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Birth weight following frozen *versus* fresh embryo transfer: a retrospective cohort study

Aghdas **Safari** [1,*], Shima **Mohammadian** [2], Bahareh **Khakifirooz** [2]

[1] Department of Obstetrics and Gynecology, Faculty of Medicine, Aja University of Medical Sciences, Imam Reza Hospital, Tehran, Iran.
[2] Department of Gynecology Oncology, Faculty of Medicine, Alborz University of Medical Sciences, Kamali Hospital, Tehran, Iran.

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***Corresponding author:** Aghdas **Safari**, Dr., M.D., Assistant Professor. Department of Obstetrics and Gynecology, Imam Reza Hospital, Western Fatemi Street, Tehran, Iran 1411718541.
Email: dr.safari@ajaums.ac.ir.
ORCID: 0009-0006-4871-2316.

ABSTRACT

Objective. Birth weight is an outcome to evaluate the safety of assisted reproductive technology. The objective of this study was to compare the effect of frozen *versus* fresh embryo transfer on newborn birth weight.

Patients and Methods. In the infertility department of a teaching hospital affiliated with a university of medical sciences, we performed a retrospective cohort study. Eligible women were ≥ 18 years old and conceived a singleton pregnancy (≥ 22 weeks or ≥ 500 g) with either frozen or fresh embryo transfer. None of the patients had diabetes, hypertension. We recorded maternal characteristics, newborn features, and perinatal outcomes.

Results. In total, 116 eligible patients with a mean (SD) age of 32.7 (5.8) years and a mean body mass index of 25.6 (2.5) were included. Of these, 84 had a frozen and 32 had a fresh embryo transfer. Mean birth weights were 3,050.7 (587.6) and 2,983.6 (423.5) in the frozen and fresh embryo transfer groups, respectively ($p = 0.568$). However, after adjusting for confounding factors, including maternal age, gravidity, body mass index, fasting blood sugar, blood pressure, and gestational age, the difference in birth weight was statistically significant [b = 230.8 (103.6), $p = 0.003$]. There was no statistically significant difference between the two groups in the percentages of low birth weight, small or large for gestational age, preterm, stillbirth, or intra-uterine foetal death singletons.

Conclusions. Frozen embryo transfer results in higher birth weight compared to fresh embryo transfer. This difference was statistically significant despite similar perinatal outcomes, warranting further investigation into underlying mechanisms.

INTRODUCTION

Globally, 15% of couples of reproductive age are estimated to be infertile [1, 2]. Assisted reproductive technology (ART) is a viable option for infertile couples [2, 3]. Some studies suggest that the risks of preterm birth, low birth weight (LBW), congenital anomalies, and perinatal mortality are increased for ART singletons [4-6]. Despite these risks observed in children conceived by ART, a growing number of pregnancies are conceived through the use of ART [4]. Early-life exposure to risk factors is believed to influence the likelihood of developing diseases later in life [7, 8]. Meanwhile, ART has undergone consid-

erable changes over the last decade, and its effects on newborn's health are still an open question [5, 9, 10]. Considering the association between LBW and chronic disease in adulthood, BW is an outcome to evaluate the safety of ART [3]. The literature reports an increased proportion of LBW following fresh embryo transfer (fresh-ET) compared with spontaneous conception [11, 12]. Other studies showed a heavier birth weights, a higher proportion of macrosomia (> 4,000 g) or large for gestational age, and a lower prematurity rate following frozen embryo transfer (frozen-ET) [13-15]. Study findings might also be influenced by confounding effects of variables other than the ART procedure such as maternal age and parity, gestational age, and neonatal sex [14, 16, 17]. For the safety evaluation and standardization of the practice, the perinatal outcomes of ART still require careful evaluation [10, 18]. Also, there is limited research on the variation in BW between frozen-ET and fresh-ET based on gestational age (GA) [19].
With the increasing use of ART and conflicting reports on perinatal outcomes, a careful assessment of birth weight in ART pregnancies, particularly comparing the effects of fresh- *versus* frozen-ET, is imperative to elucidate potential risks, inform clinical decision-making, and advance our understanding of the complex relationships between ART procedures and neonatal health. We conducted this study to compare the effect of frozen-ET *versus* fresh-ET on BW. Our hypothesis was that newborn weight following frozen-ET is different from BW in pregnancies conceived with fresh-ET. We also incorporated variables other than ART procedure into our statistical models to control their confounding effects on BW.

