

Review Article

Differences between fresh embryo transfer and frozen embryo transfer in Asian populations: a meta-analysis

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Received November 29, 2017; Accepted July 5, 2018; Epub September 15, 2018; Published September 30, 2018

Abstract: Objective: We appraise and identify the current evidence regarding the clinical outcomes in frozen embryo transfer and fresh embryo transfer to improve assisted reproductive technology in the Asian population. Methods: A literature search of the PubMed, Web of Science, and EMBASE databases was conducted for articles published from inception to August 13, 2017. The primary outcomes were clinical pregnancy, ectopic gestation, premature delivery, small-for-gestational-age infants, and large-for-gestational-age infants. The secondary outcomes were still-birth, very low birth weight, pregnancy-induced hypertension syndrome, placental accreta, and placental abruption. Results: Of 1660 screened records, nine eligible studies (431316 patients) met the inclusion criteria. The results demonstrated that frozen embryo transfer had lower risks of ectopic gestation (OR = 0.42; 95% CI = 0.37-0.49), premature delivery (OR = 0.94; 95% CI = 0.91-0.97), small-for-gestational-age infants (OR = 0.60; 95% CI = 0.58-0.62), very low birth weight (OR = 0.76; 95% CI = 0.71-0.81), placental abruption (OR = 0.65; 95% CI = 0.53-0.78), and still birth (OR = 0.83; 95% CI = 0.73-0.95) than fresh embryo transfer. However, risks of large-for-gestational-age infants (OR = 1.66; 95% CI = 1.43-1.93), pregnancy-induced hypertension syndrome (OR = 1.52; 95% CI = 1.43-1.61), and placental accreta (OR = 2.27; 95% CI = 1.58-3.25) were high in frozen embryo transfer. We further found that there were no significant differences in miscarriage (OR = 1.10; 95% CI = 0.91-1.31) when we compared frozen embryo transfer and fresh embryo transfer protocols. Conclusion: For most Asians, frozen embryo transfer is a better choice than fresh embryo transfer, although the former has some side effects.

Keywords: Assisted reproductive techniques, fresh embryo transfer, frozen embryo transfer, abortion, infant, meta-analysis

Introduction

Since the birth of the first infant conceived by frozen-thawed embryo transfer (T-ET, Frozen ET) in 1984 [1, 2], the proportion of thawed embryo transfer has increased significantly, not only because of the refinement of laboratory techniques, but also because protocols of frozen-thawed embryo transfer are simpler than fresh embryo transfer (Fresh ET). In frozen-thawed embryo transfer cycles, the main aim is to prepare suitable endometrium, giving time to the ovary to recover from controlled ovarian stimulation (COS), avoiding embryo transfer into an adverse endocrinologic profile or endometrial cavity. Shifting fresh embryo transfer

(Fresh ET) to frozen-thawed embryo transfer (Frozen ET) is becoming more common in many programs [3]. However, some still disagree about how to choose a transplant protocol (frozen or fresh), and the safety of mothers and infants after transplant is also a matter of concern. Multiple studies compared the obstetric and perinatal outcomes, but the results were controversial. A Catalan cohort study showed that infants born after frozen embryo transfer were likely to get a higher birth weight and a higher risk of being large-for-gestational-age infants (LGA). Luke et al. drew the same conclusions [4, 5], whereas some clinical experiments concluded that frozen-thawed and fresh transfer had similar possibilities of pregnancy and

perinatal outcomes [6, 7]. In addition, some meta-analyses proved that frozen-thawed ET had a better perinatal outcome than fresh in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) transfer [8, 9], although a meta-analysis of four randomized clinical trials demonstrated that the freeze-all strategy had a higher rate of pregnancy complications and no difference in cumulative live birth rate than the IVF/ICSI strategy [10].

Different researchers maintain different opinions when comparing the differences between Fresh ET and Frozen ET. Most of them ignored the impact of race on fertility. Racial disparities emerged in many aspects of female reproductive health, such as spontaneous abortion, infertility, and pregnancy-related mortality. The current study shows that the fertility of different races are not identical, and racial disparities could have some effects on the outcomes of in vitro fertilization (IVF) [11, 12]. Thus, several eligible studies concerning Asian people were sought and analyzed, and this systematic review was performed to compare and assess the differences of pregnancy and perinatal outcomes between Fresh ET and Frozen-thawed ET in the Asian population.

Materials and methods

Search strategy

A systematic search of the Web of Science, PubMed, and EMBASE was conducted for articles published from inception to August 13, 2017. We used the following key words and combined them variously: fresh embryo transfer, fresh ET, in vitro fertilization, intracytoplasmic sperm injection, frozen embryo transfer, frozen-thawed embryo transfer, outcome, complication, IVF, ICSI, and FET. We scanned the reference lists of the included articles for any additional relevant studies.

