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ORIGINAL ARTICLE

The effect of assisted reproductive technology on postpartum bleeding: hormonal cycle frozen embryo transfer might increase blood loss

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Abstract

Background Among assisted reproductive technologies, frozen thawed embryo transfer (FET) is associated with increased blood loss at delivery. Anesthesiologists need to be aware of new factors that affect postpartum blood loss. This study investigated whether FET cycles with or without hormonal support affect the amount of postpartum bleeding.

Methods We conducted a retrospective cohort study of patients admitted for delivery at a single university hospital between January 2015 and December 2018. Patients were divided into no-assisted reproductive technology (No-ART), hormonal cycle FET (HC-FET) and natural cycle FET (NC-FET) group. The primary outcome was the amount of blood loss after delivery (median [interquartile range]), which was compared among the three groups. Multiple regression analysis was performed to investigate the factors affecting blood loss.

Results Between 2015 and 2018, 3187 women delivered neonates. In vaginal delivery, postpartum blood loss in the HC-FET group (1060 [830] g) was significantly greater than in the NC-FET group (650 [485] g, $P = 0.001$) and in the No-ART group (590 [420] g $P < 0.001$). Multiple linear regression analysis showed that HC-FET ($P < 0.001$) was one of the independent factors for the amount of bleeding. In cesarean delivery, the HC-FET group had more blood loss than the No-ART group (910 [676] g vs. 784 [524] g, $P = 0.039$). However, HC-FET was not an independent factor for postpartum blood loss.

Conclusions The HC-FET group had more blood loss than the No-ART group for both vaginal and cesarean deliveries. Furthermore, HC-FET was an independent factor that increased postpartum blood loss in vaginal deliveries.

Keywords Assisted reproductive technology · Hormonal cycle frozen embryo transfer · Postpartum bleeding · Blood loss after delivery · Postpartum hemorrhage

Introduction

Assisted Reproductive Technology (ART) has been established as a fertility treatment with a high success rate. The use of ART is increasing worldwide; thus, in Europe, 2.9% of all babies born in 2016 were derived from ART [1], and in the USA, ART produced 1.5% of singleton births in 2017 [2]. In Japan, about 1 in 16 pregnancies results from ART.

ART includes procedures that involve the in vitro handling of human oocytes and spermatozoa or embryos with the purpose of obtaining a pregnancy [3]. If necessary, human chorionic gonadotropins are administered for the purpose of ovulation. In a fresh embryo transfer, the ovum collection and transfer of a dividing embryo or blastocyst that has been fertilized in vitro are performed in the same menstrual cycle. In a frozen–thawed embryo transfer (FET),

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an embryo that has been cultured and cryopreserved during in vitro fertilization is thawed and transferred. In the natural cycle FET (NC-FET), the embryo is transferred according to the patient's hormonal cycle. In the hormonal cycle FET (HC-FET), the embryo is transferred after endometrial preparation for facilitating implantation with estrogen / progesterone hormone therapy with or without gonadotropin-releasing hormone agonist suppression. HC-FET used to be more common than other types of FET, such as NC-FET, but its rate appears to be changing.

According to a statement from the Society for Assisted Reproductive Technology, FET are now more successful than fresh embryo transfers in terms of clinical pregnancy rates [4]. With recent advances in ART technology, FET is more common than fresh embryo transfer. However, it has been reported that it might increase the risk of hypertensive disorders of pregnancy (HDP), and macrosomia [5, 6].

ART has also been reported to be a risk factor for increased postpartum hemorrhage (PPH) [7–14] and PPH is more frequent in FET than in fresh embryo transfers [10, 15]. However, few studies have examined the relationship between HC-FET, NC-FET and PPH. Therefore, the aim of this study was to investigate whether FET (i.e., HC-FET and NC-FET) affects the amount of blood loss after delivery.

Subjects and methods

This study was approved by the Institutional Review Board of Hamamatsu University School of Medicine Hospital (IRB 18–097). The requirement for written informed consent was waived by the IRB.

