The Difference in Birthweight in Singletons Born After Fresh Embryo Transfer and After Frozen Embryo Transfer Becomes Significant in the Late Third Trimester

Yu-Chen Chen

Chang Gung Memorial Hospital Kaohsiung Branch

Pei-Fang Lee

Chang Gung Memorial Hospital Kaohsiung Branch

Te-Yao Hsu

Chang Gung Memorial Hospital Kaohsiung Branch

Ni-Chin Tsai

Chang Gung Memorial Hospital Kaohsiung Branch

Ching-Chang Tsai

Chang Gung Memorial Hospital Kaohsiung Branch

Fu-Jen Huang

Chang Gung Memorial Hospital Kaohsiung Branch

Kuo-Chung Lan (✉ lankuochung@gmail.com)

Department of Obstetrics and Gynecology ,Kaohsiung Chang Gung Memorial Hospital and Chang Gung University college of Medicine ,Kaohsiung ,Taiwan <https://orcid.org/0000-0003-3702-0091>

Research

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Abstract

Background: Although it seems to be the consensus that the birth weight of the fetus has increased in FET, few studies have explored the pattern of fetal weight change during pregnancy. The purpose of this study is to explore when fetal weight begins to differ between singletons born after fresh embryo transfer (ET) and those born after frozen embryo transfer (FET).

Methods: This was a hospital-based cohort study using clinical data from the Kaohsiung Chang Gung Memorial Hospital Obstetric and Neonatal Database (KCGMHOND) from January 1, 2007, to December 1, 2018. A sample of 784 eligible women who had singleton pregnancies and live-born deliveries after 428 fresh ET or 356 FET between January 2007 and December 2018.

Results: Compared to those in the fresh ET group, singletons in the FET group had higher birthweight (3137 g [2880-3441] vs. 3060 g [2710-3340], $P<0.05$), were born later (39.0 weeks of gestation [38.0-40.0] vs. 38.0 weeks of gestation [37.0-39.0], $P<0.05$) and had a lower ratio of preterm birth (10.4% vs. 15.2%, $P<0.05$).

The difference in birthweight was not associated with maternal body weight (BW) and body mass index (BMI), maternal BW gained in the third trimester or total BW gained during pregnancy. When second- and third-trimester gestational ages were compared by estimated date of delivery (EDD, days) using ultrasound measurement, there were also no significant differences.

Conclusions: The birthweight of singletons born following FET and fresh ET became significant in the late third trimester. The main reason is that singletons conceived from FET were at a lower relative risk of preterm delivery and had a higher gestational age at birth.

Background

The first birth after embryo freezing occurred in 1984 [1]. With the improvement of vitrification techniques, the number of frozen embryo transfers has steadily increased in recent years. Frozen embryo transfer (FET) can increase the cumulative pregnancy rate, reducing the risk of multiple pregnancy and hyperstimulation syndrome[2]. In the past ten years, many studies have compared obstetrics and perinatal outcomes in singletons following fresh embryo transfer (ET) and FET. It has been reported that singletons conceived from FET were at a lower relative risk of preterm delivery, low birth weight and small for gestational age (SGA) than were those conceived from fresh ET, but the risks of hypertensive disorders of pregnancy, large for gestational age (LGA) and high birth weight are relatively increased[3, 4].

Many studies have tried to explain the adverse perinatal outcomes and birthweight differences associated with fresh ET and FET. It has been hypothesized that FET may provide a more favorable intrauterine environment for embryo implantation and placentation through the avoidance of premature endometrial maturation[5–7], which often occurs after ovarian hyperstimulation in fresh ET. Hyperestrogenism as a result of ovarian stimulation in fresh ET was hypothesized to impair endometrial

angiogenesis that leads to reduced implantation and abnormal placentation, which may account for increased risks of small for gestational age, preterm delivery and low birth weight[8–10]. Another possible explanation for why FETs have better perinatal outcomes is that the freezing-thawing procedure may alter epigenetic modification and leave only the superior embryos with better fetal growth potential by filtering away "weak" embryos[11–14].