PATIENTS AND METHODS

Design and setting
This was a retrospective cohort study of deliveries following frozen-ET or fresh-ET from 2018 to 2022. All patients were treated for infertility in the department of infertility at the Be'sat centre; a teaching hospital affiliated with Aja University of Medical Sciences, Tehran, Iran. The department is a well-equipped setting and the hospital is a large referral and subspecialty centre.

Ethical considerations
The study protocol was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the Institutional Review Board of Aja University of Medical Sciences with reference number IR.AJAUMS.REC1399.026. We used information from participants' medical records, and did not carry out measurements on any patient. No identifying information was extracted from patients' records. All participants had provided written consents for their treatment. They had received verbal and written explanations of the nature and purpose of the procedures.

Eligibility
Inclusion criteria
We included women (≥ 18 years old) who conceived a singleton pregnancy (≥ 22 weeks or ≥ 500 g) through either frozen-ET or fresh-ET. Based on the available information, the two procedures were commonly performed for patients with a tubal factor of infertility, polycystic ovary syndrome, mild to moderate decreased semen quality in the male partner, or unexplained infertility.

Exclusion criteria
None of the included patients had ovarian cysts > 12 mm, ensuring a more homogeneous study population by avoiding confounding effects from treatment measures. This allowed for a focused analysis of the specific effects of frozen- *versus* fresh-ET on birth weight. Moreover, patients with hypogonadotropic hypogonadism, endometriosis stage 3-4, and liver, kidney, or thyroid disease did not enter the study. Also, the procedures were not prescribed for women with severe diabetes, cardiovascular disease, or other comorbidities that interfered with the treatments [20]. Women who developed gestational hypertension or diabetes [21], those who underwent previous in-vitro fertilization or intracytoplasmic sperm injection (ICSI) with their current partner, and the users of donor oocytes or frozen oocytes were excluded as well. We also excluded patients with incomplete records.

Protocols and procedures
For ICSI, we performed controlled ovary stimulation. Gonadotropin-releasing hormone agonists or antagonists was used to prevent premature ovulation and to perform eggs retrieval at the optimal time. This was followed by injections of follicle-stimulating hormone until the follicular diameter of 18 mm was reached [22-24]. Then a 10,000-unit human chorionic gonadotropin (hCG) was injected and after 36 hours the oocytes were retrieved. The

process of oocyte retrieval was performed using a transvaginal ultrasound probe to guide a specialized needle through the vaginal wall and into the ovaries. A needle was used to aspirate the mature follicles and transfer them to the laboratory. The oocyte was carefully examined under a microscope for maturity, the sperm was injected into the oocyte cytoplasm using a micromanipulator, and the oocyte was monitored for signs of fertilization. Three to five days later, the embryo was transferred into the uterus using a thin catheter through the cervix. Patients underwent frozen-ET, following a consistent protocol across the study cohort [25-27]. The retrieved oocytes were fertilized in the laboratory with ICSI. The resulting embryos were cultured for several days until the endometrial thickness reached to at least 7 mm. Then the embryos were cryopreserved using vitrification. Embryos were frozen for 3 months to 2 years. They were frozen in 8-cell form and transferred to the incubator for 2 days. They were transferred to the uterus as 5-day embryos. The endometrium was primed with estradiol and the frozen embryos were thawed and transferred into the uterus using a flexible catheter under ultrasound guidance. The luteal phase was supported using progesterone injections. Two weeks later, pregnancy was investigated using a serum beta-hCG test and sonography.