We retrospectively reviewed the medical records, obstetric delivery database, and anesthesia records of 3187 women who delivered at gestational week ≥ 22 at our hospital between January 1 2015 and December 31 2018. The following items were recorded: the amount of blood loss (amniotic fluid was included); the number and rate of patients with bleeding over 1000 ml for vaginal delivery and 2000 ml for cesarean delivery [CD]; how pregnancy was achieved; maternal age; gestational age; primiparity; body mass index (BMI); any maternal comorbidities (e.g., thyroid disease, psychiatric disorders, gestational diabetes mellitus [GDM], uterine myoma, previous CD, HDP, or anemia); smoking habit; obstetric information (e.g., preterm labor, threatened abortion, placenta accreta, placenta previa, perineal laceration, birth canal laceration, vacuum extraction, use of the Kristeller maneuver at delivery, or twin pregnancy); indications for CD; and delivery information (vaginal delivery or CD, duration of labor, labor epidural analgesia, emergency CD rate or the need for blood transfusion). We also recorded the embryo transfer method as NC-FET, or HC-FET.

Patients with hematological disorders, intrauterine fetal demise, inadequate data recording, and patients who underwent CD for suspected placenta accreta and underwent temporary closure of the abdomen for later hysterectomy were excluded.

The patients were divided into the following two groups: the all frozen embryo transfer (All-FET) group comprised women who became pregnant by FET, and the no assisted reproductive technology (No-ART) group comprised women who conceived without ART. Furthermore, the All-FET group was divided into HC-FET and NC-FET subgroups according to the type of embryo transfer cycle. The No-ART group included women with spontaneous pregnancies, timed pregnancies, the use of fertility-promoting drugs, and those undergoing artificial insemination with their husband's spermatozoa.

The primary outcome of the analysis was the amount of blood loss (in g), and the secondary outcomes were factors contributing to this. First, we compared the data between All-FET and No-ART groups. After identifying differences between these two groups, we compared the data (included the amount of blood loss) among HC-FET, NC-FET subgroups, and No-ART group. Differences between any of the groups were determined by two-sample t-tests in each group. Patients lacking data of the embryo transfer method were included only in the analysis of the All-FET vs. No-ART comparison. We compared the amount of bleeding separately by mode of delivery because CD involves more blood loss than a vaginal delivery [16]. Persistent postpartum hemorrhage has been treated with certain therapeutic options depending on the individual condition: uterine contractions, uterine massage, intrauterine balloon tamponade, blood transfusion therapy, cryoprecipitate or fibrinogen administration, interventional radiology, compression suture, and hysterectomy. In our hospital, we routinely use these standard methods of treatment for PPH. All patients with suspected placenta accreta were prophylactically inserted with an arterial occlusion balloon because of the high risk of massive hemorrhage.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used in reporting.

Data are expressed as case numbers with percentages, or as the median with interquartile range. Statistical comparisons of demographic data and the amount of bleeding between groups were performed using Kruskal–Wallis and chi-square tests. The Shapiro–Wilk test was used to assess the normality of distribution for continuous variables.

Multiple regression analysis was performed to evaluate factors that might have affected the volume of postpartum bleeding. The candidate independent variables included in this analysis were selected from the literature and from the results of univariate analysis. In patients who had a vaginal

delivery, FET, age, primiparous, BMI, use of the Kristeller maneuver, duration of the second stage of labor, uterine myoma, GDM, HDP, placenta accreta, perineal laceration, birth canal laceration, vacuum extraction, and the requirement for epidural analgesia during labor were selected as independent variables. In patients who had a CD, FET, emergency CD, general anesthesia, age, parity, BMI, any previous CD, thyroid disease, GDM, uterine myoma, HDP, premature rupture of membranes (PROM), placenta previa, twin pregnancy and placenta accreta were selected as candidate independent variables. Multiple linear regression analysis was performed to investigate factors affecting blood loss. To confirm the validity of the sample size, we calculated the power of a two-sample t-test for differences in blood loss in the comparison between each group. Two-sided test results with $P < 0.05$ were considered to be significant. All statistical procedures were conducted using SAS for Windows (v. 9.4; SAS Institute, Cary, NC, USA) and IBM SPSS Statistics (v. 25.0; IBM Corp., Armonk, NY, USA).

