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Meta-analysis

Comparing the incidence of pre-eclampsia following freeze-all versus conventional *in-vitro* fertilization: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

In vitro fertilization (IVF) is commonly used to treat infertility, but its association with pre-eclampsia is well-documented. The freeze-all strategy in IVF has gained popularity, but its impact on the incidence of pre-eclampsia compared to conventional fresh embryo transfer remains uncertain. This systematic review and meta-analysis aimed to compare the incidence of pre-eclampsia in pregnancies following freeze-all versus conventional fresh embryo transfers in randomized controlled trials (RCTs). A comprehensive search was conducted across PubMed, Web of Science, Scopus, Medline, the Cochrane Library, and Google Scholar databases. A total of 611 records were identified and screened for suitability for inclusion in the quantitative synthesis. Data extraction and quality assessment were performed, and pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated using fixed-effects models. Heterogeneity was assessed using Chi² and I² statistics. The meta-analysis included data from 7 RCTs, involving a total of 4,749 participants (2,434 in the freeze-all group and 2,315 in the conventional group). The pooled analysis revealed a significantly higher risk of pre-eclampsia in the freeze-all group, with an OR of 2.14 (95% CI 1.47, 3.11; p<0.0001). The heterogeneity among the studies was low (Chi square=5.88, df=6, p=0.44; I²=0%). This meta-analysis indicates that the freeze-all strategy in IVF is associated with a significantly higher risk of pre-eclampsia compared to conventional fresh embryo transfer. Clinicians should consider this increased risk when planning IVF treatments and counsel patients accordingly.

Keywords: *In-vitro* fertilization, Pre-eclampsia, Freeze-all strategy, Conventional embryo transfer, Randomized controlled trials, Meta-analysis

INTRODUCTION

Pre-eclampsia is a complex and multifactorial hypertensive disorder of pregnancy, typically emerging after the 20th week of gestation.[1,2] It is characterized by new-onset hypertension and often proteinuria, with potential severe complications for both the mother and fetus if left untreated. The global prevalence of pre-eclampsia is approximately 2-8% of all pregnancies, making it a leading cause of maternal and perinatal morbidity and mortality.[1] The pathophysiology of pre-eclampsia is not completely understood, but it is believed to involve abnormal placental development and subsequent placental ischemia, oxidative stress, and systemic inflammation.[1,3,4]

In vitro fertilization (IVF) is a cornerstone treatment for infertility, helping millions of couples worldwide to conceive. Since its introduction, IVF has undergone numerous advancements leading to improving success rates and expanding its applicability.[3] However, IVF pregnancies have been associated with a higher incidence

of complications such as pre-eclampsia, compared to natural conceptions. Several factors contribute to this increased risk, including the higher prevalence of multiple pregnancies, the older age of IVF patients, and underlying infertility-related conditions.[3,5] One significant development in IVF technology is the freeze-all strategy, where all viable embryos are cryopreserved and transferred in subsequent cycles rather than immediately transferring fresh embryos. This approach was initially introduced to mitigate the risk of ovarian hyper-stimulation syndrome (OHSS), a potentially life-threatening condition triggered by fertility medications.[6,7] The freeze-all strategy allows for ovarian stimulation and egg retrieval in one cycle, followed by embryo transfer in a later, more physiologically optimal environment.[3,6,8]

The freeze-all strategy offers several potential benefits. By separating the embryo transfer from the ovarian stimulation cycle, the endometrial receptivity is improved, which may enhance implantation rates and overall pregnancy outcomes.[6,8] Moreover, the freeze-all approach can reduce the incidence of OHSS, a significant complication in IVF treatments. Additionally, advances in cryopreservation techniques, particularly vitrification, have significantly improved the survival rates and developmental potential of frozen-thawed embryos, making the freeze-all strategy increasingly viable and attractive.[7-9]

Despite these advantages, the impact of the freeze-all strategy on the risk of pre-eclampsia remains a topic of debate. Some studies suggest that freeze-all cycles might alter the hormonal milieu during the peri-implantation period, potentially affecting placental development and increasing the risk of hypertensive disorders.[8,9] The hormonal environment in frozen-thawed embryo transfer cycles differs significantly from that in fresh cycles. In fresh cycles, elevated levels of estrogen and progesterone immediately after ovarian stimulation may impact placental development differently than the more controlled hormonal environment in frozen-thawed cycles. This altered hormonal milieu could potentially contribute to an increased risk of pre-eclampsia.[6,9,10]