Data collection

Body mass index (BMI; kg/m^2) was calculated using recorded weight (kg) and height (m) squared [28]. Systolic (SBP) and diastolic (DBP) blood pressures (mmHg) were documented with a cuff mercury sphygmomanometer after a 10 min rest. Patients were classified as having blood hypertension if SBP ≥ 130 and/or diastolic ≥ 85 mmHg, or if they were using anti-hypertensive medication due to a history of hypertension. Gestational hypertension was identified if recorded blood pressure > 140/90 mm Hg in a woman who had normal blood pressure prior to 20 weeks and without proteinuria [29]. Preeclampsia was diagnosed if a patient with gestational hypertension also had proteinuria [30]. Diabetes was assessed if a fasting blood sugar (FBS) was ≥100 mg/dL or if the patient was using medication for elevated glucose levels. Gestational diabetes was diagnosed if two or more of the following criteria were met: FBS ≥ 95, a 100 g glucose oral tolerance test result ≥ 180 at one hour, ≥ 155 at two hours, or ≥ 140 mg/dL at three hours [31].

Statistical analyses

Results are presented as mean (SD) for continuous variables, and as absolute numbers (%) for categorical data. The means of the continuous variables were compared using independent t-tests. For testing differences among the study groups, χ^2 tests were used. We developed a multivariable linear model to predict neonates' BW using maternal characteristics and neonates' sex. The level of significance was set at two-tailed $\alpha = 0.05$. All data analyses were performed with R version 4.0.2 for Windows (https://www.r-project.org/).

RESULTS

Sample

Out of 232 reviewed records, 116 were excluded for the following reasons: 22 women were still pregnant, 10 had thyroid disease, 11 developed gestational diabetes, 12 were diagnosed with gestational hypertension, 30 conceived twins or multiple pregnancies, 20 were users of donated oocytes, and 11 had incomplete records. The remaining analytic sample included 116 patients (32 fresh-ET and 84 frozen-ET) with a mean (SD) age of 32.7 (5.8) years and a range of 19 and 46 years.

Mean gestational age was 30.43 (12.56) with a range of 5 to 41 months. Mean BMI was 25.6 (2.5) with a minimum and maximum of 20.5 and 30.1 kg/m^2. **Table 1** shows the characteristics of the study sample. The two ART groups did not differ significantly in maternal characteristics. Lack of difference in the sex of neonates indicates that the results of our analysis was not confounded by neonate sex.

Univariate Analysis

Table 2 shows the univariate comparisons of pregnancy outcomes in fresh-ET *versus* frozen-ET. There were no statistically significant differences between the two ART groups in pairwise comparisons. Meanwhile, of the 6 large for gestational age (LGA) singletons, all belonged to the frozen-ET group. Also, most low-birth-weight singletons belonged to the frozen-ET group. This might be due to more frequent preterm infants in the frozen-ET group. These showed a higher variability of BW for frozen-ET. **Figure 1** illustrates BW distribution (left panel) and its relation with GA (right panel) in both ART groups. Live preterm (< 37 w) neonates were more frequent in the frozen-ET group. The regression lines are not coincident.

Table 1. *Pairwise comparisons of maternal characteristics between the study groups.*

Characteristic	ART Group		p
	fresh-ET (n = 32)	frozen-ET (n = 84)	
Age (year)	31.7 (5.4)	33.0 (6.3)	0.252
Gestational Age (month)	30.5 (13.0)	30.4 (12.5)	0.972
Baseline BMI (kg/m^2)	26.1 (2.7)	25.4 (2.4)	0.196
SBP (mmHg)	117.2 (6.5)	117.4 (7.3)	0.857
DBP (mmHg)	81.6 (5.9)	82.5 (6.8)	0.465
FBS (mg/dL)	87.3 (9.6)	89.3 (8.5)	0.318
Sex of the Neonate (male)	10 (45.5%)	32 (50.8%)	0.854
Gravidity 0	18 (56.2%)	57 (67.9%)	0.341
Gravidity 1	14 (43.8%)	27 (32.1%)	

*Significant at p < 0.05; ART: Assisted Reproductive Technology; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBS: Fasting Blood Sugar.