Results

A total of 3187 women delivered during the study period. After excluding 31 women with insufficient medical records, 22 with hematological disorders, 9 with fresh embryo transfer, 9 with intrauterine fetal demise, and 2 who had hysterectomy performed 1 week after CD for placenta accreta, the total number of eligible women was 3114. Study participants were assigned according to the delivery method and embryo transfer method (Fig. 1).

Demographic and obstetric data are shown in Tables 1, 2, Electronic Supplementary material (Suppl.) 1–1, 1–2. In vaginal deliveries, maternal age, BMI, the rate of primipara, the duration of the second stage of labor, the rate of concomitant psychiatric disorders, HDP, placenta ccrete, birth canal laceration, vacuum extraction, use of the Kristeller maneuver, the requirement for blood transfusion, number and rate of patients with bleeding over 1000 ml, and labor epidural analgesia, were significantly different among the No-ART, HC-FET, and NC-FET groups (Table 2).

The data for blood loss are presented as the median (interquartile range). The amount of bleeding in the All-FET and No-ART groups was 907 (735) g and 590 (420) g respectively ($P < 0.001$) (Table 1). Postpartum blood loss in the HC-FET group (1060 [830] g) was significantly greater than that in the NC-FET group (650 [485] g, $P = 0.001$) and in the No-ART group ($P < 0.001$) (Table 2). No difference in postpartum blood loss was found between the NC-FET and No-ART groups. The blood transfusion rate was significantly higher in the HC-FET group than in the No-ART and NC-FET groups (both $P < 0.001$). Detection power was > 0.99 for

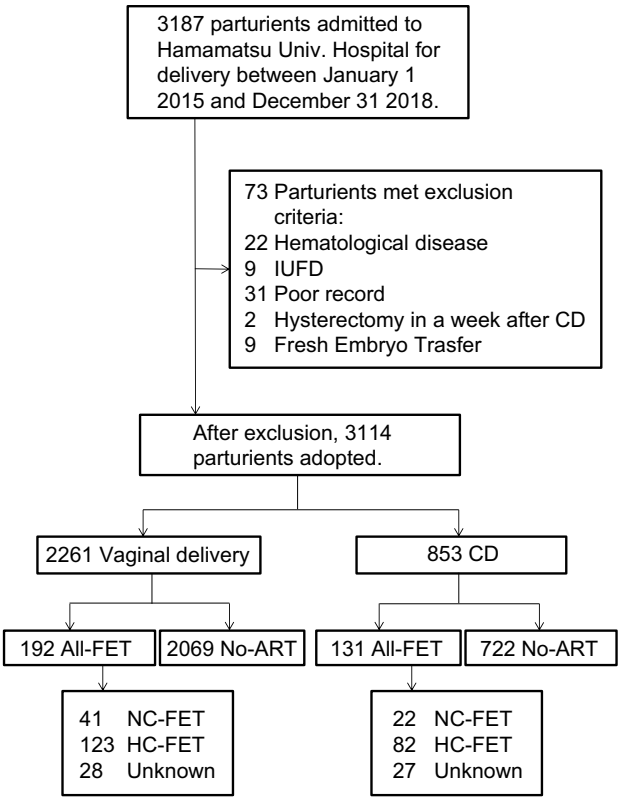

Fig. 1 Profiles of the study participants

No-ART vs. All-FET and No-ART vs. HC-FET, and 0.403 for HC-FET vs. NC-FET.

