# Use of the endometrial receptivity array to guide personalized embryo transfer after a failed transfer attempt was associated with a lower cumulative and per transfer live birth rate during donor and autologous cycles

Mauro Cozzolino, M.D.,[a,b,c] Patricia Diáz-Gimeno, Ph.D.,[b] Antonio Pellicer, M.D., Ph.D.,[a,b] and Nicolas Garrido, M.Sc., Ph.D.[b]

[a] IVIRMA Roma, Italy; [b] IVI Foundation, Instituto de Investigación Sanitaria La Fe (IIS La Fe), Valencia, Spain; and [c] Universidad Rey Juan Carlos, Madrid, Spain

**Objective:** To determine whether personalized embryo transfer (pET) guided by endometrial receptivity array (ERA) test improves reproductive outcomes for fresh embryo transfers (fsETs) or frozen embryo transfers (FETs) during autologous and donor cycles.
**Design:** A retrospective, observational, multicenter cohort study.
**Setting:** University-affiliated in vitro fertilization center.
**Patient(s):** The study included patients with a single previous failed transfer and yielded 3,239 autologous transfers and 2,133 donor transfers. Among autologous transfers, 255 were pET guided by ERA; among unguided autologous transfers, 1,122 and 1,862 transfers involved fresh or previously frozen embryos, respectively. Among donor transfers, 319 were ERA-guided; among unguided donor transfers, 1,175 and 639 involved fsETs or FETs, respectively.
**Intervention(s):** None.
**Main Outcome Measure(s):** Primary outcomes were live birth rate per embryo transfer and cumulative live birth rate on consecutive transfers until live birth or cessation of pregnancy. Secondary outcomes were implantation, pregnancy rate, clinical pregnancy rates per embryo transfer, and miscarriage rate per pregnancy.
**Result(s):** During both autologous or donor transfers, live birth rate and cumulative live birth rate were higher in FET and fsET than in pET groups, even with euploid transfers. Logistic regression analysis, considering possible confounders, indicated patients receiving pET had poorer outcomes than those undergoing FET and fsET in autologous and donor cycles. Implantation, pregnancy, and clinical pregnancy rates were lower in patients undergoing pET.
**Conclusion(s):** Using ERA to guide pET during either autologous or donor cycles after a failed transfer attempt did not improve reproductive outcomes. Conversely, worse outcomes were detected when ERA was used. (Fertil Steril® 2022;118:724-36. ©2022 by American Society for Reproductive Medicine.)
**El resumen está disponible en Español al final del artículo.**

Received December 7, 2021; revised July 7, 2022; accepted July 12, 2022.
M.C. has nothing to disclose. P.D.G. has nothing to disclose. A.P. has nothing to disclose. N.G. has nothing to disclose.
P.D.G and A.P. are inventors of the endometrial receptivity array patent encompassing the endometrial receptivity array signature as a biomarker of endometrial progression; these investigators solely contributed as authors and do not receive any commercial interest or economic benefit from the commercialized test. Further, Instituto Valenciano de Infertilidad and iGenomix have been independent companies since 2016. P.D.G and A.P. continue researching other methods to evaluate endometrial-factor infertility.
Supported by IVIRMA global. No additional external funding was received for this study.
Correspondence: Mauro Cozzolino, M.D., IVIRMA Roma, Italy (E-mail: mauro.cozzolino@ivirma.com).

Fertility and Sterility® Vol. 118, No. 4, October 2022 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2022.07.007

**Key Words:** ERA test, pET, personalized embryo transfer, donor cycles, fresh embryo transfer, cumulative live birth, precision medicine, endometrium, infertility



Advances in the reproductive medicine have achieved a cumulative live birth rate (CLBR) of approximately 95% after three consecutive transfers of previously frozen euploid embryos in patients with good prognosis (1). However, live birth rates (LBRs) of each transfer could be improved by only 64.8%, 54.4%, and 54.1% of the transfers that yield live births at the first, second, or third attempts, respectively (1). Although preimplantation genetic testing for aneuploidy (PGT-A) reduces the miscarriage rates per transfer (2), a euploid embryo does not guarantee success in in vitro fertilization (IVF) cycles; a receptive endometrium must interact with the euploid embryo to achieve pregnancy (3). Thus, endometrial factors could contribute to individual failed transfer attempts even when transferring euploid embryos.