The birthweight and LGA of singletons born after FET are higher than those of fresh ET and naturally conceived singletons. The mechanism of how the FET procedure influences birth weight or LGA is still unclear. Obviously, the difference between the length of gestational age after fresh ET and FET leads to a difference in fetal birth weight. It may be related to intrinsic maternal factors but may also be partly related to freezing/thawing procedures *per se*[11]. Korosec *et al*/found that FET and maternal BMI are risk factors for LGA birth weight in IVF patients, but smoking, hypertension, multiparity, Gestational Diabetes Mellitus(GDM), ICSI procedure, or the number of embryos transferred do not influence LGA birth weight risk significantly[15].

Although it seems to be the consensus that the birth weight of the fetus has increased in FET, few studies have explored the pattern of fetal weight change during pregnancy. We agree that obstetric or perinatal outcomes should be studied using the singleton model due to cases of multiple neonates of differences in treatment strategies for obstetrical and neonatal management and various complications found in each of the institutes [16]. The main goal of our study is to explore when fetal weight begins to differ between singletons born after fresh ET and FET.

Material And Methods

Study design and participants

This was a hospital-based cohort study using clinical data from the Kaohsiung Chang Gung Memorial Hospital Obstetric and Neonatal Database (KCGMHOND) from January 1, 2007, to December 1, 2018. The KCGMHOND records all live births and stillbirths weighing at least 500 grams and pregnancies delivered after 20 weeks gestation (calculated using the date of the last normal menstrual period, if available, or the estimated date of confinement by ultrasound otherwise) at a tertiary university hospital in Kaohsiung, Taiwan. Maternal age, parity, birth weight, gestational age (GA) at delivery, mode of delivery, and sex were recorded for all live births. We supplemented prenatal data and medical comorbidities, including chronic hypertension, diabetes mellitus, renal disease, and hypothyroidism, from KCGMH prenatal clinic charts matched to the index pregnancy in the KCGMHOND.

The reproductive clinic data were linked with the KCGMHOND using unique patient identifiers as well as the date and time of delivery associated with the fresh IVF/ICSI fertility treatment procedures. The study was conducted following the approval of the Ethics Committee of the Institutional Review Board (CGMH 201901565B0). Among those who were eligible, those who gave birth to live-born (≥ 25 weeks of gestation) singletons were enrolled. Women were excluded if they had utilized donor oocytes or fetuses with malformation need for intervention.

Laboratory protocols

Our previous research described the methods used for controlled ovarian stimulation (COS), oocyte retrieval, embryo culture, and embryo transfer (ET) [17, 18]. The long protocol and the GnRH-ant protocol for COS were individualized according to each patient's ovarian reserve, age, baseline level of serum follicle-stimulating hormone (FSH), and prior response to COS. One team of embryologists oversaw all laboratory procedures to ensure standardization. Our program has routinely offered elective blastocyst transfer to patients with three or more 8-cell embryos on day 3[18]. Luteal phase support continued until the day pregnancy was confirmed by detection of hCG in the urine. If conception occurred, micronized progesterone supplementation was provided for an additional 4 weeks. In our institute, patients may provide one or more frozen blastocysts for storage. The protocol for vitrification and warming was adapted from publications by Mukaida *et al.* and other researchers [19, 20]. The blastocysts were assessed based on their morphologic appearance and the presence of blastocoel expansion under a dissecting microscope approximately 2 h after warming. Blastocysts with a morphologically intact inner cell mass, a trophectoderm, and a re-expanding blastocoel were determined to have survived. The endometrium was prepared either by artificial hormone replacement or by natural cycling[21]. The embryos were transferred on day 6 of progesterone administration.