Multiple regression analysis showed that FET, placenta ccrete, labor epidural analgesia, use of the Kristeller maneuver, and vacuum extraction were confounders associated with blood loss in vaginal delivery (Table 3). The least squares means of blood loss for No-ART and FET after adjusting for confounding factors were 3058 (95% confidence interval, CI: 2789–3327) and 3428 (95% CI: 3154–3702), respectively, which were statistically significant (least squares mean difference = 370 (95% CI: 268–471) $P < 0.001$). When the All-FET group was divided into HC-FET and NC-FET subgroups, placenta ccrete, HC-FET, labor epidural analgesia and use of the Kristeller maneuver were considered confounders associated with blood loss (Table 4). The least square means of bleeding volume for the HC-FET, NC-FET, and No-ART groups after adjusting for confounding factors were 3554 (95% CI: 3270–3838), 3114 (95% CI: 2776–3453), and 3038 (95% CI: 2761–3314), respectively. The least squares mean differences between HC-FET and NC-FET was 439 (95% CI: 211–668), $P < 0.001$), and between HC-FET and No-ART it was 516 (95% CI: 393–639), $P < 0.001$).

In patients with a CD, there were significant differences in maternal age, and the rate of primipara, concomitant thyroid disease, and previous CD among the HC-FET, NC-FET,

Table 1 Patients' demographic and obstetric data in vaginal delivery comparing between All-FET and No-ART

	All FET n = 192	No-ART n = 2069	P value
Age	36 (5)	31.0 (7)	< 0.001
≧35 y	119 (62.0)	543 (26.2)	< 0.001
BMI (kg/m^2)	24.1 (3.9)	24.6 (4.03)	0.002
Gestation (week)	39 (2)	39 (2)	0.137
Primipara	124 (64.6)	1035 (50)	< 0.001
Blood loss	907 (735)	590 (420)	< 0.001
Blood loss ≧ 1000 mL	89 (46,4)	3.7 (14.8)	< 0.001
Comorbidities			
Thyroid disease	11 (5.7)	79 (3.8)	0.195
Psychiatric disorder	2 (1.0)	122 (5.9)	0.005
GDM	8 (4.2)	72 (3.5)	0.622
Smoking	1 (0.5)	27 (1.3)	0.298
Uterine myoma	0	54 (100)	0.008
HDP	9 (4.7)	42 (2.1)	0.028
Gestational anemia	92 (47.9)	987 (47.7)	0.945
Preterm labor	22 (11.5)	190 (9.2)	0.301
Threatened abortion	2 (1.0)	6 (0.3)	0.618
Maternal outcome			
PROM	32 (16.7)	261 (12.6)	0.110
Placenta accreta	6 (3.1)	5 (0.2)	< 0.001
Perineal Laceration	5 (2.6)	29 (1.4)	0.152
Birth Canal Laceration	53 (28.6)	398 (19.4)	0.003
Vacuum Extraction	65 (33.9)	324 (15.1)	< 0.001
Kristeller maneuver	100 (52.1)	519 (25.1)	< 0.001
Blood transfusion	5 (2.6)	14 (0.7)	< 0.001
Delivery information			
1st stage of labor (min)	340 (435)	360 (380)	0.797
2nd stage of labor (min)	47 (75)	27 (49)	< 0.001
Epidural analgesia	35 (18.2)	164 (7.9)	< 0.001

Data are presented as median (IQR) or number (%)

BMI body mass index, *GDM* gestational diabetes mellitus, *HDP* hypertensive disorder of pregnancy, *PROM* premature rupture of membrane

and No-ART groups (Suppl. 1–2). The indications for the CD are shown in Suppl. 2–1 and 2–2. Blood loss was significantly higher in the All-FET group (889 [681] g) than in the No-ART group (784 [524] g; P = 0.008) (Suppl. 1–1). Comparisons of blood loss among the NC-FET (909 [560] g), HC-FET (910 [676] g), and No-ART groups showed that the HC-FET group had significantly more postpartum blood loss than the No-ART group (P = 0.039) (Suppl. 1–2). The power was 0.275 for No-ART vs. All-FET, and 0.277 and 0.025 for No-ART vs. HC-FET and HC-FET vs. NC-FET, respectively.