Given the potential implications for clinical practice, understanding the relationship between the freeze-all strategy and the risk of pre-eclampsia is crucial. If the freeze-all approach is associated with a higher risk of pre-eclampsia, this would necessitate careful consideration when selecting patients for this strategy and underscore the need for vigilant monitoring during pregnancy. Conversely, if no significant difference or a lower risk is observed, the freeze-all strategy could be more widely adopted, leveraging its benefits in improving pregnancy outcomes and reducing the risk of OHSS. The aim of this study is to systematically review and quantitatively synthesize the available evidence from randomized controlled trials (RCTs) to compare the incidence of pre-eclampsia in pregnancies following freeze-all versus conventional fresh embryo transfers.

METHODS

This meta-analysis adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[11] The aim was to compare the incidence of pre-eclampsia in pregnancies resulting from freeze-all versus conventional fresh embryo transfer in RCTs. The analysis involved a comprehensive search, selection, and synthesis of data from relevant studies. The study was conducted over a period of six months, from January 2024 to June 2024. This timeframe included the stages of literature search, study selection, data extraction, and quantitative synthesis.

Search strategy

A systematic search was performed across multiple databases including PubMed, Web of Science, Scopus, Medline, the Cochrane Library, and Google Scholar. The search terms included combinations of "pre-eclampsia," "freeze-all," "conventional embryo transfer," "*in-vitro* fertilization," "IVF," and "randomized controlled trials". Searches were restricted to studies published in English. References of relevant articles were also reviewed to identify additional studies.

Inclusion criteria

Studies were included based on the following criteria: RCTs study type, population of women undergoing IVF, the intervention type was freeze-all embryo transfer, the comparison group was conventional fresh embryo transfer, and the outcome was the incidence of pre-eclampsia. We included articles published in English language only.

Exclusion criteria

The following exclusion criteria were applied: non-RCT studies such as observational studies, case reports, and reviews; different intervention types such as studies not specifically comparing freeze-all with conventional fresh embryo transfer; insufficient data such as studies lacking data on the incidence of pre-eclampsia; and non-English language articles.

Data extraction was conducted independently by two reviewers using a standardized data extraction form. Discrepancies were resolved through discussion or consultation with a third reviewer. Extracted data included study characteristics (author, year, country, design), participant characteristics (sample size, age, BMI), and outcome measures (incidence of pre-eclampsia).

The quantitative synthesis was performed using RevMan 5.4 software. The primary outcome was the incidence of pre-eclampsia in freeze-all versus conventional embryo transfer groups. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each study. A fixed-effects model was employed due to the low heterogeneity among studies. Heterogeneity was assessed using Chi^2 and

I^2 statistics, with Chi^2 p value <0.10 and I^2 >50% indicating significant heterogeneity. No ethical approval is required for this type of studies as we used secondary data only.

RESULTS

As shown in Figure 1, the systematic search initially identified 611 records across multiple databases, including PubMed, Web of Science, Scopus, Medline, the Cochrane Library, and Google Scholar. After removing 262 duplicates, 349 records remained for title and abstract screening. Of these, 298 were excluded based on irrelevance to the study criteria. Full-text retrieval was attempted for the remaining 51 records; however, 2 records could not be retrieved. Following full-text assessment of the remaining 49 records, 42 studies were excluded for reasons such as not meeting the inclusion criteria or insufficient data for meta-analysis. Ultimately, 7 RCTs were included in the quantitative synthesis, as depicted in Figure 1 of the PRISMA flow diagram.

Characteristics of the included studies

Study design and geographical distribution

All seven included studies were RCTs, ensuring a high level of evidence. Geographically, the studies were conducted in diverse regions, with the majority based in China by Chen et al, Shi et al, Wei et al, and Zhang et al, one in the United Kingdom by Maheshwari et al, one spanning Denmark, Sweden, and Spain by Stormlund et al, and one in Vietnam by Voung et al.[12-18] This geographical diversity enhances the generalizability of the findings across different populations and healthcare settings (Table 1).

Sample size

The sample sizes varied significantly among the studies, ranging from 223 to 1080 participants per group. The largest studies were conducted by Shi et al and Wei et al, with 1077 and 825 participants in the freeze-all groups, and 1080 and 825 participants in the conventional groups, respectively.[13,14] The smallest study was conducted by Stormlund et al, with 223 participants in the freeze-all group and 230 in the conventional group.[17] Overall, the total number of participants across all studies was substantial, ensuring robust statistical power (Table 1).

