in the incidence of preterm birth between fresh ET and frozen ET (OR = 0.92, 95% CI: 0.80–1.06, p = 0.26), with high heterogeneity (I^2 = 62%, p = 0.003). In subgroup analysis, pooling of the 3 RCTs revealed no significant difference in the risk of preterm birth between the two groups (OR = 1.10, 95% CI: 0.81–1.48, p = 0.54), with

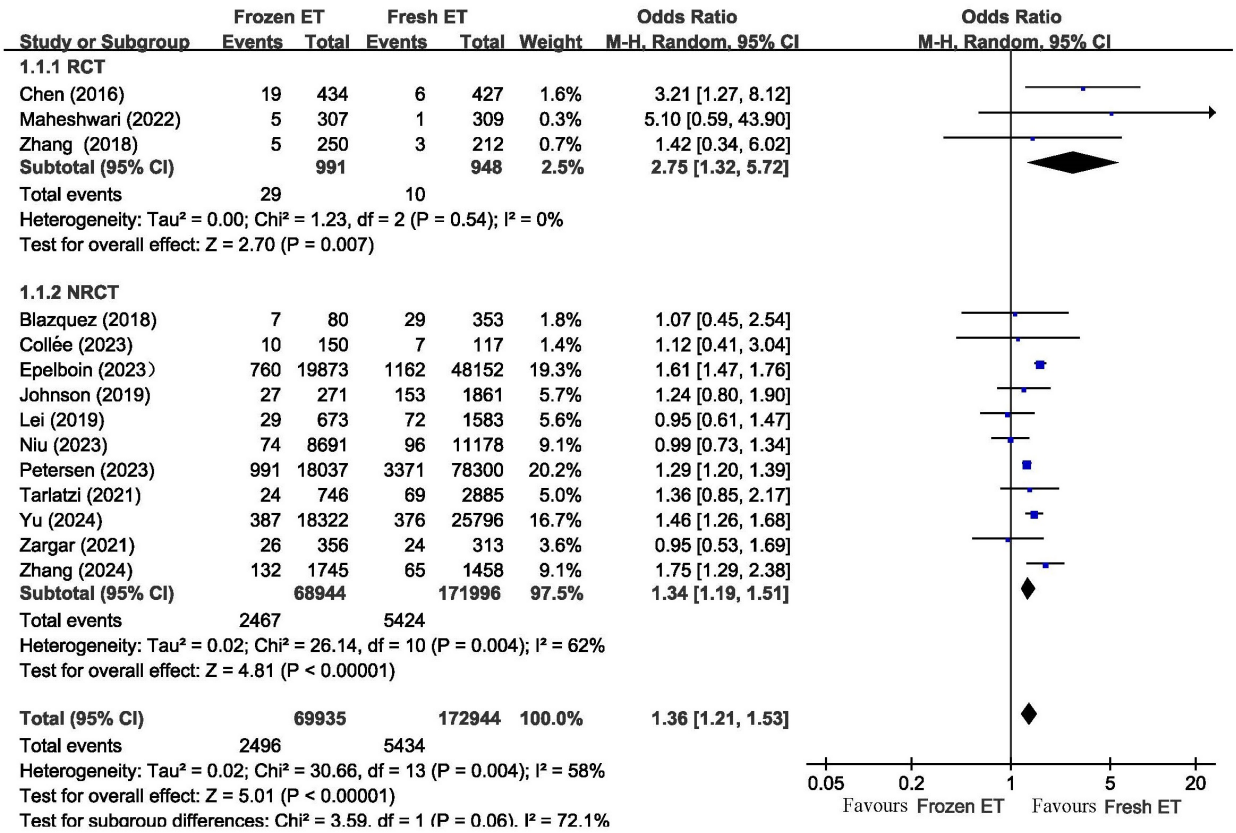

Fig. 2. Forest plot comparing the risk of PE between the frozen ET and fresh ET groups.

no heterogeneity (I^2 = 0%). Pooling of the 8 NRCTs also revealed no significant difference in the risk of preterm birth between the two groups (OR = 0.90, 95% CI: 0.76–1.06, p = 0.19), with high heterogeneity (I^2 = 71%). The absence of a statistically significant difference between the subgroups (p = 0.24) suggests that the study type did not affect the results for preterm birth outcomes (Fig. 3).