Selection criteria and quality appraisal

The inclusion criteria were as follows: (1) original articles comparing pregnancy and neonatal outcomes after fresh embryo transfer versus frozen embryo transfer; (2) studies that explored Asian-specific ethnicity; (3) the freezing technique of the studies were vitrification freezing; (4) the articles were published in English or Chinese language; (5) retrospective

study, cohort study, and randomized controlled trial. Because most of the included literature did not specify ethnicity, we classified race based on the region and language. For example, if the study was conducted in China, we assumed all patients were Asian. The exclusion criteria were as follows: (1) case reports, editorials, letters, reviews, and meta-analyses; (2) duplication trials, subanalysis, substudies, and extension studies; (4) incomplete data.

Outcome measures

The primary outcomes were clinical pregnancy, ectopic gestation, miscarriage, premature delivery, small-for-gestational-age infants (SGA), and large-for-gestational-age infants (LGA). The secondary outcomes were stillbirth, very low birth weight (VLBW), pregnancy-induced hypertension syndrome (PIH), placental accreta, and placental abruption. We defined clinical pregnancy as pregnancy with gestational sac observed on ultrasound scan before the eighth week of gestation. Ectopic gestation was embryo implanting extra-uterus, diagnosed by laparoscopy or ultrasound. Miscarriage was defined as spontaneous abortion before 20 weeks. Premature delivery was infants born before 37th week of gestation. According to the local standard of newborns' weight, VLEW, SGA, and LGA infants were defined as babies with birth weight less than 1500 g, less than 10th percentile, and over 90th percentile of local standards.

Data extraction and quality assessment

According the inclusion criteria and exclusion criteria, all relevant data was extracted from each research process by two investigators (Yezhou Su, Ying Zhang); if they disagreed during this process, they discussed their differences with the professional investigator (Yunxia Cao) until a consistent opinion was reached. The article quality was evaluated by two authors (Huifen Xiang and Zuying Xu) independently, using Newcastle-Ottawa Quality Assessment Scales, and any disagreement would be solved by team discussion. If necessary, study authors were contacted for more information.

Statistical analysis

Nine studies were included for data extraction. Review Manager 5.3 software was used to per-

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Table 1. The general characteristic of the included studies

Study	Country	Sample size	Study duration	Type of study	The number of embryo transfer	The type of transplanted embryo		Outcome
						Frozen ET	Fresh ET	
Abbas 2010	Iran	700	2006-2008	Retrospective study	2/3	D2/D3 embryo	D2/D3 embryo	Abortion, Preterm birth, Birth weight (LBW), Still birth
Ali 2016	Iran	1419	2010-2014	Retrospective study	2/3	D2 embryo	D2 embryo	Ectopic pregnancy, Still birth, LBW, SGA
Kato 2012	Japan	6623	2008-2008	Retrospective study	1	Cleavage stage embryo/blastocyst	Cleavage stage embryo/blastocyst	Preterm birth, Still birth, SGA, LGA, Birth weight (LBW, vLBW)
Kazumi 2015	Japan	141228	2007-2012	Retrospective study	1/2/3/more	Early cleavage stage embryo/blastocyst	Early cleavage stage embryo/blastocyst	Preterm birth, SGA, LGA, Birth weight (LBW, VLBW), Pregnancy complications
Osamu2014	Japan	277,042	2008-2010	Retrospective study	1	Blastocyst	Blastocyst	Clinical pregnancy, Ectopic pregnancy, Miscarriage, SGA, LGA, Birth weight (LBW, vLBW), Pregnancy complications
Ku 2012	China (Taiwan)	177	2009-2011	Retrospective study	No mention	Blastocyst	Blastocyst	Clinical pregnancy, Miscarriage
Kemal 2015	Turkey	1166	2012-2013	Retrospective study	2	Blastocyst	Blastocyst	Clinical pregnancy, Miscarriage, Still birth, Preterm birth, Birth weight (LBW, vLBW)
Sun 2017	China	2091	2011-2015	Retrospective study	2/3	D3 embryo	D3 embryo	Clinical pregnancy, Preterm birth, Birth weight (LBW)
Wang 2015	China	870	2013-2014	Retrospective study	1/2/3	D3 embryo/Blastocyst	D3 embryo/Blastocyst	Clinical pregnancy, Miscarriage