Participant age

The mean age of participants was relatively consistent across studies. For the freeze-all groups, the mean age ranged from 28.1±3.0 years by Chen et al to 34.7±3.8 years by Maheshwari et al.[12,16] Similarly, the conventional IVF groups had mean ages ranging from 28.1±3.1 years by Zhang et al to 34.6±3.6 years by Maheshwari et al.[15,16] This indicates that the included studies predominantly involved women in their late twenties to mid-thirties, which is typical for IVF treatment populations (Table 1).

Body mass index

Body mass index (BMI) values were also comparable across studies, with mean BMI for freeze-all groups ranging from 20.8±2.2 by Voung et al to 24.1±4.0 by Stormlund et al.[17,18] For conventional IVF groups, the BMI ranged from 20.8±2.2 by Voung et al to 24.1±3.9 by Stormlund et al.[17,18] These values suggest that participants generally had BMIs within the normal to slightly overweight range, which is reflective of the general population undergoing IVF treatments (Table 1).

Incidence of pre-eclampsia

The incidence of pre-eclampsia varied notably between studies and treatment groups. In the freeze-all groups, the incidence ranged from 0.5% by Voung et al to 7.0% by Stormlund et al, whereas in the conventional groups, the incidence ranged from 0.3% by Voung et al to 7.3% by Stormlund et al.[17,18] Some studies reported a higher incidence of pre-eclampsia in the freeze-all groups compared to the conventional groups, such as Maheshwari et al (5.7% versus 0.9%) and Zhang et al (5.2% versus 1.9%).[15,16] Conversely, Stormlund et al reported similar incidences in both groups (7.0% versus 7.3%) (Table 1).[17]

Quantitative data synthesis

Forest plot analysis

The forest plot (Figure 2) provides a visual comparison of the incidence of pre-eclampsia between the freeze-all and conventional embryo transfer groups across the included studies. The combined analysis yielded significant overall odds ratio (OR) of 2.14 (95% CI 1.47, 3.11; p<0.0001), indicating a more than two-fold increase in the risk of pre-eclampsia associated with freeze-all embryo transfer.

Individual study results varied. Chen et al found an OR of 3.21 (95% CI 1.27, 8.12), indicating a significantly higher risk in the freeze-all group.[12] Maheshwari et al reported an OR of 6.40 (95% CI 0.73, 55.87), although the wide confidence interval reflects a high level of uncertainty.[16] Shi et al observed an OR of 1.38 (95% CI 0.76, 2.50), contributing the most weight (46.10%) due to its large sample size, but did not find a significant difference.[13] Stormlund et al reported an OR of 0.96 (95% CI 0.23, 4.05), suggesting no significant difference between the groups.[17] Voung et al found an OR of 2.01 (95% CI 0.18, 22.20), with limited events contributing to the wide confidence interval.[18] Wei et al reported an OR of 3.20 (95% CI 1.06, 9.65), indicating a significantly higher risk in the freeze-all group.[14] Zhang et al observed an OR of 2.86 (95% CI 1.13, 7.24), also indicating a higher risk in the freeze-all group.[15]

The heterogeneity among the studies was low, with a Chi^2 value of 5.88 (df=6, p=0.44) and an I^2 of 0%, indicating consistency across the studies. The test for overall effect was highly significant (Z=4.00, p<0.0001).

Table 1: Characters of the included RCT studies (n=7).

Study	Country	Sample size (F)	Sample size (C)	Age in years (F)	Age in years (C)	BMI (F)	BMI (C)	Pre-eclampsia incidence (F) (%)	Pre-eclampsia incidence (C) (%)
Chen et al 2016[12]	China	746	762	28.1 ±3.0	28.2 ±3.1	23.8 ±3.8	23.9 ±3.6	4.4	1.4
Maheshwari et al 2022[16]	UK	307	309	34.7 ±3.8	34.6 ±3.6	24.1 ±3.4	24.1 ±3.2	5.7	0.9
Shi et al 2018[13]	China	1077	1080	28.5 ±3.0	28.4 ±3.1	22.0 ±3.0	22.2 ±3.1	4.4	3.3
Stormlund et al 2020[17]	Denmark, Sweden, Spain	223	230	32.4 ±3.9	32.3 ±4.2	24.1 ±4.0	24.1 ±3.9	7.0	7.3
Vuong et al 2018[18]	Vietnam	391	391	32 ±4	32 ±4	20.8 ±2.2	20.8 ±2.2	0.5	0.3
Wei et al 2019[14]	China	825	825	28.3 ±3.0	28.3 ±3.0	22.4± 3.2	22.5 ±3.1	3.1	1.0
Zhang et al 2018[15]	China	367	320	28.4 ±2.9	28.1 ±3.1	23.5± 3.5	23.8 ±3.5	5.2	1.9

F: Freeze-All IVF, C: conventional IVF.