Leave-one-out sensitivity analysis demonstrated that exclusion of any single study resulted in pooled odds ratios that crossed the null value (range of point estimates: 0.89–0.98). Across all iterations, the 95% confidence intervals consistently crossed unity (lower limit 0.75; upper limit 1.10). These findings indicate that the meta-analysis did not identify a statistically significant difference in preterm birth risk between fresh and frozen ET (see **Supplementary Fig. 8**).

3.2.3 Comparison Between Frozen ET and Fresh ET for Placental Abruption

Four studies were included in the analysis of the risk of placental abruption following fresh or frozen ET, with a random-effects model used for pooled analysis. The incidence of placental abruption in the frozen ET group was significantly lower than in the fresh ET group (OR = 0.57, 95% CI: 0.33–0.97, p = 0.04). The heterogeneity was moderately high (I^2 = 62%, p = 0.05). Johnson et al. (2019) [27] and Yu et al. (2024) [33] found no significant difference in placental abruption between the two groups (OR = 0.90, 95% CI: 0.42–1.90 and OR = 0.80, 95% CI: 0.56–1.14, respectively), whereas Zhang et al. (2024) [31] and Lei et al. (2019) [28] reported a lower risk in the frozen ET group (OR = 0.35, 95% CI: 0.19–0.66 and OR = 0.27, 95% CI: 0.08–0.89, respectively), as shown in Fig. 4.

Leave-one-out sensitivity analysis showed that exclusion of any single study yielded pooled odds ratios below 1 (range of point estimates: 0.46–0.71), although the 95% confidence intervals extended across unity (lower limit 0.23; upper limit 1.16). Exclusion of the study by Zhang et al. (2024) [31] reduced heterogeneity substantially (I^2 from 62% to 38%), indicating that this study was the primary contributor to between-study heterogeneity. Overall, these findings suggest a trend toward a lower risk of placental abruption with frozen compared to fresh ET, but the results should be interpreted with caution given the limited number of included studies (see **Supplementary Fig. 9**).

3.2.4 Comparison Between Frozen ET and Fresh ET for the Rate of Cesarean Section

A total of 5 studies reported on the relationship between the type of ET and cesarean section. A random-effects model showed that frozen ET increased the risk of cesarean section compared to fresh ET (OR = 1.27, 95% CI:

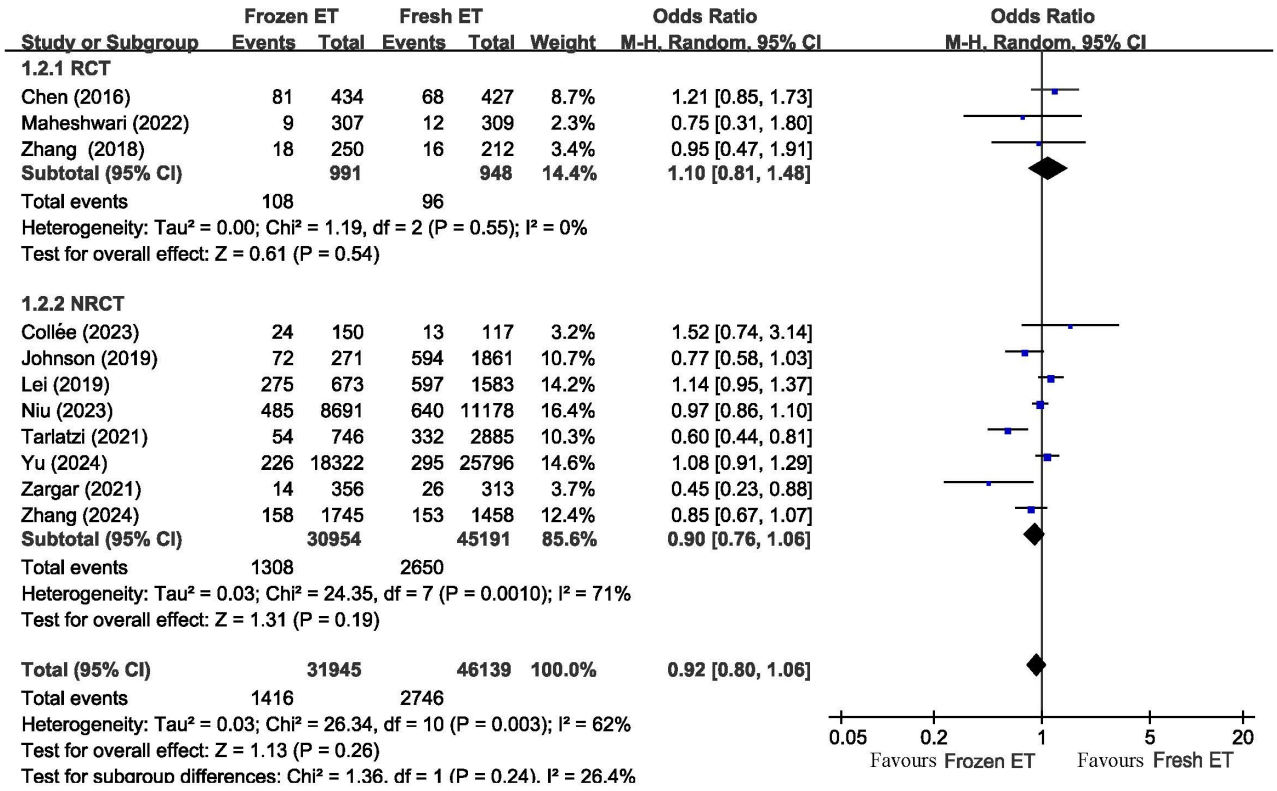

Fig. 3. Forest plot comparing the risk of preterm birth between the frozen ET and fresh ET groups.

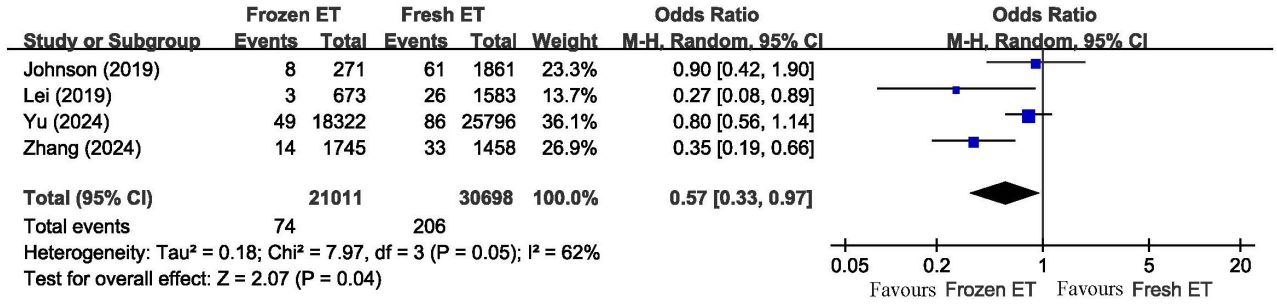

Fig. 4. Forest plot comparing the risk of placental abruption between the frozen and fresh ET groups.

1.00–1.60, $p = 0.05$), although a high degree of heterogeneity was seen amongst the studies ($I^2 = 85\%$, $p < 0.0001$). Two studies with a large sample size, Zhang et al. (2024) [31] reported the risk in the frozen ET group (OR = 1.77, 95% CI: 1.51–2.06) and H Petersen et al. (2023) [29] reported the risk in the frozen ET group (OR = 1.17, 95% CI: 1.13–1.21), both showed that frozen ET significantly increased the risk of cesarean section. Confidence intervals for the remaining two studies all crossed the null line (OR = 1), indicating a lack of statistical significance (Fig. 5).

Leave-one-out sensitivity analysis yielded a pooled odds ratio of 1.27 with borderline statistical significance (95% CI: 1.00–1.60); however, the result was highly sensitive to the exclusion of individual studies. Exclusion of the study by Zhang et al. (2024) [31] resulted in a more precise and statistically significant association (OR = 1.16; 95% CI: 1.12–1.21), whereas exclusion of any of the remaining studies led to loss of statistical significance with confidence intervals crossing unity. These findings indicate that the overall association between frozen ET and cesarean section risk is unstable and largely driven by the inclusion of Zhang et al. (2024) [31] (see **Supplementary Fig. 10**).