Gestational age by the estimated date of delivery

GA according to fresh IVF was calculated by adding 14 days from the day of oocyte retrieval[22, 23], Thaw blastocyst and transfer program GA according was calculated by adding 9 days from the day of transfer. For fetuses with IVF gestation age less than 12 weeks, all CRL measurements were performed using transvaginal ultrasound (Voluson GE 739, P6, E8) by the method described by Bovicelli et al[24]. we also followed the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Practice Guidelines: performance of first-trimester fetal ultrasound scan to establish gestational age accurately[25] and to appropriate assessment of fetal biometry and diagnosis of fetal growth disorders[26].

Obstetric outcomes

The primary outcomes were birth weight, second trimester gestational age (21-23 weeks gestation+6 days), third trimester gestational age (30-33 weeks gestation+6 days) by ultrasound measurement compared with gestational age by the estimated date of delivery (EDD, days), maternal body weight (BW) and body mass index (BMI) before pregnancy, BW at second trimester at the time of ultrasound measurement, BW and BMI during labor, BW gained at the third trimester, and total BW gained during pregnancy.

The secondary outcomes were gestational age at delivery, preterm birth (PTB, <37 weeks), low birth weight (LBW, <2500 g), very low birth weight (VLBW, <1500 g), small for gestational age (SGA, < 10%

below the nationwide singleton birth weight percentiles in Taiwan), large for gestational age (LGA, > 90% above the nationwide singleton birth weight percentiles in Taiwan)[27], high birthweight (>4000 g, macrosomia), pregnancy-related hypertensive disorders (including HELLP syndrome, eclampsia, severe preeclampsia, preeclampsia, pregnancy-induced hypertension) and gestational diabetes mellitus (GDM) [28].

Statistical analysis

The differences between fresh ET and FET were analyzed by statistical analysis using the Statistical Package for the Social Sciences (SPSS) version 23 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant. Categorical variables were expressed as percentages of occurrence (%), and continuous variables were expressed as medians (interquartile ranges [IQRs]) or means $\pm$ SDs, as appropriate. The Shapiro-Wilk normality test was used to check for normality, in addition to visual inspection of the distributions. Continuous and categorical variables were compared using the Mann-Whitney U test and Fisher's exact test, respectively.

Results

From January 2007 through December 2018, 784 singletons met the eligibility criteria. Among them, 428 singletons were born following fresh ET, and 356 singletons were born following FET. Singletons in the fresh ET group were born earlier than those in the FET group (38.0 weeks of gestation [37.0–39.0] vs. 39.0 weeks of gestation [38.0–40.0], $P < 0.05$) and had a higher ratio of preterm birth (15.2% vs. 10.4%, $P < 0.05$).

Singletons born after FET had a higher birthweight (3137 g [2880–3441] vs. 3060 g [2710–3340], $P < 0.001$) and a lower proportion of LBW (< 2500 g, 8.5% vs. 13.5%, $P < 0.05$). Pregnancy-related hypertensive disorders were also higher in the FET group (11.9% vs. 6.1%, $P < 0.05$). No significant differences could be found regarding cesarean section rate, maternal age, placenta weight, VLBW (< 1500 g), high birth weight (BW > 4000 g), SGA, LGA, GDM, second- and third-trimester gestational age by ultrasound measurement compared with gestational age by EDD (days), maternal BW and BMI before pregnancy, BW at second trimester at the time of ultrasound measurement, BW and BMI during labor, BW gained during the third trimester or total BW gained during pregnancy (Table 1, Table 2).

Table 1

Comparison of perinatal outcomes of singleton pregnancies after Fresh-embryo transfer and Frozen-embryo transfer(FET)