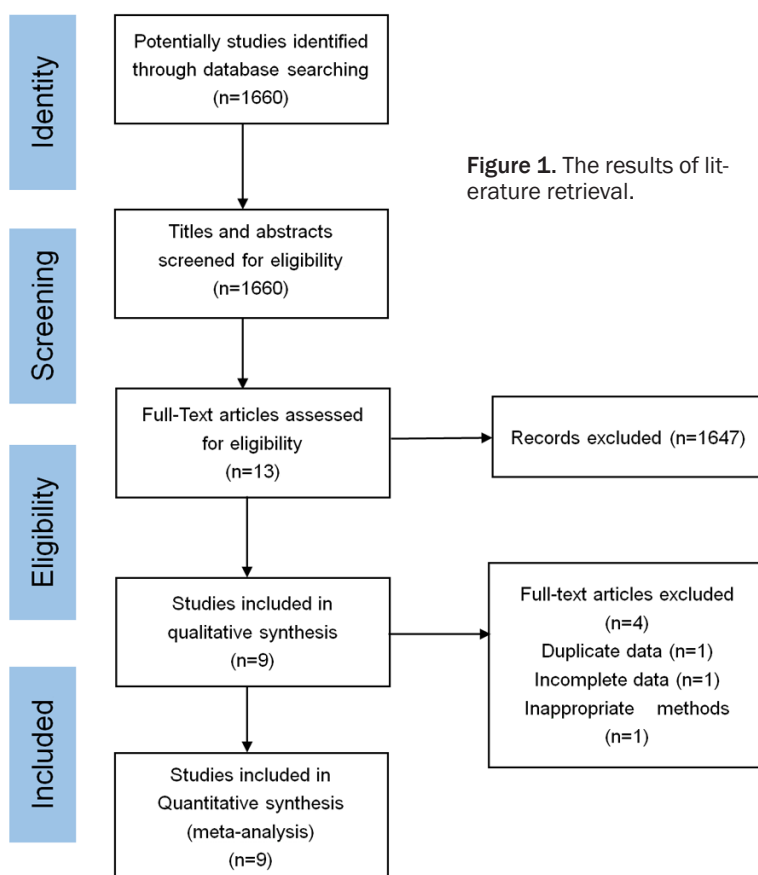


Figure 1. The results of literature retrieval.

st of these articles have been published since 2014. The number of patients in each study ranged from 177 to 277,042. Three studies were from China, three from Japan, two from Iran, and one from Turkey. Seven studies explored the rates of premature delivery and miscarriage after Frozen ET and Fresh ET in Asian women, six and five papers investigated clinical pregnancy in Frozen and Fresh ET, respectively. Four eligible studies involved ectopic gestation, SGA infants, and VLBW after Frozen and Fresh ET. Three articles included LGA infants, and two articles compared differences of complications between Frozen and Fresh ET in Asian individuals. The detailed study characteristics were listed in **Table 1**. The flowchart was depicted in **Figure 1**.

Meta-analysis

form the meta-analysis. Odds risk (ORs) and 95% confidence intervals were calculated to describe the results. I^2 and P -value were used to explore the heterogeneity; if $I^2 < 50\%$ or $P < 0.10$, the ORs were pooled using the fixed-effect model; if not, a random-effect model was considered. A P -value less than 0.05 was significant. A forest plot and a funnel plot display the results and publication bias.

Result

The search strategy yielded 1660 studies. After reading the titles, abstracts, and authors' addresses, 1647 articles were excluded because of unrelated study, repetition, and non-Asian studies. Among the remaining articles, one article was excluded because the data had been reused, and the data for another one was incomplete; another two articles were excluded because their methods were not appropriate.

In the end, 9 papers [7, 12-19] (431316 patients) were chosen for this meta-analysis. Mo-

Clinic pregnancy (Figure 2): Five studies were included to compare clinical pregnancy in Frozen ET versus Fresh ET. No significant differences were found ($OR = 1.06$; 95% $CI = 0.63-1.76$; $P = 0.83$). There was an important heterogeneity ($I^2 = 97\%$, $P < 0.00001$).

Ectopic gestation rate (Figure 3): Four studies assessed ectopic gestation between Frozen ET and Fresh ET, and there were no significant differences between the two groups ($OR = 0.42$; 95% $CI = 0.37-0.49$; $P < 0.00001$). Because heterogeneity was found in this comparison ($I^2 = 0\%$, $P = 0.71$), the fixed-effect model was applied.

Miscarriage rate (Figure 4): Seven studies were enrolled in the comparison. Miscarriage rate of Frozen and Fresh ET was obtained from these papers, and the data was pooled. No significant differences of miscarriage were found between Frozen ET and Fresh ET, and there was no significant heterogeneity in this comparison ($OR = 1.10$, 95% $CI = 0.91-1.31$, $P = 0.32$; $I^2 = 44\%$; $P = 0.1$).