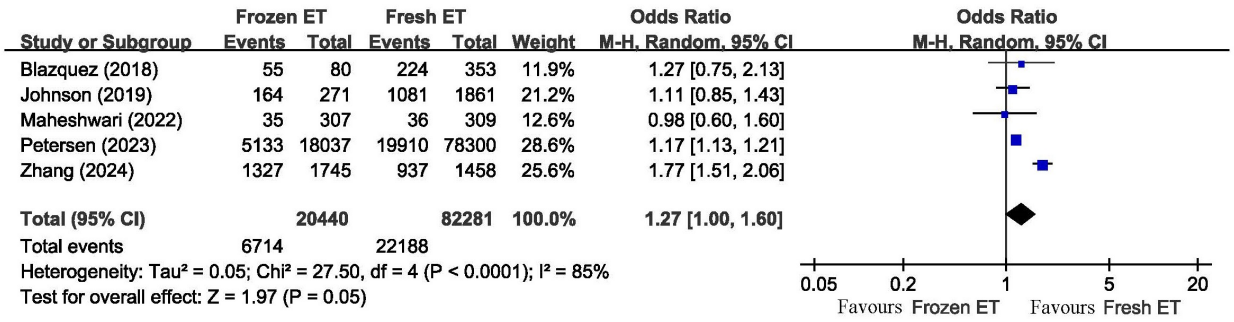

Fig. 5. Forest plot comparing the risk of Cesarean section between the frozen ET and fresh ET groups.

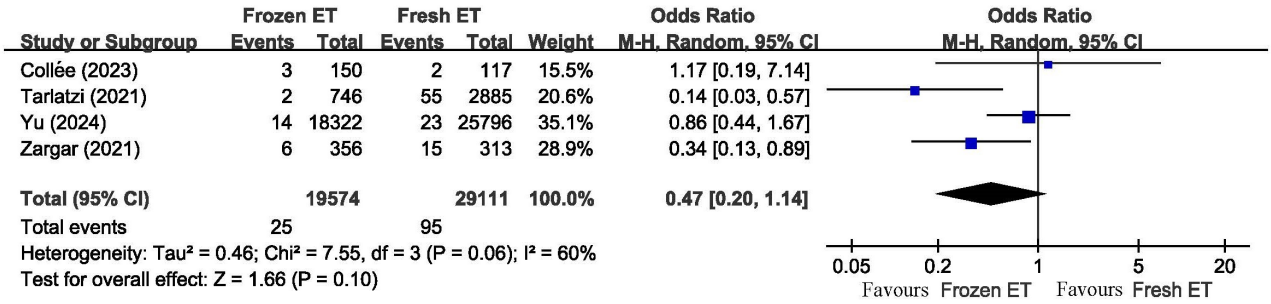

Fig. 6. Forest plot comparing the risk of stillbirth between the frozen ET and fresh ET groups.

3.2.5 Comparison Between Frozen ET and Fresh ET for Stillbirth

The aggregated results revealed no statistically significant difference in the incidence of fetal birth between the frozen ET and fresh ET groups (OR = 0.47, 95% CI: 0.20–1.14, $p = 0.10$), with moderate heterogeneity ($I^2 = 60\%$, $p = 0.06$). Tarlatzi et al. (2021) [3] reportd that the risk of stillbirth in the frozen ET group was significantly lower than in the fresh ET group (OR = 0.14, 95% CI: 0.03–0.57). Zargar et al. (2021) [30] also found a lower risk of stillbirth in the frozen ET group (OR = 0.34, 95% CI: 0.13–0.89). The other two studies by Yu et al. (2024) [33] and Collée et al. (2023) [32] showed no significant difference between the frozen and fresh ET groups (Fig. 6; Fig. 7, Ref. [33]).

Leave-one-out sensitivity analysis showed that exclusion of any single study yielded a non-significant pooled estimate (OR = 0.47; 95% CI: 0.20–1.14). However, exclusion of the study by Yu et al. (2024) [33] resulted in a statistically significant association (OR = 0.34; 95% CI: 0.12–0.97), whereas exclusion of any other study did not materially alter the non-significant result. These findings indicate that the overal estimate is highly sensitive to the inclusion of Yu et al. (2024) [33], suggesting a substantial influece of this study on the pooled effect (see **Supplementary Fig. 11**).

3.2.6 Comparison Between Frozen ET and Fresh ET for Low Birth Weight

The risk of low birth weight was significantly lower in the frozen ET group compared to the fresh ET group (OR = 0.73, 95% CI: 0.65–0.83, $p < 0.00001$), as shown in Fig. 8. Moderate Heterogeneity was observed between the studies ($I^2 = 26\%$, $p = 0.25$).