	Fresh-embryo transfer	FET	P value
Deliveries, n	428	356	
Maternal age(year)	35.0 [21.0-37.3]	34.9 [31.4–37.1]	0.812
Parity nulliparity	327(76.4%)	257(72.2%)	0.178
Gestational age at delivery(weeks)	38.0 [37.0–39.0]	39.0 [38.0–40.0]	0.005
Birthweight(g)	3060 [2710–3340]	3137 [2880–3441]	0.001
Placenta weight(g)	620[460–780]	640[480–800]	0.326
Preterm birth < 37 weeks, n(%)	65 (15.2%)	37 (10.4%)	0.047
Low birth weight(LBW,<2500 g), n(%)	57 (13.5%)	30 (8.5%)	0.028
Very low birth weight(VLBW,<1500 g), n(%)	11 (2.6%)	4 (1.1%)	0.138
Small for gestational age(SGA,birthweight < 10%), n(%)	46 (10.9%)	28 (7.9%)	0.161
Large for gestational age(LGA,birthweight > 90%), n(%)	34 (8.0%)	38 (10.7%)	0.197
High birth weight(birthweight > 4000 g), n(%)	4 (1.2%)	7 (2.0%)	0.225
Pregnancy related Hypertensive disorder, n(%)	15/246 (6.1%)	22/185 (11.9%)	0.034
Gestational diabetes mellitus, n(%)	18 (7.3%)	19 (10.3%)	0.279
Infant sex, male(%)	54.4%	55.5%	0.771
Results expressed as median [interquartile range], or n (%).			

Table 2
Comparison of prenatal maternal body weight and fetus by ultrasound measurement in singleton pregnancies after Fresh-embryo transfer and Frozen-embryo transfer(FET)

	Fresh-embryo transfer	FET	<i>P</i> value
Second trimester gestational age by ultrasound measurement compared with gestational age by EDD(days)	1.0 [-1.5-4.0]	1.0 [-1.0-4.0]	0.676
Third trimester gestational age by ultrasound measurement compared with gestational age by EDD(days)	1.0[-4.0-6.0]	2.0[-6.0-7.0]	0.328
BW before pregnancy(kg),	56.0 [51.0–63.0]	56.8 [51.8–62.0]	0.711
BMI before pregnancy	21.7 [20.0-24.2]	21.9 [20.3–24.1]	0.380
BW at second trimester at the time of ultrasound measurement(kg)	62.5 [58.0–70.0]	63.7 [57.8–71.0]	0.680
BW when in labor(kg)	69.2 [63.0–76.0]	69.4 [63.2–76.9]	0.359
BMI when in labor	26.9 [24.7–29.3]	26.9 [24.9–30.1]	0.369
BW gained at third trimester(kg)	6.6 [4.3–8.5]	6.3 [4.0–9.0]	0.581
Total BW gained during pregnancy(kg)	12.1 [9.0-15.7]	12.3 [8.7–16.5]	0.805
Results expressed as median [interquartile range], or n (%).			
BW: body weight, BMI: body mass index, EDD: estimated date of delivery			

To eliminate birth method interference, we divided the singletons into a normal spontaneous delivery (NSD) group and a cesarean section (CS) group. Compared with those born in the fresh ET/NSD group, singletons born in the FET/NSD group had higher birthweight (3132 g [2896–3450] vs. 3090 g [2775–3345], $P < 0.05$) and were born at later gestational age (39.0 weeks of gestation [38.0–40.0] vs. 39.0 weeks of gestation [37.0–39.0], $P < 0.05$). Additionally, compared with those born in the fresh ET/CS group, singletons born in the FET/CS group also had higher birthweight (3130 g [2860–3420] vs. 3025 g [2640–3300], $P < 0.05$) but showed no difference in gestational age at delivery. No significant differences were observed in the cesarean section rate, maternal age, preterm birth rate, LBW, VLBW, high birth weight, SGA, LGA, GDM, pregnancy-related hypertensive disorders, second- and third-trimester gestational age by

ultrasound measurement compared with gestational age by EDD (days), maternal BW and BMI before pregnancy, BW in the second trimester at the time of ultrasound measurement, BW and BMI during labor, BW gained in the third trimester or total BW gained during pregnancy (Table 3, Table 4).