The "implantation window" (WOI) is the time interval during the midsecretory phase when the endometrium is synchronized to receive a blastocyst, permitting invasion of the trophoblast into the endometrium (4, 5). Traditionally, efforts to identify the midsecretory phase in individual women required a pathologist to evaluate the histologic features of endometrial biopsies. However, pathologists' subjective interpretation of histology introduces variability and risk of errors (6–8). In contrast, contemporary methods use transcriptomic endometrial dating, which is less subjective and more accurate in predicting the menstrual cycle phase through identifying gene expression changes across the cycle (8, 9).

One such approach, the endometrial receptivity array (ERA), uses a transcriptomic signature for dating human endometrial receptivity on the basis of 238 genes combined with an artificial intelligence algorithm and establishes computational thresholds for avoiding inter and intrapathologist variability (8). Indeed, machine learning removes subjective variation; consequently, this capability of the ERA signature to date endometrial biopsies is applied in the clinical setting for personalized embryo transfer (pET) according to the ERA result, e.g., tailoring transfer timing for patients with recurrent implantation failure (RIF) (10).

The pET procedure aims to synchronize the embryo transfer day to each patient's WOI, with modification of the days of progesterone administration according to the ERA results (6, 10). However, the clinical benefits of this approach remain controversial (11), although the ERA test can accurately detect endometrial progression (6, 12, 13). Further, ERA-based endometrial dating shows an inconsistent association between progesterone in the serum and progesterone in the endometrium (12, 14). This finding calls into question the use of a WOI based solely on the administration of progesterone. Additional factors may affect implantation, such as estrogen priming, progesterone type and route of administration, including local and peripheral levels, and endometrial changes induced by progesterone.

In addition, the success of performing pET based on ERA results is questioned. One study reported that ERA-guided pET improved implantation and ongoing pregnancy rates in RIF patients (15), even during euploid embryo transfer cycles (16), but other studies reported no improvement (17–20). The ERA-guided pET significantly improved the cumulative pregnancy rate in a randomized controlled study (RCT) of a population with infertility, but did not improve the success rate of the first attempt compared with the standard practice of previously frozen embryo transfers (FETs) or fresh embryo transfers (fsETs) (21).

Moreover, the results of that RCT are questioned because of several methodological concerns (22). In particular, the study was not blinded as reported in the protocol registration, and many patients received a different treatment than the one planned in the initial allocation, eliminating the advantage of randomization. Further, CLBR was not listed as an outcome in the registered statistical analysis plan and was incorrectly computed; statistical analysis was not conducted under the intention to treat principle (as is mandatory in RCTs); and there was an imbalance in the distribution of cases in the 2 study arms. These limitations in approach and execution raise the need for caution around the RCT's conclusions.

Recent studies also failed to support the routine use of ERA in populations with infertility undergoing single autologous euploid embryo transfers. In those cohorts, the LBR did not differ between patients who had embryo transfers with standard timing compared with patients who underwent pET (23–25). In addition, no data have been reported on the possible use of pET in cycles with donated oocytes, a transfer type best suited for testing endometrial factors.

Considering the methodological limitations of previous studies and lack of data on CLBR and donor cycles, we aimed to determine whether ERA-guided pET improves LBR, implantation, clinical pregnancy, and CLBRs compared with standard FET or fsET in unselected patients with infertility, each having experienced 1 unsuccessful embryo transfer after IVF.

## MATERIALS AND METHODS

### Study Design

This retrospective multicenter cohort study included medical information from the patients presenting with a previously failed embryo transfer at the IVIRMA clinics in Spain to evaluate pET guided by the ERA vs. standard FET or fsET. For clinical management, our group did not consider the ERA for patients at their first embryo transfer; therefore, such data are not available in this retrospective analysis.