Leave-one-out sensitivity analysis demonstrated that the pooled association remained stable following exclusion of any single study (overall OR = 0.73; 95% CI: 0.6–0.83). Across all iterations, recalculated odds ratios ranged from 0.65 to 0.77, and the upper bounds of the 95% confidence intervals consistently remained below unity (range: 0.79–0.88). These findings indicate that the association between frozen embryo transfer and reduced risk of low birth weight is robust and not driven by any individual study (see **Supplementary Fig. 12**).

4. Discussion

This meta-analysis integrated data from 14 studies to systematically compare perinatal outcomes between frozen ET and fresh ET. The results demonstrate that frozen ET is associated with a significantly increased risk of PE, indicating a relative protective effect of fresh ET againstthis disorder. On the other hand, fresh ET is associated with elevated risks of placental abruption and low birth weight. No statistically significant differences were observed between fresh and frozen ET for the risks of preterm birth or

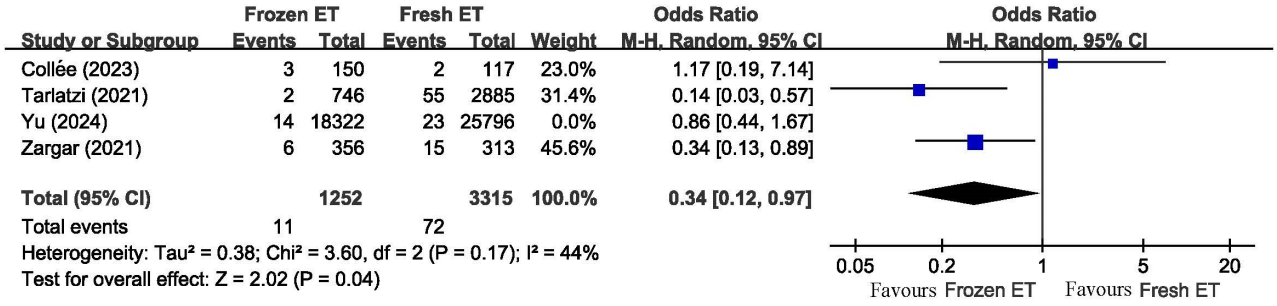

Fig. 7. Forest plot comparing the risk of stillbirth between the frozen ET and fresh ET groups, with exclusion of the study by Yu et al. [33].