Table 2. *Univariate pairwise comparisons of perinatal outcomes between the two ART groups.*

Characteristic	ART Group		p
	fresh-ET (n = 32)	frozen-ET (n = 84)	
BW (g)	2,983.6 (423.5)	3,050.7 (587.6)	0.568
LBW	2 (9.1%)	14 (22.2%)	0.298
SGA	6 (27.3%)	7 (11.5%)	0.160
AGA	16 (72.7%)	48 (78.7%)	0.784
LGA	0 (0.0%)	6 (9.8%)	0.295
Preterm	14 (43.8%)	46 (54.8%)	0.394
Stillbirth or IUFD	10 (31.2%)	21 (25.0%)	0.656

*Significant at p < 0.05; BW: Birth Weight; LBW: Low Birth Weight; SGA: Small for Gestational Age; AGA: Appropriate for Gestational Age; LGA: Large for Gestational Age; GA: Gestational Age; IUFD: Intra-Uterine Foetal Death.

Multivariate Analysis

To more investigate the effects of ART on BW we developed a multivariable linear model for predicting BW adjusted for age, baseline BMI, FBS, gravidity, SBP, and GA and neonate's sex. However, because of the difference in GA range between fresh-ET and frozen-ET, we restricted GA to the range of 36 to 40 weeks (n = 69). **Table 3** shows the result of the linear regression, $F(9, 59) = 4.409$, $p < 0.001$, adjusted R squared = 0.31. Overall, the model implied that ART and GA were significant predictors of BW. These are plausibly compatible with the scatterplot of BW *versus* GA (Figure 1; Right) as BW increases with increasing GA and the regression line for frozen-ET was higher than fresh-ET. Neither the sex of the neonate nor the maternal characteristics had a significant effect on the weight of the neonate. Overall, while the univariate analyses did not find a statistically significant effect on BW, the adjusted results in the multivariate model showed a significant association of ART type with BW. The model showed that ART type is a significant predictor of BW.

DISCUSSION

We conducted this study to investigate the effects of frozen-ET *versus* fresh-ET on BW. Patients without pregnancy complications were included in our study. The two ART groups of mothers were comparable in their maternal characteristics. Also, the two procedures were not statistically different concerning BW and the percentages of neonates' sex, preterm babies, and stillbirth or IUFD singletons. However, we incorporated variables in addition to ART into a multivariable linear model to control their effects on BW. Our model indicated that newborn weight following frozen-ET is different from BW in pregnancies conceived with fresh-ET. Considering the same GA interval, neonates in the frozen-ET were heavier on average than the