In multiple regression analysis for CD, FET was not an independent factor associated with the amount of bleeding, but placenta accreta, placenta previa, twin pregnancy, and gestational diabetes were significantly associated with blood loss (Suppl. 3 and 4). In this study, the frequency of placenta accreta in CD cases did not differ between the three groups. Since there were no cases of prophylactic hysterectomy without placental detachment and cases of total hysterectomy at a later date without placental detachment were excluded, there was no difference in the basic treatment of placenta accreta. In the multiple regression analysis, there were at least 10 cases for one independent variable, and the number of independent variables was adequate.

Discussion

Since 2017, it has been noted that ART appears to be a risk factor for PPH [7–14]. A recent report suggested that FET was associated with a higher risk of PPH than fresh embryo

Table 2 Patients' demographic and obstetric data in vaginal delivery compared among HC-FET, NC-FET and No-ART

	All-FET		No-ART n = 2069	P value
	HC-FET n = 123	NC-FET n = 41		
Age	36.0 (7)	36.0 (5)	31.0 (7)	< 0.001‡#
≧35 y	75 (61.0)	27 (65.9)	543 (26.2)	< 0.001‡#
BMI (kg/m^2)	24.1 (3.77)	24.8 (3.21)	24.6 (4.03)	0.023#
Gestation (week)	39 (2)	40 (1)	39 (2)	0.103
Primipara	81 (65.9)	25 (61.0)	1035 (50)	0.001#
Blood Loss	1060 (830)	650 (485)	590 (420)	< 0.001 #✞
Blood loss ≧ 1000 mL	67 (54.5)	9 (22.0)	3.7 (14.8)	< 0.001#✞
Comorbidities				
Thyroid disease	8 (6.5)	1 (2.4)	79 (3.8)	0.292
Psychiatric disorder	1 (0.8)	0	122 (5.9)	0.017‡#
GDM	5 (4.1)	3 (7.3)	72 (3.5)	0.406
Smoking	1 (0.8)	0	27 (1.3)	0.685
Uterine myoma	0	0	54 (100)	0.112
HDP	9 (7.3)	0	42 (2.1)	0.001#
Gestational anemia	52 (42.3)	25 (61.0)	987 (47.7)	0.114
Preterm labor	15 (12.2)	5 (12.2)	190 (9.2)	0.444
Threatened abortion	1 (0.8)	0	6 (0.3)	0.741
Maternal outcome				
PROM	23 (18.7)	5 (12.2)	261 (12.6)	0.146
Placenta accreta	5 (4.1)	0	5 (0.2)	< 0.001#
Perineal Laceration	4 (3.3)	1 (2.4)	29 (1.4)	0.236
Birth Canal Laceration	35 (29.2)	13 (33.3)	398 (19.4)	< 0.001‡#
Vacuum Extraction	47 (38.2)	11 (26.8)	324 (15.1)	< 0.001‡#
Kristeller maneuver	71 (57.7)	15 (36.6)	519 (25.1)	< 0.001#
Blood transfusion	5 (4.1)	0	14 (0.7)	< 0.001#✞
Delivery information				
1st stage of labor (min)	360 (415)	325 (470)	360 (380)	0.573
2nd stage of labor (min)	54 (82)	46 (71)	27 (49)	< 0.001#
Epidural analgesia	23 (18.7)	7 (17.1)	164 (7.9)	< 0.001‡#

Dates are presented as median (IQR) or number (%)

‡Statistical difference between NC-FET and No-ART ($P < 0.05$), # Statistical difference between HC-FET and No-ART ($P < 0.05$), ✞Statistical difference between HC-FET and NC-FET ($P < 0.05$)

BMI body mass index, *GDM* gestational diabetes mellitus, *HDP* hypertensive disorder of pregnancy, *PROM* premature rupture of membrane

transfer [15]. However, there are few reports on whether the type of FET cycle affects the rate of PPH [17, 18].