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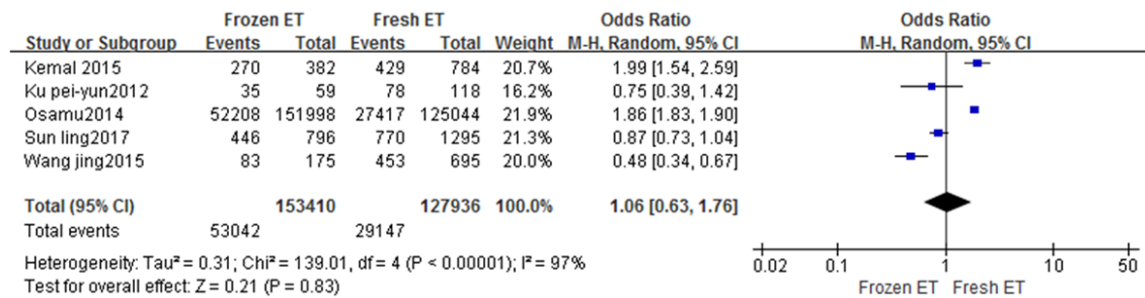


Figure 2. Forest plot of study assessing clinical pregnancy rate of frozen ET and fresh ET.

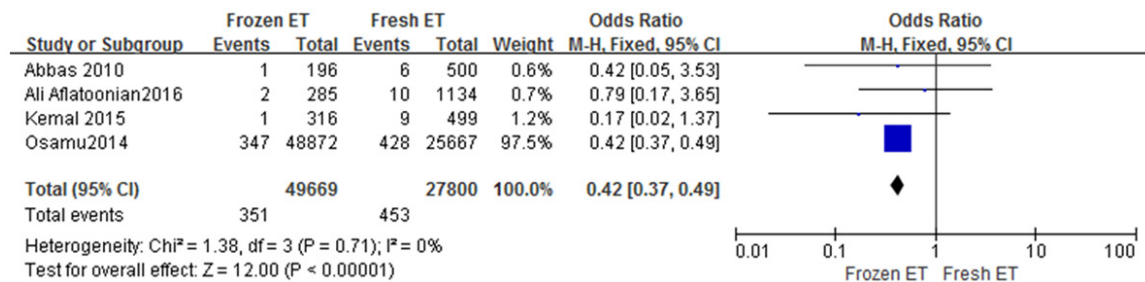


Figure 3. Forest plot of study assessing ectopic gestation rate of frozen ET and fresh ET.

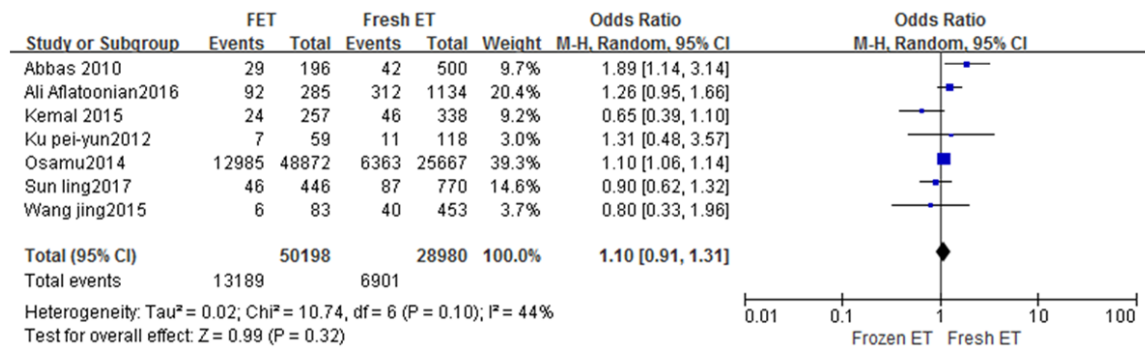


Figure 4. Forest plot of study assessing miscarriage rate of frozen ET and fresh ET.

Premature delivery rate (Figure 5): Seven eligible studies evaluated the difference of premature delivery rate in Frozen and Fresh ET, and a significant difference was found between the two groups (OR = 0.94, 95% CI = 0.91-0.97, P = 0.0001); this comparison had no heterogeneity (I² = 0%, P = 1).

Stillbirth rate (Figure 6): We identified five studies that reported on stillbirth. We found a significant decline of stillbirth rate in Frozen ET compared with Fresh ET (OR = 0.83; 95% CI = 0.73-0.95; P = 0.009). There was no heterogeneity in the comparison (I² = 0%, P = 0.97).