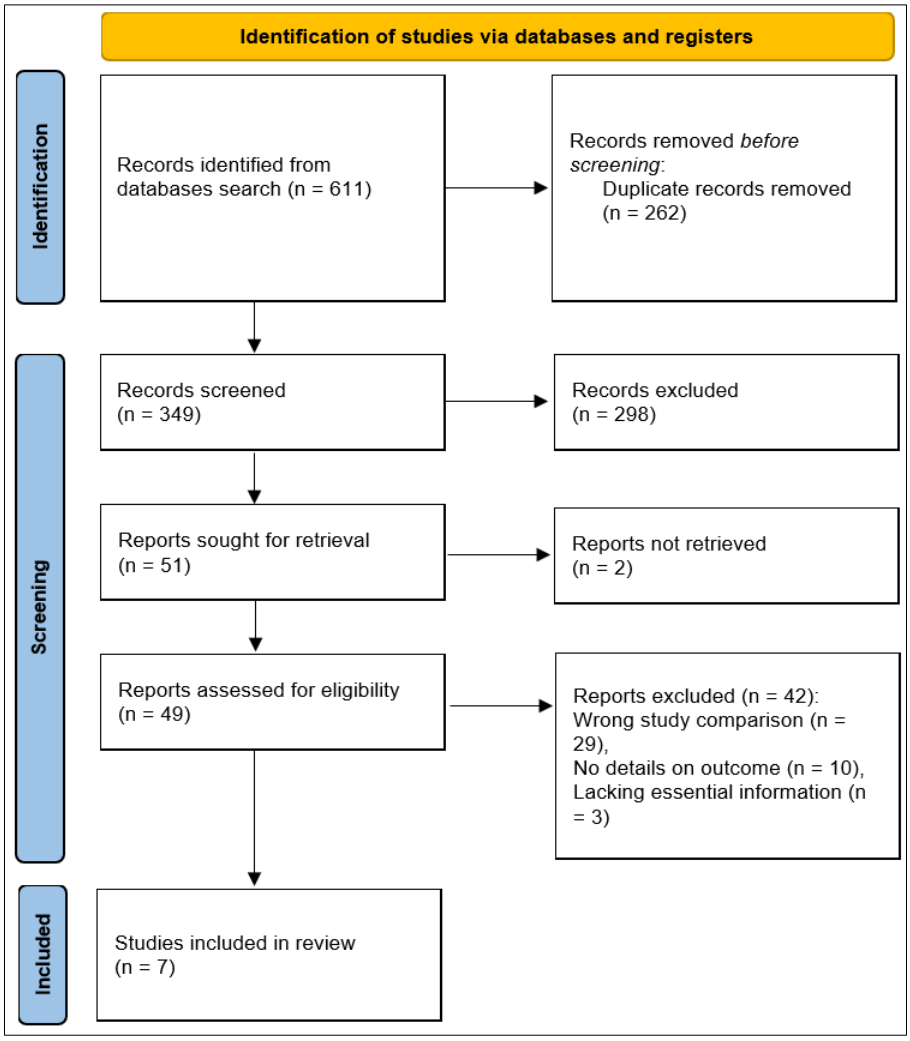

Figure 1: PRISMA flow diagram for the study search process.