In our study, the HC-FET group had more blood loss than the No-ART and NC-FET groups in women with vaginal deliveries. The rate of blood transfusion was also higher in the HC-FET group than in the other two groups. Since the comparison between HC-FET and NC-FET showed insufficient detection power, it is necessary to conduct future studies after an adequate number of cases is secured.

Healy et al. reported that parturients who conceived with ART had a higher risk of PPH than women with spontaneous pregnancies who had not been treated for infertility [17]. They also reported that among women undergoing FET, FET in the hormonal cycle group had a higher PPH rate than FET in the natural cycle group. In this study, we compared three groups (HC-FET, NC-FET, and No-ART) and used the amount of bleeding as the outcome rather than the rate of PPH. The period of data collection in the study by Healy et al. was 1991–2004, and the approach to diagnosis and treatment might have changed with the advancement of ART. In our study, the data were collected from 2015 to 2018, which might better reflect the current state of ART.

Table 3 Multiple linear regression analysis to evaluate the association between postpartum blood loss and each factor in vaginal delivery

Variables	β	SE	95%CI		P value
FET	370.10	51.81	268.50	471.70	< 0.0001
Non-ART	Reference				
Vacuum extraction	101.34	47.52	8.15	194.53	0.033
Normal VD	Reference				
Age ≧35	− 19.68	31.64	− 81.73	42.37	0.534
Age < 35	Reference				
Primipara	− 56.43	31.30	− 117.81	4.95	0.072
Multipara	Reference				
BMI	4.80	2.47	− 0.04	9.64	0.052
Uterine Myoma					
Yes	39.72	90.47	− 137.70	217.14	0.661
No	Reference				
GDM					
Yes	28.64	73.62	− 115.74	173.01	0.697
No	Reference				
HDP					
Yes	59.65	91.99	− 120.74	240.05	0.517
No	Reference				
Placenta Accreta					
Yes	4249.02	195.95	3864.76	4633.28	< .0001
No	Reference				
Perineal Laceration					
Yes	118.97	111.30	− 99.30	337.24	0.285
No	Reference				
Birth Canal Laceration					
Yes	61.81	34.01	− 4.89	128.52	0.069
No	Reference				
Epidural Anagesia					
Yes	158.02	49.31	61.31	254.72	0.001
No	Reference				
Kristeller maneuver					
Yes	103.56	35.50	33.94	173.19	0.004
No	Reference				
Second stage of labor	0.19	0.21	− 0.22	0.60	0.355

FET Frozen–thawed Embryo Transfer, *ART* Assisted Reproductive Technology, *VD* vaginal delivery, *BMI* body mass index, *GDM* gestational diabetes mellitus, *HDP* hypertensive disorder of pregnancy

Another report on the obstetric outcome of FET stated that HC-FET increased the odds ratio of PPH compared with NC-FET and fresh embryo transfer [18]. However, in this previous study, only cases with PPH were analyzed, and the authors did not investigate blood loss separately for vaginal deliveries and CD.

The increase in PPH can be caused by morphological changes to the basal plate of the placenta. Nakamura et al. reported that the FET in the hormonal cycle group results—at least in part—in morphological changes to the placental basal plate, such as an increased thickness of the Rohr fibrinoid layer and/or an increased loss of decidua [19]. They also suggested that artificial endocrinological circumstances in the early pregnancy period, especially with FET in hormonal cycles, might cause changes in the structure and/or function of the extracellular matrix, and these increase postpartum blood loss. In our study, FET (especially HC-FET), placenta accreta, labor epidural analgesia, and use of the Kristeller maneuver were relevant confounders of blood loss at vaginal delivery. Placenta accreta is defined as a placenta that completely or partially invades the uterine wall and is inseparable from it, and typically results in severe hemorrhage [20].