Large-for-gestation-age (LGA) infants (Figure 7): In the assessment of LGA from three stud-

ies, the risk of LGA after Frozen ET was higher than it was after Fresh ET (OR = 1.66, 95% CI = 1.43-1.93, P < 0.00001), and a remarkable heterogeneity should be noticed (I² = 94%; P < 0.00001).

Small-for-gestation-age (SGA) infants (Figure 8): We enrolled four studies to compare SGA between Frozen ET and Fresh ET. The risk of SGA in Frozen ET was lower (OR = 0.60, 95% CI = 0.58-0.62, P < 0.00001), and heterogeneity was not significant (I² = 45%, P = 0.14).

Very low birth weight (VLBW) infants (Figure 9): Four studies were considered to analyze the risk of VLBW; we discovered that Frozen ET had

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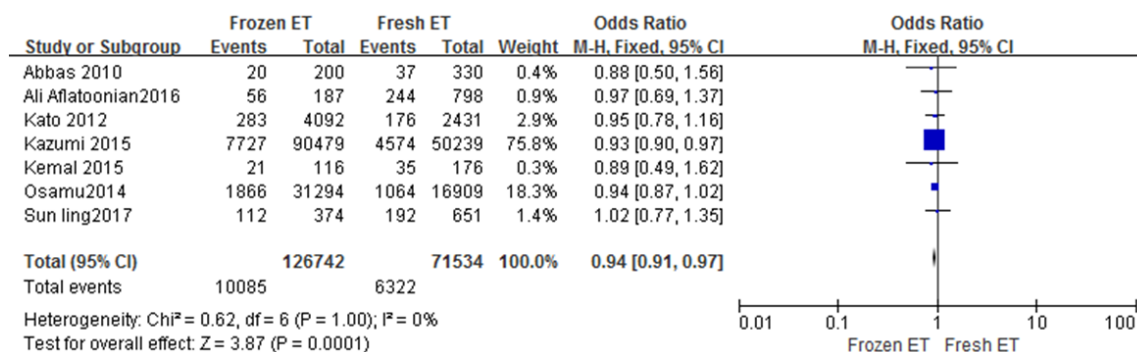


Figure 5. Forest plot of study assessing premature delivery rate of frozen ET and fresh ET.

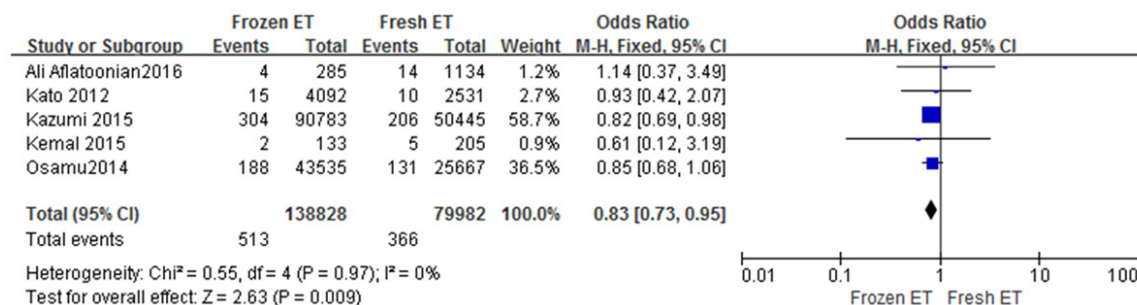


Figure 6. Forest plot of study assessing stillbirth rate of frozen ET and fresh ET.

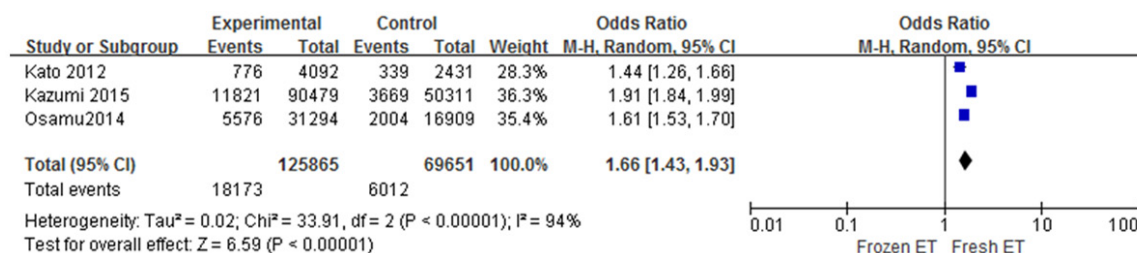


Figure 7. Forest plot of study assessing LGA rate of frozen ET and fresh ET.