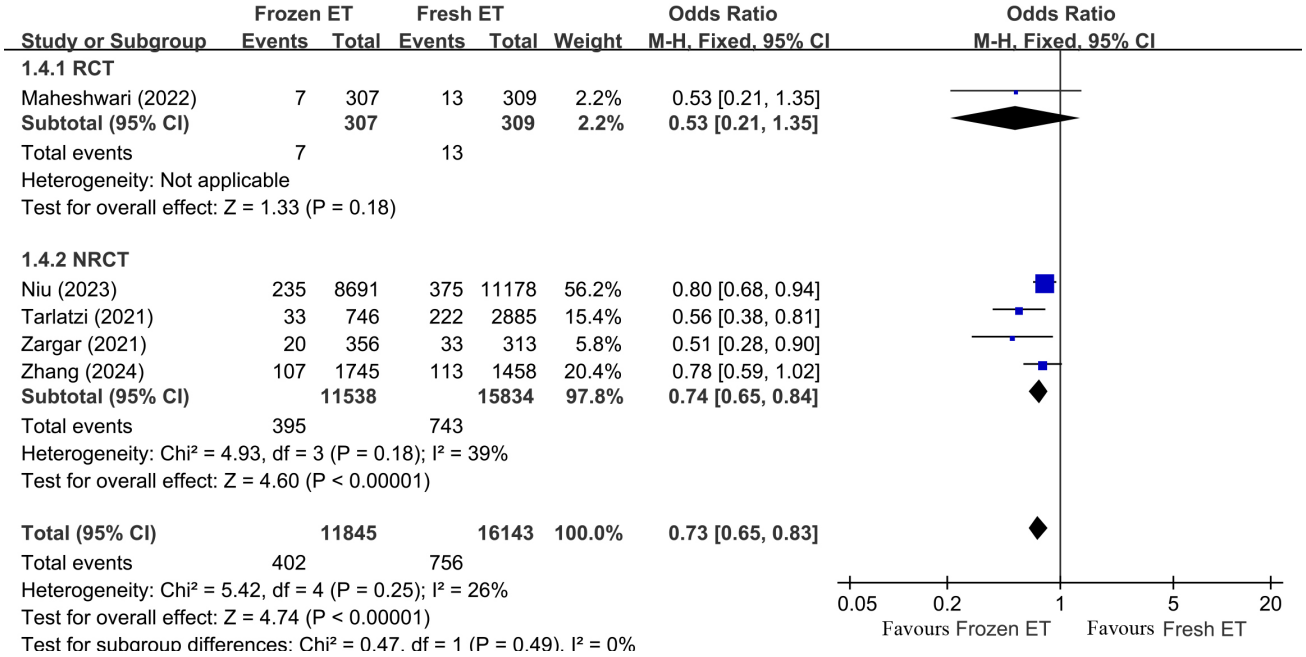

Fig. 8. Forest plot comparing the risk of low birth weight between frozen ET and fresh ET groups.

stillbirth. These findings underscore the distinct impact of ET strategies on pregnancy outcomes and highlight the necessity for individualized clinical decision-making in ART. The elevated risk of PE observed with frozen ET in this meta-analysis can be explained by several interconnected pathophysiological pathways supported by the cited literature. A primary factor is the frequent absence of the corpus luteum in programmed frozen ET cycles [36]. This deficiency leads to a marked reduction in the secretion of key vasoactive substances such as relaxin, vascular endothelial growth factor (VEGF), and vasodilatory progesterone metabolites, which are crucial for systemic cardiovascular adaptation and early placental development [37,38]. The lack of these factors, particularly during hormone replacement therapy (HRT) cycles, is postulated to compromise uteroplacental hemodynamics and the remodeling of spiral arteries. This mechanism is supported by clinical evidence linking the absence of the corpus luteum to a substantially higher risk of gestational hypertension [39]. Beyond the endocrine milieu, the cryopreservation process itself may induce persistent molecular alterations. Foundational research on frozen ET as an independent risk factor for PE has revealed significant dysregulation of placental transcriptomes and DNA methylation profiles, particularly affecting genes involved in iron metabolism, immune response, and angiogenesis [40]. These epigenetic modifications, together with *in vitro* evidence that cryopreservation directly impairs trophoblast differentiation [41,42], and thus compromises trophoblast migration and invasion, are likely to disrupt normal placental formation and lead to preeclampsia [43]. The functional consequence is reflected in the increased levels of anti-angiogenic factors such as sFlt-1 in frozen ET pregnancies, contributing to the endothelial dysfunction which is characteristic of PE [44]. Furthermore, the artificial endocrine environment of HRT-based frozen ET cycles, characterized by supraphysiological exogenous

estrogen without the broader hormonal context of a fresh cycle, may adversely affect the delicate process of spiral artery remodeling, thus increasing the risk of uteroplacental malperfusion [45]. Although supraphysiologic estrogen in fresh ET cycles also carries risks, such as potential vascular toxicity [45,46], the context, timing, and hormonal profile differ fundamentally between the fresh and frozen ET protocols, explaining their distinct complication profiles. This triad of mechanisms—corpus luteum deficiency, cryopreservation-induced molecular changes, and an artificial hormonal environment—provides a coherent explanation for the clinical observation of increased PE risk following frozen ET, aligning with findings from large cohort studies [8,29]. In contrast, the elevated risks of placental abruption and low birth weight linked to fresh ET may be due to the unique endocrine landscape of ovarian stimulation. Supraphysiological hormone levels in fresh cycles can promote a pro-thrombotic state and adversely affect deep trophoblast invasion, thereby increasing susceptibility to placental ischemia and subsequent abruption [42,47]. Regarding fetal growth, the fresh cycle environment has been associated with dysregulation of imprinted genes critical for placental development, such as *PEG10* [48]. Altered expression of such genes may compromise placental function, contributing to restricted fetal growth. This pathophysiological understanding is consistent with prior meta-analytic evidence indicating that frozen ET significantl reduces the incidence of very low birth weight compared to fresh ET [21].