Table 3

Comparison of perinatal outcomes of singleton pregnancies after Fresh-embryo transfer and Frozen-embryo transfer(FET): Vaginal delivery and Cesarean section

	NSD (n = 415)			CS (n = 362)		
	Fresh-embryo transfer	FET	<i>P value</i>	Fresh-embryo transfer	FET	<i>P value</i>
Deliveries, n(%)	239 (57.6%)	176 (42.4%)		185 (51.1%)	177 (48.9%)	
Maternal age(year)	34.0 [31.0-36.5]	34.5 [31.1-36.4]	0.821	35.6 [32.1-38.0]	35.1 [32.1-37.7]	0.460
Gestational age at delivery(weeks)	39.0 [37.0-39.0]	39.0 [38.0-40.0]	0.001	38.0 [37.0-39.0]	38.0 [37.0-39.0]	0.128
Birthweight(g)	3090 [2775-3345]	3132 [2896-3450]	0.031	3025 [2640-3300]	3130 [2860-3420]	0.015
Placenta weight(g)	620[515-720]	620[555-705]	0.385	632[540-700]	660[581-728]	0.918
Preterm birth < 37 weeks, n(%)	29 (12.1%)	13 (7.4%)	0.113	34 (18.4%)	24 (13.6%)	0.211
Low birth weight(LBW, <2500 g), n(%)	28 (11.8%)	12 (6.9%)	0.097	19 (15.8%)	18 (10.2%)	0.110
Very low birth weight(VLBW, <1500 g), n(%)	6 (2.5%)	2 (1.1%)	0.476	5 (2.7%)	2 (1.1%)	0.449
Small for gestational age(SGA, birthweight < 10%), n(%)	25 (10.5%)	18 (10.3%)	0.947	20 (10.9%)	10 (5.6%)	0.070
Large for gestational age(LGA, birthweight > 90%), n(%)	11 (4.6%)	10 (5.7%)	0.615	23 (12.6%)	26 (14.7%)	0.557
High birth weight(birthweight > 4000 g), n(%)	2 (0.8%)	4 (2.3%)	0.247	2 (1.1%)	3 (1.7%)	0.681
Pregnancy related Hypertensive disorder, n(%)	7/156 (4.5%)	8/109 (7.3%)	0.323	8/90 (8.9%)	14/76 (18.4%)	0.071
Gestational diabetes mellitus, n(%)	11 (7.1%)	8 (7.3%)	0.929	7 (7.8%)	11 (14.5%)	0.167
Infant sex, male(%)	56.1%	54.9%	0.808	52.2%	56.5%	0.410

NSD: Normal Spontaneous Delivery, CS: Cesarean Section

	NSD (n = 415)			CS (n = 362)		
	Fresh-embryo transfer	FET	<i>P value</i>	Fresh-embryo transfer	FET	<i>P value</i>
Results expressed as median [interquartile range], or n (%).						
NSD: Normal Spontaneous Delivery, CS: Cesarean Section						

Table 4

Comparison of prenatal maternal body weight and in singleton pregnancies after Fresh-embryo transfer and Frozen-embryo transfer(FET): Vaginal delivery and Cesarean section

	NSD (n = 415)			CS (n = 362)		
	Fresh-embryo transfer	FET	P value	Fresh-embryo transfer	FET	P value
Second trimester gestational age by ultrasound measurement compared with gestational age by EDD(days)	1.0 [-1.0-4.0]	1.0 [-1.0-4.0]	0.758	1.0 [-2.0-4.0]	1.0 [-1.8-4.0]	0.711
Third trimester gestational age by ultrasound measurement compared with gestational age by EDD(days)	1.0 [-4.0-6.0]	2.0 [-7.0-8.5]	0.551	1.0 [-4.0-7.0]	2.0 [5.0-7.0]	0.560
BW before pregnancy(kg)	55.0 [51.0-61.0]	56.0 [52.0-61.0]	0.469	57.0 [51.0-64.0]	57.0 [51.8-62.3]	0.980
BMI before pregnancy	21.5 [19.8-23.4]	21.4 [20.4-23.4]	0.464	22.0 [20.0-24.9]	22.4 [20.3-24.6]	0.583
BW at second trimester at the time of ultrasound measurement(kg)	62.2 [57.0-68.6]	63.8 [58.2-69.3]	0.164	64.4 [59.0-75.0]	70.3 [63.4-77.8]	0.245
BW when in labor(kg)	68.0 [62.0-75.0]	69.3 [64.4-76.9]	0.113	71.1 [65.0-80.0]	70.3 [63.4-77.8]	0.535
BMI when in labor	26.2 [24.3-28.5]	26.7 [24.4-29.7]	0.152	27.9 [25.5-31.0]	27.1 [25.4-30.5]	0.493
BW gained at third trimester(kg)	6.6 [4.6-8.4]	6.6 [5.0-9.1]	0.316	6.6 [3.5-8.6]	5.5 [2.8-8.7]	0.768
Total BW gained during pregnancy(kg)	12.0 [9.0-16.0]	12.3 [9.3-16.3]	0.625	13.0 [8.9-15.4]	12.9 [8.0-16.9]	0.868
Results expressed as median [interquartile range], or n (%).						
BW: body weight, BMI: body mass index, EDD: estimated date of delivery, NSD: Normal Spontaneous Delivery, CS: Cesarean Section						