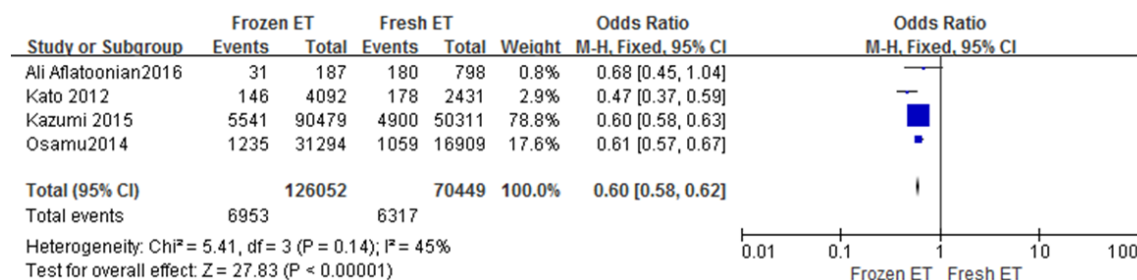


Figure 8. Forest plot of study assessing SGA rate of frozen ET and fresh ET.

a lower risk of VLBW than Fresh ET (OR = 0.76, 95% CI = 0.71-0.81, $P < 0.00001$), and heterogeneity was not significant ($I^2 = 49\%$, $P = 0.12$).

Complications

Two articles compared complications (including pregnancy-induced hypertension syndrome,

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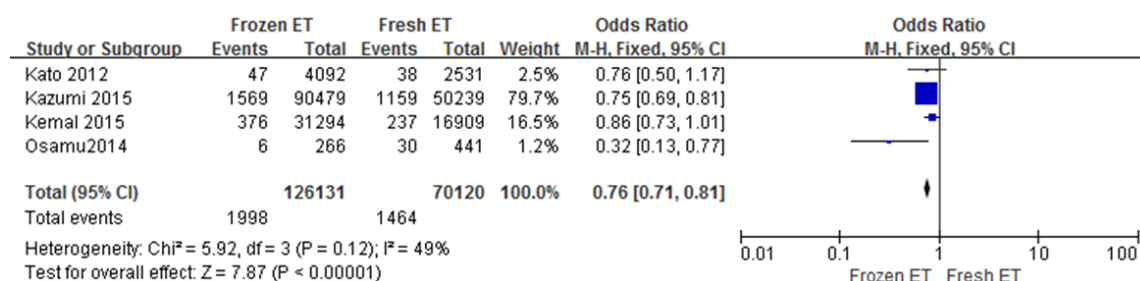


Figure 9. Forest plot of study assessing VLBL rate of frozen ET and fresh ET.

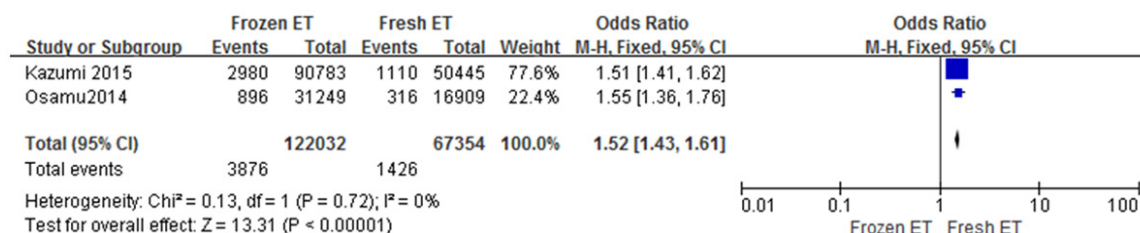


Figure 10. Forest plot of study assessing PIH rate of frozen ET and fresh ET.

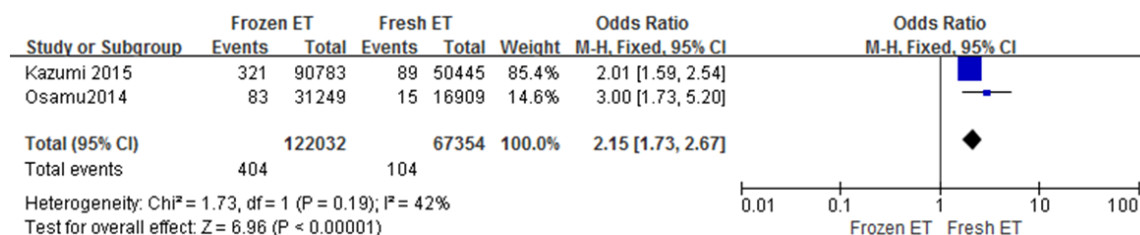


Figure 11. Forest plot of study assessing placental accreta rate of frozen ET and fresh ET.