Limitations

This systematic review has limitations. First, the number of studies including certain outcome measures such as cesarean section rate, placental abruption, and stillbirth was limited, with uneven sample distribution. Second, the robustness of the pooled analysis for placental abruption requires cautious evaluation. Although the analysis included four studies, sensitivity analysis and random effects model validation revealed that the overall results still require further confirmation through high-quality studies with balanced sample sizes. The one-study exclusion sensitivity analysis showed that the pooled odds ratios remained below 1 (point estimate range: 0.33–0.97) after excluding any single study. However, excluding the studies by Zhang et al. (2024) [31] or Lei et al.(2019) [28] resulted in 95% confidence intervals exceeding 1. The significance was maintained when excluding the other two studies. This phenomenon indicates that the current statistically significant pooled results largely depend on the contributions of a few specific studies. Although the direction of the core effect remained consistent across analyses, suggesting a potential trend, the establishment of statistical significance was fragile. Therefore, the "positive" conclusions for this outcome should be considered preliminary or inconclusive, strongly indicating the need for more high-quality, large-sample studies to provide more robust evidencedue to the limited number of included studies, excluding the corresponding articles would affect the overall results and lead to misinterpretation, so this article does not exclude the relevant literature. Additionally, the pooled analysis for stillbirth has limitations in statistical robustness. Although the initial analysis showed no statistical significance (OR = 0.47, 95% CI: 0.20–1.14, $p = 0.10$), sensitivity analysis revealed that this significance was not robust. Specifically, when Yu et al. (2024) [33] was excluded, although the exclusion of this study yielded statistical significance, the confidence interval (OR = 0.34; 95% CI: 0.12–0.97), the upper limit of the confidence interval was close to the null line (0.97), indicating that the significance was marginal. Therefore, the current meta-analytic evidence lacks sufficient statistical robustness, and the overall conclusion should be interpreted with caution, warranting further validation by more high-quality original studies. Additionally, this meta-analysis of cesarean section outcomes has limitations. First, sensitivity analysis showed that the overall association between frozen embryo transfer and cesarean section risk was unstable. More importantly, cesarean section decisions are influenced by clinical factors, so the conclusions should be regarded as preliminary and interpreted cautiously in the context of clinical practice. Finally, this review is limited to data from observational studies that are, for the most part, constrained by their retrospective nature. And bias may have been introduced as data not published as full-text articles and in languages other than English were excluded from the meta-analysis.

5. Conclusions

This study found that the risk of pre-eclampsia occurrence was significantly reduced in fresh ET compared to frozen ET, suggesting that fresh cycles may offer potential protective effects against this placenta-derived pregnancy complication. However, it is noteworthy that fresh ET is also associated with an increased risk of placental abruption and low birth weight in newborns. These perinatal complications pose direct threats to fetal and neonatal health. Based on the findings of this meta-analysis and supporting evidence, future research should compare hormonal dynamics (e.g., estrogen, progesterone, relaxin, and renin–angiotensin system markers) between programmed and natural-cycle frozen ET, as well as their impact on placental function and perinatal outcomes. Epigenetic studies may clarify the underlying mechanisms and inform safer protocols, particularly on imprinted genes such as **MEST/PEG1**, which is downregulated in early-onset pre-eclampsia and sensitive to ART-induced methylation changes. While frozen ET is associated with a higher cesarean section rates, it is also related to neonatal birth weight. It can reduce the risk of low birth weight, although some studies have indicated that it may increase the risk of macrosomia [49], and a lower risk of placental abrup-

tion, it also increases the risk of PE. Treatment planning should therefore account for patient-specific factors, including age, BMI, infertility etiology, prior ART outcomes, endometrial status, and the type of endometrial preparation. Risk-stratified management is advised. Prior to transfer, patients should be screened for PE risk factors such as advanced maternal age (≥35 years), PCOS (Whether the patient has ovulation disorders?) [50], obesity (BMI ≥30 kg/m^2), chronic hypertension, renal disease, autoimmune disorders, and previous PE [51]. In high-risk cases, the choice between programmed frozen ET (with careful counseling) and fresh ET or modified natural-cycle frozen ET—with attention to luteal phase support—should be carefully considered. A multidisciplinary approach and enhanced patient counseling are encouraged to shift the focus from success rates alone to a balanced assessment of risks and benefits, ensuring that safety remains central to treatment decisions.

Availability of Data and Materials

The datasets analyzed during the current study are derived from published studies. The extracted data used for this meta-analysis are available from the corresponding author upon reasonable request.

Author Contributions

YZ, MC and JZ designed the study. YZ, MC, ZY and JZ contributed to the analysis. YZ, MC analyzed the data. YZ wrote the manuscript. JZ and ZY reviewed and edited the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT-3.5 and deepseek in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG47456.

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