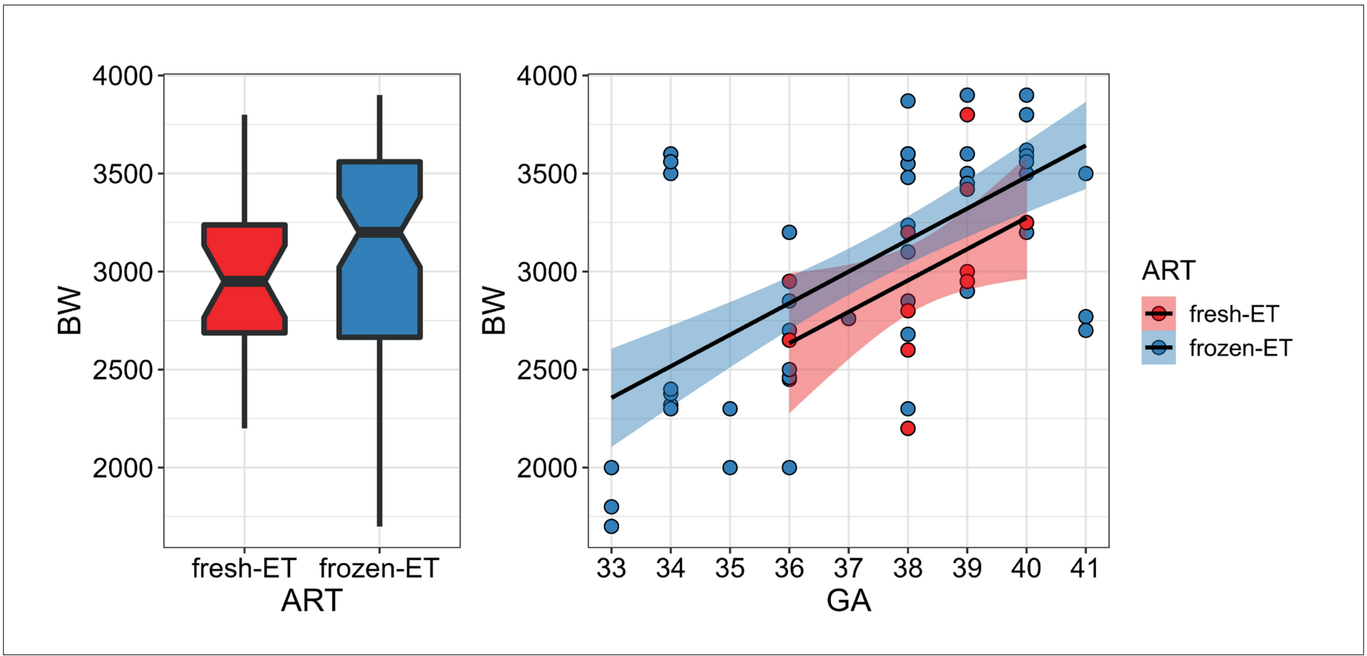

Figure 1. *Left: boxplots of BW in the study ART groups. Singletons in the frozen-ET group showed a larger variance in BW. Right: scatterplot of BW versus GA for fresh-ET and frozen-ET.*

The black lines represent linear regression and the shaded coloured areas display confidence intervals around the regression lines.

Table 3. *Multivariate linear model specification for predicting BW adjusting for cofounder variables. The ART type and GA were significant predictors of BW.*

Predictor	B (SE)	t	p
(Intercept)	-5,377.7 (1,701.2)	-3.161	0.002*
ART (frozen-ET)	230.8 (103.6)	2.229	0.003*
Age	-0.6 (8.0)	-0.077	0.939
BMI	10.0 (20.8)	0.482	0.632
FBS	7.2 (6.0)	1.187	0.240
Gravidity	55.4 (104.7)	0.529	0.599
SBP	7.5 (7.2)	1.044	0.301
GA	174.5 (35.3)	4.940	< 0.001*
Neonate's Sex (Boy)	62.4 (97.0)	0.643	0.523

* Significant at p < 0.001; ART: Assisted Reproductive Technology; BMI: Body Mass Index; FBS: Fasting Blood Sugar; SBP: Systolic Blood Pressure; GA: Gestational Age.

fresh-ET group. Not many studies have explored the differences in BW between frozen-ET *versus* fresh-ET based on specific GA [19]. However, some of our results are in accordance with a number of previously published studies.

Neonatal BW is closely associated with various perinatal and postnatal complications, such as LBW, SGA, LGA, and macrosomia. These conditions are linked to an increased risk of neonatal morbidity and mortality, as well as adverse developmental outcomes later in life, including metabolic disorders, cardiovascular diseases, and neurodevelopmental impairments [32]. In the context of ART, different embryo transfer methods – frozen *versus* fresh – may influence intrauterine growth due to variations in the uterine environment, hormonal state, and timing of implantation [33]. Therefore, comparing BW between frozen-ET and fresh-ET groups is crucial for understanding the potential different impacts of these ART procedures on foetal growth and subsequent neonatal health. Establishing whether one method confers a higher risk for aberrant BW can guide clinicians in selecting the most appropriate ART strategy, ultimately contributing to improved perinatal outcomes and long-term health of the offspring [34].

In a recently published retrospective cohort by Ding *et al.*, researchers investigated the GA-specific differences in BW between singletons born after frozen-ET (n = 13,542) and fresh-ET (n = 12,321)