Labor epidural analgesia did not increase the rate of PPH [22], and helped protect against severe blood loss in women with PPH [23]. However, the use of epidural analgesia in labor was an independent factor associated

Table 4 Multiple linear regression analysis to evaluate the association between postpartum blood loss and each factor in vaginal delivery. FET examined by embryo transfer cycle

Variables	β	SE	95%CI		P value
HC-FET	515.73	62.84	392.51	638.96	< .0001
NC-FET	76.33	102.57	− 124.81	277.46	0.457
Non-ART	Reference				
Vacuum Extraction	93.97	47.96	− 0.09	188.03	0.050
Normal VD	Reference				
Age ≧35	− 15.89	31.82	− 78.28	46.51	0.618
Age < 35	Reference				
Primipara	− 52.27	31.42	− 113.88	9.33	0.096
Multipara	Reference				
BMI	4.82	2.47	− 0.02	9.66	0.051
Uterine myoma	Reference				
Yes	38.25	90.38	− 138.98	215.49	0.672
No	Reference				
GDM					
Yes	32.89	73.58	− 111.41	177.18	0.655
No	Reference				
HDP					
Yes	34.69	92.10	− 145.91	215.29	0.707
No	Reference				
Placenta Accreta					
Yes	4236.87	205.64	3833.60	4640.13	< .0001
No	Reference				
Perineal Laceration					
Yes	114.44	111.22	− 103.67	332.55	0.304
No	Reference				
Birth Canal Laceration					
Yes	64.70	34.17	− 2.31	131.72	0.058
No	Reference				
Epidural Anagesia					
Yes	162.23	49.80	64.57	259.88	0.001
	Reference				
Kristeller maneuver					
Yes	95.43	35.77	25.28	165.57	0.008
No	Reference				
2nd stage of labor	0.20	0.21	− 0.22	0.61	0.351

HC-FET: Hormonal Cycle-Frozen Embryo Transfer, NC-FET: Natural Cycle-Frozen Embryo Transfer, ART: Assisted Reproductive Technology, VD: vaginal delivery, BMI: body mass index, GDM: gestational diabetes mellitus, HDP: hypertensive disorder of pregnancy

with blood loss at vaginal delivery in our study. At our hospital, labor is induced or augmented with oxytocin for women who request epidural analgesia. The relationship between induction or augmentation of labor using oxytocin and PPH is still controversial [24–27]. Further research is required to determine why labor epidural analgesia appeared to be an independent factor for blood loss. In our study, the proportion of patients who received epidural analgesia was higher in the All-FET group than in the No-ART group. FET and epidural analgesia were associated with increased postpartum blood loss, suggesting that patients who become pregnant with FET should receive more attention to blood loss when they choose labor epidural analgesia. The Kristeller maneuver is a method used to expel the fetus by compressing the uterine fundus along the pelvic axis in response to uterine contractions; vacuum extraction may be added. Although we could not find any

report describing the effects of the Kristeller maneuver on the amount of blood loss at delivery, it is usually used in cases of prolonged or weak labor and in urgent deliveries. These circumstances could contribute to increased blood loss at delivery.

In patients with CD, there was more blood loss in the All-FET and HC-FET groups than in the No-ART group, but they were not independent factors of blood loss in multiple regression analysis after adjusting for confounders. Inadequate detection due to insufficient sample size could have been the cause. Multiple linear regression analysis of patients with CD showed that the factors associated with the amount of blood loss at delivery were placenta accreta, placenta previa, twin pregnancies, and GDM. Placenta accreta, placenta previa, and multiple pregnancies have been reported to be risk factors for increased PPH, which is consistent with our study [28, 29]. In this study, GDM was also associated with blood loss at CD but not with vaginal delivery. In Australia, pregnant women with GDM have a higher PPH rate than normoglycemic pregnant women in the indigenous population, but there was no difference in the PPH rate in the non-indigenous population [30]. However, the relationship between GDM and PPH is unclear in countries where many people have access to advanced medical care. Although GDM is associated with macrosomia, which has been reported to be a risk factor for PPH [13], we did not examine the weight of the neonates. Therefore, the relationship between GDM and blood loss at CD remains to be investigated. General anesthesia was not an independent factor for the amount of blood loss in our study, which is inconsistent with a previous report [29]. However, the small number of women who received CD under general anesthesia could explain this discrepancy between studies.