Discussion

Our findings are consistent with the pre-existing meta-analysis[3, 29] and retrospective studies[30, 31] published until 2018 showing that singletons born after FET have higher birth weight and higher gestational age at birth but a higher risk of hypertensive disorders of pregnancy, while singletons born

after fresh ET tend to have a higher risk of preterm birth and low birthweight. However, our single-center singleton study showed that compared to those born after fresh ET, singletons born after FET had higher birth weight but not increased LGA. The birthweight difference was also not associated with maternal BW and BMI before pregnancy or during labor, maternal BW gained after the second trimester, and total BW gained during pregnancy. Furthermore, the birth weight increase in our FET subgroup seems favorable due to a lower frequency of preterm birth and no increase in the proportion of births with LGA or macrosomia. When the second- and third-trimester gestational ages by ultrasound measurement were compared with EDD and estimated fetal weight, there were also no significant differences. Thus, the difference in birthweight among singletons born after FET and fresh ET becomes significant in the late third trimester. The main reason is that singletons conceived from FET were at a lower relative risk of preterm delivery and had greater gestational age at birth.

The absolute sequence of events that trigger and sustain human parturition has not yet been fully clarified. However, there are several factors involved in the initiation of human parturition[32]. Placental corticotropin-releasing hormone production seems to serve as a placental clock that might be set to ring earlier or later, determining the duration of pregnancy and timing of labor[32]. In addition, infection and microbe invasion resulting in chorioamnionitis also represents a common cause of early preterm labor[32].

In a mouse model, ART treatment can disturb mouse placental and fetal development during late gestation; ART can result in the down regulation of a majority of placental nutrient transporters and reduce placental efficiency during mid- to late gestation[33]. After humans receive ART, is it possible that fetal weight growth or initiation parturition will only start to make a difference from the second to the third trimester?

A single-center retrospective cohort study compared crown-rump length (CRL) at the first trimester (T1: 11–13 weeks of gestation [WG] + 6 days) and estimated fetal weight (EFW) at the second (T2: 21–23 WG + 6 days) and third (T3: 31–33 WG + 6 days) trimesters in singleton pregnancies conceived after ICSI, IVF, FET, and IUI. It was found that for all ART fetuses, growth kinetics differed from T2 but became significant at T3. For all ART fetuses, the ultrasounds of CRL at T1 and EFW at T2 were significantly higher than the reference curves. However, only FET singletons remained to have a greater EFW above the reference curve at T3. The EFW of ICSI, IVF, and IUI dropped below the reference curves at T3, indicating a higher proportion of decelerated growth from the second trimester than among those in the FET group[34]. Our study did not find a difference in T3. Besharati et al. also examined fetal growth trajectories following infertility treatment and suggested no significant differences in fetal growth of fresh ET and FET conception[35].