[19]. They developed multivariable regression models and found that there were differences in BW and the incidence of LGA and SGA between frozen-ET and fresh-ET in full-term singletons born at ≥ 37 gestational weeks. Specifically, full-term singletons born after frozen-ET had higher BW, a higher risk of LGA, and a lower risk of SGA compared to those born after fresh-ET. However, there were no significant differences in BW or incidence of LGA and SGA between the groups in preterm singletons. They estimated a mean difference of 58.3 g in BW between frozen-ET and fresh-ET. Ding *et al*. included a large number of mothers in their study. Consequently, their study had the risk of being overpowered. Meanwhile, the difference of 58.3 g in BW is not clinically important. The reason might be the differences in maternal characteristics. Based on their published article, there were a large number of statistically significant differences in maternal features between their frozen-ET and fresh-ET groups. This might confound the results even after statistical adjustments. Our study groups were comparable in their characteristics relevant to the study question thereby reducing the potential for bias. Our study confirmed Ding's result in BW; however, we estimated a difference of 230 g in BW between the frozen-ET and fresh-ET groups within a GA range similar to their study. Our study showed that the frozen-ET group had a higher percentage for LGA and a lower for SGA. Meanwhile, the differences were not significant.

Another recent retrospective cohort was conducted with 200,075 live births in 151,561 women who underwent in-vitro fertilization between 1992 and 2017 [35]. It was reported that frozen-ET was associated with a lower risk of preterm birth, low BW, SGA, and congenital anomaly in singletons. However, frozen-ET was associated with a higher risk of high BW and LGA. Zhang *et al*. compared fresh-ET (n = 2,059) with frozen-ET (n = 2,053) in full-term singletons births [36]. The results showed that frozen-ET was associated with a higher neonatal BW, lower rates of LBW and SGA, and higher rates of macrosomia and LGA than fresh-ET. In a previous Finnish cohort study, Pelkonen *et al*. studied the perinatal outcome of children born after frozen-ET (n = 2293), fresh-ET (n = 4151), and those born after spontaneous pregnancy (reference group; n = 31 946) [14]. The data were collected between 1995 and 2006. The frozen-ET group had decreased risks of preterm birth, LBW, and SGA compared with the fresh embryo transfer group. Mean BW was 134 g higher in the frozen-ET singletons compared with the fresh-ET. Our analysis did not show significant differences between frozen-ET and fresh-ET in preterm birth, LBW, and SGA. Meanwhile, this study replicated Pelkonen's results regarding BW. The difference in BW between the frozen-ET and fresh-ET groups was higher in our study. Overall, we found that frozen-ET did not adversely affect perinatal outcomes compared to fresh-ET. But, a retrospective cohort by Ainsworth *et al*. did not imply an association between frozen-ET and increased BW when controlling for maternal factors [37]. Of course, in Ainsworth's study, most of the patients in the frozen-ET group were gravid 1, while the majority of the fresh-ET was gravid 2+. Also, patients in the fresh-ET group had higher baseline BMI. These may explain the difference between Ainsworth's results and ours regarding the association of ART with BW. Aflatoonian *et al*. included 1,134 patients using fresh-ET and 285 women who underwent frozen-ET in their study and concluded that there is no major difference regarding perinatal outcome between fresh and frozen embryo transfer. A systematic review and cumulative meta-analysis were conducted by Maheshwari *et al*. to examine perinatal outcomes in singleton pregnancies following frozen-ET and fresh-ET [38]. The review included 26 studies and found that singleton babies conceived from frozen-thawed embryos had a lower risk of preterm delivery, low BW, and SGA but faced an increased risk of hypertensive disorders of pregnancy, LGA, and high BW compared to those conceived from fresh-ET. They suggested replication in a number of different populations to provide external validity for BW and preterm delivery. We provided more evidence on the comparison of outcomes between frozen-ET and fresh-ET in an Iranian population. Aside from the variance in population and techniques, limitations and methodological shortcomings (including our study) should be considered for proper clinical decision-making and individualized care planning.