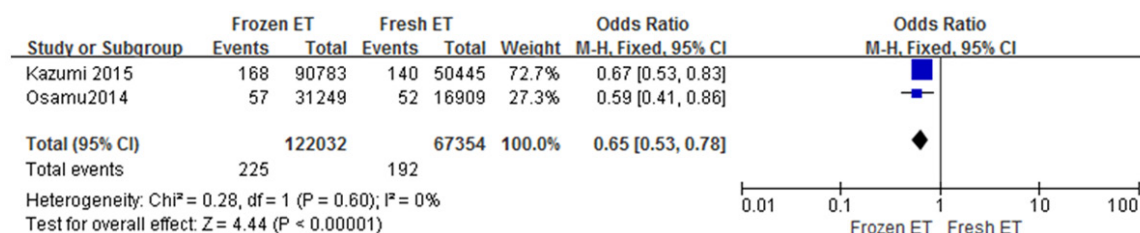


Figure 12. Forest plot of study assessing placental abruption rate of frozen ET and fresh ET.

placenta previa, placenta abruption, and placenta accreta) between frozen single-embryo transfer and fresh single-embryo transfer. We found Frozen ET had a higher risk of pregnancy-induced hypertension syndrome (OR = 1.52, 95% CI = 1.43-1.61) (Figure 10) and placental accreta (OR = 2.27, 95% CI = 1.58-3.25) (Figure 11) and a lower risk of placental abruption (OR = 0.65, 95% CI = 0.53-0.78) (Figure 12) than Fresh ET. The heterogeneity of these comparisons was not significant. In addition,

there was no significant difference of placental previa between Frozen ET and Fresh ET (OR = 0.77, 95% CI = 0.59-1.00) (Figure 13), but the result was not certain because the heterogeneity was high ($I^2 = 79\%$, $P = 0.03$).

Publication bias

We performed funnel plots (not listed in this article) for every comparison to investigate whether most of the studies were on the same

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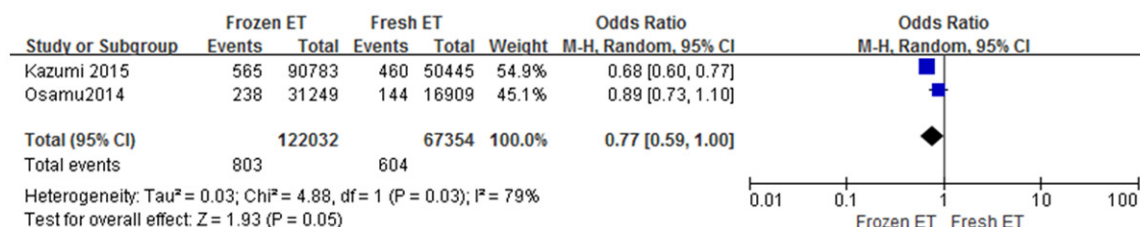


Figure 13. Forest plot of study assessing placental previa rate of frozen ET and fresh ET.

side of the plots, and we did not find significant publication bias, according to each symmetrical shape.

Discussion

A meta-analysis is an important tool to solve a problem with an uncertain conclusion. It synthesizes individual data, which is less influenced by authors, so it can provide unbiased conclusions. Between Frozen ET and Fresh ET, which one has better pregnancy and perinatal outcomes and what is the best way to choose the appropriate strategies? The reviewers hold different opinions. Although some meta-analyses have compared the outcomes between Frozen ET and Fresh ET [8, 9, 12, 20-22], few of them take into account racial disparities. Besides, different areas and racial disparities could influence the results [11, 23]. Our meta-analysis compared pregnancy and perinatal outcomes subsequent to Frozen ET and Fresh ET based on the Asian population, and we demonstrated that Frozen ET had lower risks of ectopic gestation, premature delivery, small-for-gestational-age infants, very low birth weight, placental abruption, and stillbirth than Fresh ET. However, risks of large-for-gestational-age, pregnancy-induced hypertension syndrome, and placental accreta were high in Frozen ET. We further found that there were no significant differences in the rate of miscarriage when we compared frozen embryo transfer and fresh embryo transfer protocols. In addition, the conclusions were uncertain about the differences of clinical pregnancy and placental previa between Frozen ET and Fresh ET because of the obvious heterogeneity.

Our results provided strong evidence that the risk for ectopic pregnancy in the Frozen ET group was lower than in the Fresh ET group among the Asian population. It was consistent with some non-Asian studies [24-26]. The possible explanation was that supraphysiologic hormone levels resulting from the controlled

ovarian stimulation (COS) could influence endometrial receptivity [18, 19, 21-30], and uterine contractility [31]. Some authors suggested COS might also induce endometrial morphology, biochemistry, and functional genomic modifications [32, 33]. Furthermore, some studies indicated oral contraceptives [34] or progestins 1071426 which were used to initiate an ovarian stimulation cycle might have adverse effects on endometrial receptivity. Poor endometrial receptivity and uterine contractility may prevent normal intrauterine implantation in Asian individuals.