FET is increasingly being used in clinical practice in women undergoing ART in an attempt to increase the chances of pregnancy. In Japan, in 2017, a study reported that approximately 85% of live births conceived by ART were FET pregnancies, and the percentage of FET is expected to continue increasing. However, fresh embryo transfer is becoming less common. Between 2015 and 2018, there were only nine cases of fresh embryo transfer that resulted in pregnancy at our hospital. Because the number of such cases during the study period was very small, and the rate of fresh embryo transfer in the future will continue to be low, we limited this study to FET cycles.

Although ART pregnancies are increasing, the majority of pregnant women do not have ART performed. We found a significant difference in blood loss between the All-FET and No-ART groups. During the study period, approximately three-quarters of FETs were HC-FET. However, the rate of NC-FET has increased to approximately the same as that for HC-FET in our hospital, and NC-FET may become the standard procedure in the future. We consider that not only HC-FET, but also NC-FET, may be risk factors for PPH compared with No-ART. Therefore, we examined which of the three groups showed a difference in PPH. We suggest that anesthesiologists should collect information to distinguish between HC-FET and NC-FET.

Endometrial damage before embryo transfer is associated with improved live birth and clinical pregnancy rates [31], but in a more recent report, the effects were uncertain [32]. Implantation on a damaged endometrium might cause placenta accreta and increased postpartum bleeding, but this was not investigated in our study. Whether ART caused endometrial damage before embryo transfer is unclear.

Severe PPH still substantially contributes to maternal morbidity in high-income countries. In 2020, PPH was the leading cause of maternal death in Japan, accounting for approximately 8% of all maternal deaths. To avoid death from PPH and to reduce the amount of blood loss during delivery, the patient's risk factors for bleeding need to be understood in advance, and preventive measures should be taken. Singleton ART-generated pregnancies are usually managed as low-risk deliveries. Because anesthesiologists are involved in the management of parturients during labor epidural analgesia or CD, they also need to pay more attention to the method of conception. In this study, HC-FET was a factor in increasing postpartum blood loss. Such women should be managed during and after delivery, with attention to the potential for increased postpartum blood loss.

Limitations

Because this was a retrospective, observational study, we might not have been able to examine all confounding factors suspected to be associated with blood loss. Because pregnant women were referred to our hospital from multiple facilities using ART, there might have been differences in the technique used among them. Because most of our patients are Asian, we were not able to examine differences by ethnicity. Although the bleeding volume used in this study included amniotic fluid volume, it was not possible to rigorously study amniotic fluid volume because of the retrospective cohort study. In cases of PROM, the amount of amniotic fluid lost is unknown, which may have affected the volume of bleeding. However, since there was no statistical difference in the proportion of cases of PROM in each group, the bleeding volume in the database was used directly. It is possible that the measurement of blood loss may have differed among nurses. It was not possible to calculate the amount of hemorrhage based on changes in

hemoglobin levels before and after delivery. There was a sufficient number of samples for the No-ART vs. All-FET and No-ART vs. HC-FET comparisons in vaginal delivery. However, there was an insufficient number of samples for the No-ART vs. NC-FET and NC-FET vs. HC-FET comparisons in vaginal delivery, and for all comparisons in CD. Our single-center study was limited in ensuring adequate sample sizes.

Conclusions

Postpartum bleeding was higher in pregnancies in the All-FET group than in the No-ART group for vaginal delivery and CD. HC-FET was an independent factor for increased postpartum blood loss at vaginal delivery, but not for CD. During the management of delivery, anesthesiologists should keep in mind that HC-FET can increase the risk of hemorrhage. Since a single-center study was not able to obtain a sufficient sample size, a multicenter study is considered necessary in the future to accumulate cases.

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Authors contribution CA: This author helped with data collection, analysis, and summary. KS: This author helped with data collection. KT: This author helped with data collection. NT: This author helped to provide expertise in obstetrics and gynecology. YS and YK: These authors helped with statistical analysis. YN: This author helped write the summary.

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

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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