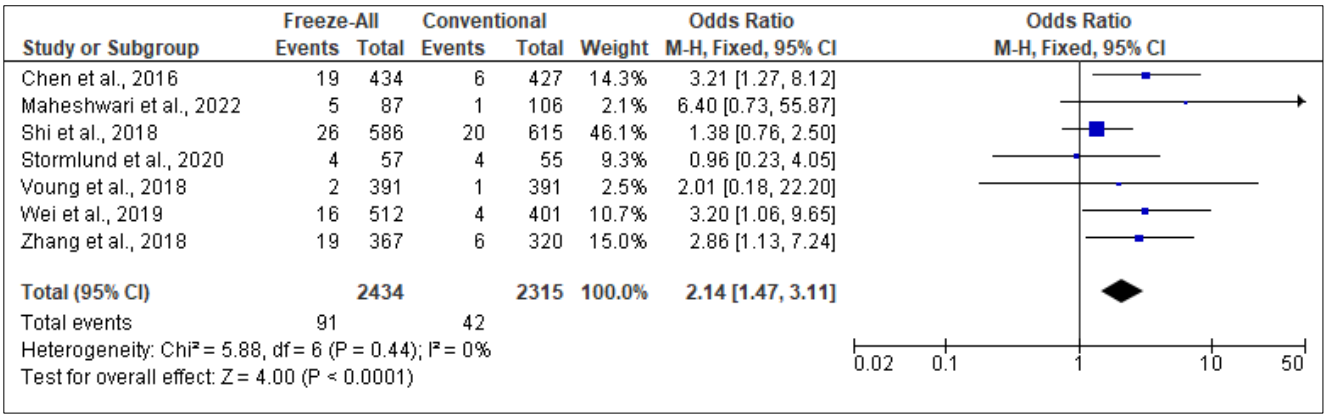

Figure 2: Forest plot of comparing pre-eclampsia in freeze-all versus conventional embryo transfer.

Funnel plot analysis

The funnel plot was used to assess publication bias (Figure 3). The plot displays the studies' effect sizes against their standard errors. In a meta-analysis without significant publication bias, studies should scatter symmetrically around the overall effect size, forming a funnel shape. In this analysis, the funnel plot appears relatively symmetrical, suggesting no substantial publication bias.

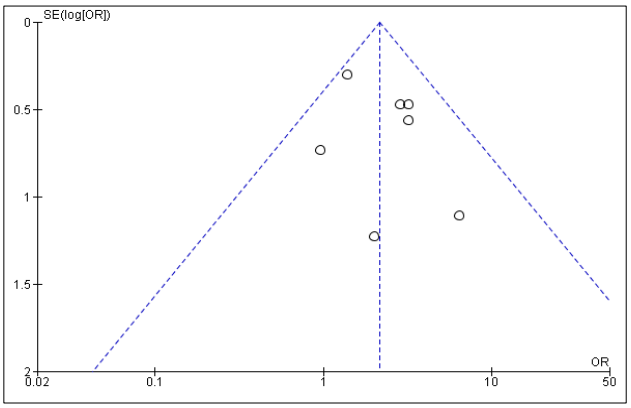

Figure 3: Funnel plot of comparing pre-eclampsia in freeze-all versus conventional embryo transfer.

DISCUSSION

Pre-eclampsia is a serious hypertensive disorder of pregnancy that poses significant risks to both the mother and the fetus. It typically presents after the 20th week of gestation and is characterized by high blood pressure and often proteinuria.[2] The exact etiology of pre-eclampsia remains unclear, but it is widely believed to involve abnormal placental development and maternal immune response to the placenta.[1-3] IVF is a common and effective treatment for infertility, but it has been associated with an increased risk of adverse pregnancy outcomes, including pre-eclampsia.[3,5] The freeze-all strategy, where all viable embryos are cryopreserved and transferred in subsequent cycles, has been suggested to improve IVF outcomes. However, the impact of the freeze-all strategy on the incidence of pre-eclampsia compared to conventional fresh embryo transfer remains contentious.[6,9]

Our meta-analysis synthesized data from seven RCTs comparing the incidence of pre-eclampsia between freeze-all and conventional fresh embryo transfer groups. The pooled analysis revealed a significantly higher risk of pre-eclampsia in the freeze-all group, with overall odds ratio (OR) of 2.14 (95% CI 1.47, 3.11; p<0.0001). This finding was consistent across the included studies, with low heterogeneity (Chi^2=5.88, df=6, p=0.44; I^2=0%), suggesting that the observed effect is reliable and robust.