It is possible that imprinted genes may also play a role in the regulation of placental development and the control of nutrient transporter expression, and, in this way, they may also indirectly control fetal growth, development or parturition[36]. Some studies claim that both ovulation induction and embryo vitrification may disrupt genomic imprinting by interfering with imprinting maintenance during preimplantation[37,

38]. Loss of imprinting caused by embryo manipulations was also found in mid-gestation extraembryonic tissues in mice[39, 40].

In our singleton study, the mean birth weight was 134 g heavier in the FET group than in the fresh ET group. A similar result was also observed for the different delivery methods: 133 g heavier in the FET/NSD group and 128 g heavier in the FET/CS group. These findings were consistent with those previously published in the literature. Multiple studies[41, 42] have found that newborns born after FET have higher birthweight than do newborns born in controlled groups or their siblings born after fresh ET. The differences in birthweight were reported to be 50 ~ 250 g greater among those born after FET than among those born after fresh ET: 50 g in China [10], 91 ~ 100 g in Japan[16, 43], 133 g in a Nordic cohort study[9], 145 g in Australia and New Zealand[44], 162 g in France[45], 166 g in the United States [41], 191 g in Spain[46] and 167 ~ 250 g in Denmark[11, 47, 48]. Interestingly, the reports of weight differences in Asia are lower than those in European and American countries.

Judging from our research, the increase in the birth weight of fetuses in FET cycles should not be viewed as negative, but the risk of the main complication, namely, preeclampsia, is still high, and this issue cannot be ignored because it is reflected in our data. Multiple studies have reported an increased risk of pregnancy-induced hypertension or preeclampsia in women conceiving by IVF with frozen embryo transfer (FET) [3, 4, 49–51]. A possible explanation for the increased risk of preeclampsia is related to the absence of the corpus luteum and the use of endometrial priming with estrogens performed during artificial FET cycles [50, 52].

One strength of our study is the large sample size (784 live singleton births) in comparison to that of other single-center studies. Most of the included cases received prenatal care and were delivered at our hospital. Thus, the data for second- and third-trimester ultrasound, perinatal maternal body weight and BMI, and maternal and neonatal outcomes were well recorded. We also took into account factors that are known to influence fetal weight, such as fetal sex, maternal age, weight, and GDM, although no significant differences in these factors were observed between the FET and fresh ET groups. To our knowledge, only one study has analyzed fetal growth by reproductive method in the second and third trimesters using ultrasound measurements[34]. The limitations include the fact that this study uses retrospective data, which are not as rigorously controlled as data collected for a prospective research study. Although the study was conducted in a single center, the embryo transfer was performed by different operators, the stimulation protocols were slightly different, some data were missing, and some patients did not return for follow-up after embryo transfer, so we could contact participants only by telephone for outcomes and associated information. Additionally, the patients in this study were Taiwanese women, so it is necessary to exercise caution when applying our results to other ethnic and racial groups.

Conclusion

The birth weight of singletons born after FET and fresh ET became significant in the late third trimester and was irrelevant to maternal BMI before pregnancy or total body weight gained during pregnancy. The main reason is that singletons conceived from FET were at a lower relative risk of preterm delivery and had greater gestational age at birth.

Abbreviations

BMI: body mass index; BW: body weight; CRL: crown-rump length; CS: cesarean section; EDD: estimated date of delivery; ET: embryo transfer; FET: frozen embryo transfer; GA: gestational age; GDM: Gestational Diabetes Mellitus; ICSI: Intracytoplasmic sperm injection; LBW: low birth weight; LGA: large for gestational age; SGA: small for gestational age; NSD: normal spontaneous delivery PTB: preterm birth; VLBW: very low birth weight

Declarations

Acknowledgments

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Ethics approval

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (CGMH 201901565B0).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception and design of study: YCC, TYH,KCL ; enrolled the subjects: YCC, PFL,KCL; analysis of data and writing of the manuscript: KCL,YCC,PFL; critical revision of the article for intellectual content: KCL,YCC,PFL,TYH,NCT,CCT,FJH. All authors read and approved the final manuscript.

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