The strengths of this study are multifaceted, enhancing its contribution to the existing literature on the effects of ART on neonatal BW. First, this research specifically targeted a clearly defined group of mothers without major comorbidities, such as severe obesity, hypertension, or diabetes. By doing so, it minimized the presence of confounding variables that could potentially obscure the true relationship between frozen- and fresh-ET and neonatal outcomes. Moreover, the study's rigorous adjustment for key maternal and perinatal factors in the multivariable analysis strengthens the reliability of the findings. The comparative analysis within a homogeneous population further ensures the internal validity of the results, making the observed differences in BW more attributable to the type of ART used rather than extraneous maternal factors. Moreover, this study adds valuable data from an Iranian population, addressing a geographical gap in the literature and providing external validity for the observed outcomes across different populations and settings. Finally, by highlighting the importance of methodological consistency and precise patient selection, this study contributes to the understanding of ART's effects, offering insights that are critical for individualized patient care and clinical decision-making. These findings highlight the importance of considering the method of ART (frozen *vs* fresh), as it can influence neonatal BW and associated perinatal outcomes. Clinicians can use this information to tailor ART protocols more effectively, potentially reducing the risks of adverse outcomes such as LBW, SGA, and LGA infants and their future complications. This study contributes to the existing literature by providing evidence that supports the differentiated impact of embryo transfer methods on foetal growth and neonatal health. The study's findings also emphasize the need for personalized ART strategies, considering patient-specific factors such as maternal BMI and hormonal environment, which could affect the choice of embryo transfer method.

Limitations and Future Studies

This study has several limitations that should be considered when interpreting the results. First, this is a retrospective cohort study, and the study sample was limited to patients who received treatment at a single centre. Additionally, our study did not evaluate long-term outcomes, such as the impact of the ART procedure on child development or health outcomes later in life, which may be important for evaluating the safety of ART. Moreover, while we controlled for potential confounding factors in our statistical analysis, there may still be unmeasured confounders that could influence the results. The study's sample size, though adequate, may not account for all relevant covariates, and a larger sample might be needed to fully address these complexities. Further prospective longitudinal studies with larger sample sizes, including the recruitment of specific patient groups, such as those with pregnancy complications, and extending the follow-up period, are necessary to substantiate our findings and provide more generalized conclusions. Future research should also focus on long-term follow-up studies to assess the impact of birth weight variations on the health and development of children conceived through ART over time. Additionally, investigations into the underlying biological mechanisms contributing to the observed differences between fresh and frozen embryo transfers could enhance our understanding and inform the optimization of ART protocols for improved perinatal and developmental outcomes. The influence of BW variations following frozen- *versus* fresh-ET could be further elucidated by considering additional factors such as maternal obesity and pre-existing conditions. Research has shown that maternal obesity significantly increases the risk of higher birth weight and related complications in pregnancies, with obesity being a prominent predictor of adverse outcomes such as elevated neonatal BW and increased neonatal complications [39]. Similarly, conditions like polycystic ovarian syndrome, which often involves obesity and insulin resistance, have been linked to varied birth weight outcomes, including higher incidences of LGA and foetal growth restriction [40]. These factors may contribute to the observed differences in birth weight between frozen- and fresh-ET, highlighting the importance of considering maternal health and metabolic conditions in future analyses.

CONCLUSIONS

We investigated the effects of frozen-ET *versus* fresh-ET on birth weight (BW) in mothers without pregnancy complications, adjusting for maternal age, BMI, fasting blood sugar, gravidity, systolic blood pressure, gestational age, and neonatal sex. Our analysis indicated that newborns resulting from frozen-ET had a significantly higher BW compared to those from fresh-ET. However, there were no significant differences between the ART methods regarding neonatal sex ratios, rates of preterm birth, or stillbirths/intrauterine foetal deaths. Our findings suggest that, in the absence of marked obesity, hypertension, or diabetes, maternal characteristics do not significantly alter the association between ART procedure type and BW. Overall, frozen-ET did not adversely affect perinatal outcomes compared to fresh-ET.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution
A.S.: Supervision, conceptualization, methodology, project administratior, writing - original draft, writing - review & editing. S.M.: Conceptualization, methodology, investigation, writing - original draft, writing - review & editing. B.K.: Methodology, investigation, formal analysis, visualization, writing - original draft, writing - review & editing.

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Study registration
N/A.

Disclosure of interests
The authors declare that they have no conflict of interests.

Ethical approval
Ethical approval was obtained from the institutional review board of Aja University of Medical Sciences with reference number IR.AJAUMS.REC1399.026.

Informed consent
All participants had signed written consents. They had received verbal and written explanations of the nature and purpose of the procedures.

Data sharing
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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