Chen et al reported a significantly higher incidence of pre-eclampsia in the freeze-all group (OR 3.21, 95% CI 1.27, 8.12), with 19 events out of 434 in the freeze-all group compared to 6 events out of 427 in the conventional group.[12] Similarly, Maheshwari et al found an OR of 6.40 (95% CI 0.73, 55.87), though the wide confidence interval suggests variability due to the smaller sample size.[16] Shi et al, with the largest sample size, observed an OR of 1.38 (95% CI 0.76, 2.50), indicating a non-significant trend towards higher risk.[13] Stormlund et al reported no significant difference (OR 0.96, 95% CI 0.23, 4.05), while Voung et al also found no significant difference but had a very wide confidence interval (OR 2.01, 95% CI 0.18, 22.20) due to the low number of events.[17,18] Wei et al (OR 3.20, 95% CI 1.06, 9.65) and Zhang et al (OR 2.86, 95% CI 1.13, 7.24) both reported significantly higher risks in the freeze-all group.[14,15]

Our findings align with some previous studies that have reported an increased risk of pre-eclampsia with freeze-all cycles. For instance, a study by Roque et al suggested that freeze-all cycles might lead to higher rates of hypertensive disorders of pregnancy compared to fresh embryo transfers, attributing this to potential alterations in the endometrial environment following ovarian stimulation. However, our study provides more definitive evidence through the synthesis of RCT data, enhancing the credibility of the association.[15,19]

Conversely, some studies have suggested potential benefits of the freeze-all strategy in reducing the risk of OHSS and

improving live birth rates. The study by Chen et al noted that while the freeze-all strategy might increase pre-eclampsia risk, it could mitigate the risk of OHSS, which remains a critical consideration in IVF treatments.[12] Therefore, the decision to employ freeze-all cycles should balance the increased risk of pre-eclampsia against these other potential benefits.

The increased risk of pre-eclampsia in freeze-all cycles may be explained by several potential mechanisms. One hypothesis suggests that the hormonal environment in frozen-thawed embryo transfer cycles differs significantly from that in fresh cycles.[10,19] In fresh cycles, elevated levels of estrogen and progesterone immediately after ovarian stimulation may impact placental development differently than the more controlled hormonal environment in frozen-thawed cycles. This altered hormonal milieu may affect the implantation process and subsequent placental development, contributing to the increased risk of pre-eclampsia.[19,20]

Another consideration is the difference in endometrial preparation between fresh and frozen cycles. In freeze-all cycles, the endometrium is prepared either through natural or hormone replacement therapy cycles, which might not perfectly mimic the natural endometrial environment following ovarian stimulation. This discrepancy could influence the uteroplacental interface and placental function, potentially leading to an increased incidence of pre-eclampsia.[19,21]

The findings of this meta-analysis have significant clinical implications. Given the higher risk of pre-eclampsia associated with freeze-all cycles, clinicians should carefully consider this risk when planning IVF treatment strategies. It may be prudent to reserve the freeze-all strategy for cases where it is clearly indicated, such as in patients at high risk for OHSS or when there are concerns about the endometrial receptivity in fresh cycles.[22,23]

Furthermore, patients should be counselled about the potential increased risk of pre-eclampsia with freeze-all cycles. This information is crucial for informed decision-making and for managing patient expectations. Additionally, close monitoring for signs of pre-eclampsia should be emphasized in pregnancies resulting from freeze-all cycles to ensure early detection and management of this condition.[6,22,23]

Limitations

While this meta-analysis provides robust evidence of an increased risk of pre-eclampsia with freeze-all cycles, several limitations should be acknowledged. First, although the included studies were RCTs, there were variations in study design, population characteristics, and methods of endometrial preparation, which could influence the findings. Second, the number of events in some studies was relatively low, leading to wide confidence intervals and less precise estimates of effect sizes in those studies.

Future research should focus on large, multicentre RCTs to confirm these findings and further elucidate the mechanisms underlying the increased risk of pre-eclampsia with freeze-all cycles. Additionally, studies should explore whether specific subgroups of patients (e.g., those with certain baseline characteristics or comorbidities) are at higher risk and might benefit more from alternative strategies. Investigating the optimal methods of endometrial preparation in frozen-thawed cycles could also provide insights into mitigating the increased risk of pre-eclampsia.

CONCLUSION

In conclusion, this meta-analysis of seven RCTs demonstrates a significant association between the freeze-all strategy in IVF and an increased risk of pre-eclampsia. The pooled odds ratio of 2.14 (95% CI 1.47, 3.11) highlights a more than two-fold increase in risk, consistent across studies with low heterogeneity. These findings underscore the need for careful consideration of the risks and benefits when choosing the freeze-all strategy for embryo transfer. Clinicians should weigh the increased risk of pre-eclampsia against potential benefits, such as reduced OHSS risk, and ensure thorough counselling and monitoring for patients undergoing freeze-all cycles. Future research should aim to confirm these findings and explore strategies to mitigate the associated risks, ultimately.

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