In terms of birth weight of Asian infants, the risk of very low birth weight (VLBW) was significantly reduced with Frozen ET compared with Fresh ET. Similarly, the low risk of VLBW subsequent to Frozen ET was reported in some cohort studies [5, 35, 36]. Because birth weight was associated tightly with gestational age, we also compared SGA and LGA and found decreased risk of SGA and increased risk of LGA with Frozen ET among Asian patients. Birth weight may affect some aspects of infants in their adulthood [37]. In clinic, when the couples want to have a child by using the Frozen ET technique, they should know the child is likely to suffer obesity, insulin resistance, and other diseases; they should also be informed that infants born after Fresh ET are prone to minor cognitive deficiencies, scholastic difficulties, and metabolic syndrome in adulthood, compared with Frozen ET [38]. The reason why babies born after Frozen ET had a heavier weight than Fresh ET was unknown. The Weinerman et al. study revealed increased median umbilical artery resistance and decreased microvascular density in the placentae of mouse near-term exposed to superovulation compared to naturally mated mouse [39]. Two other studies indicated difference in birth weight between fresh embryo transfer and frozen embryo transfer could only be observed during the autologous cycle and could not be found during the donat-

ed oocytes cycle [5, 40]. Thus, we could suppose that it was the superovulation environment, not the freezing process that affected the fetal birth weight. The stillbirth rate in Asian individuals was lower in the Frozen ET group than in the Fresh ET, according to our results. We speculated that low odds of stillbirth may be related to the decrease of SGA [41]. Another possible interpretation was that the process of freezing and thawing was a screening for embryos. High-quality embryos could be successfully frozen and thawed, whereas low-quality embryos would be excluded in this process.

Regarding pregnancy complications, Frozen ET was significantly correlated with an increase of placental accreta and pregnancy-induced hypertension (PIH). Another meta-analysis got the similar conclusion with ours [42]. Although placental accreta was an infrequent complication, it could lead to serious consequences, such as heavy bleeding at the time of attempted vaginal delivery, and even hysterectomy. The pathogenesis of placental accreta was absence of the decidua basalis and the Nitabuch layer. PIH was one of the most common disorders during pregnancy; it was also related to placenta. The actual reasons that placental accreta and PIH were associated with Frozen ET were unclear. One possible explanation was that all these placenta-related complications might be caused by abnormal placentation. Frozen ET might produce an environment that was not conducive to normal placenta formation. An earlier paper was compatible with our explanation; it suggested that Fresh ET had a lower risk of abnormal implantation than Frozen ET, and this abnormal implantation may be the early manifestation associated with abnormal placentation [24]. To our knowledge, PIH, especially preeclampsia, was one of the major causes of placental abruption [43]. Paradoxically, lower odds of placental abruption were found with Frozen ET in Asian individuals, and we did not know the reason. In addition, differences in gene expression between fresh embryo and frozen-thaw embryo were reported in frozen-thawed embryos. These differences might result in the adverse pregnancy outcomes after Frozen ET [44]. However, there were only two independent studies of these comparisons; more clinical experiments should be investigated and then included to certify these results.

Our meta-analysis assessed the risk for pregnancy-specific disease of Asian individuals

between two strategies for the first time. This study also had three limitations. First, the relevant studies in this article were searched using the English and Chinese languages; therefore, some potential non-English and non-Chinese publications may have been excluded. Second, the number of Fresh ET or Frozen-thawed ET in some studies were not sufficient, with some characteristics and outcomes not mentioned in some of them, so the comparison may have exhibited biases. Last, some findings had significant heterogeneity ($I^2 > 50\%$ or $P < 0.10$).

Conclusion

A frozen embryo transfer strategy could decrease the risks of ectopic gestation, premature delivery, SGA, VLBW, placental abruption, and stillbirth over those with a fresh embryo transfer strategy, whereas a fresh embryo transfer strategy could decrease the risks of LGA, PIH, and placental accreta over those with a frozen embryo transfer strategy in Asian people. Therefore, frozen embryo transfer is a better choice for most Asians. When the choice of frozen embryo transfer is selected by patients, they should be informed of the relevant risks in advance, especially of PIH.

Acknowledgements

This work was supported by National Natural Science Foundation of China (81501232) and Public Welfare Technology Application Research Linkage Project of Anhui Province (1704f0804022).

Disclosure of conflict of interest

None.

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