Anonymized data were exported from our electronic health record database, following all rules regarding the protection of personal information. To estimate longitudinal information for patients (all transfers performed on each

patient), as well as CLBR, we included subsequent embryo transfers from the same patient only if they used the same embryo type (FET or fsET) as the first transfer considered within the study (i.e., the transfer after the first failed attempt). For example, if the embryo transfer after the initial failed attempt was FET, only subsequent FET ($\geq 1$) was computed for the CLBR results.

Data analyzed did not include information considered confidential according to previously executed research agreements with the third parties. Cycle data from our group that was used in the ERA RCT (21) were excluded because these cases were not managed as a clinical routine practice but under the trial protocol.

## Ethical Approval

This study was approved by the Ethics Committee of the Instituto Valenciano de Infertilidad (identification code # 1910-FIVI-087-NG).

## Patients

Two different patient populations were included in the study: patients undergoing autologous oocyte cycles and patients undergoing donated oocyte cycles. Patients >50 years receiving donor oocytes were excluded from the program. Body mass indices (BMIs) in both the autologous and donor groups ranged from 18.5 to 30 kg/m$^2$. Patients scheduled for single or double embryo transfers at the cleavage stage or blastocyst stage were included in the study. Ovarian reserve was assessed through antral follicle count (AFC >8) and day 3 serum follicle-stimulating hormone (FSH) concentration (<8 mIU/mL). Patients with fsET were excluded if progesterone levels were >1.5 ng/mL on the day of human chorionic gonadotropin (hCG) treatment or they exhibited ovarian hyperstimulation syndrome. Patients with uterine pathology, such as polyps or submucosal myomas, intramural myomas >4 cm, or hydrosalpinx corrected through neosalpingostomy (which could impact the endometrial environment) before embryo transfer were not included. In pET and FET groups, embryos were transferred in the cycle of hormone replacement therapy (HRT) after embryo thawing.

## Controlled Ovarian Stimulation in Autologous and Donor Cycles

Patients were stimulated with recombinant FSH either alone or in combination with highly purified human menopausal gonadotropin. Gonadotropins were started 2–3 days after menstruation or 5 days after stopping the combined oral contraceptive; an ultrasound before starting ovarian stimulation confirmed the absence of follicles >10 mm. Follicle development was monitored by ultrasound, and serum estradiol ($E_2$) concentrations were tested from day 5 of ovarian stimulation until the day of triggering with GnRH agonist or hCG. Daily treatment with a GnRH antagonist was started when 1 follicle reached a mean diameter of 13 mm. When at least 2 follicles measured $\geq$17–18 mm in mean diameter, recombinant hCG or GnRH agonist were administered subcutaneously to trigger final oocyte maturation. Oocyte retrieval was scheduled 36 hours after administering hCG or GnRH agonist. Embryos were at blastocyst (considering D5, D6, D7) or cleavage stage (D3) in the fsET group or vitrified for pET or FET. Luteal phase supplementation was initiated on the night of oocyte retrieval with vaginal progesterone 200 mg every 12 hours. Endometrial thickness of 7 mm was considered the minimum criterion at trigger to proceed with fsET. At the blastocyst stage, PGT-A was performed; however, in a few cases embryo biopsy was performed at the cleavage stage and embryos were cocultured until blastocyst stage.

Oocyte donors were healthy as previously described (26). Recovered oocytes were inseminated using intracytoplasmic sperm injection. At 16–18 hours after microinjection, oocytes were assessed for 2 pronuclei. Intrauterine embryo transfer was performed at the blastocyst stage. Embryo transfers were performed either in natural cycles or in cycles with hormonal preparation.

## Personalized Embryo Transfer Guided by ERA

In the pET group, patients underwent 1 or 2 endometrial biopsies (the timing of the second biopsy was based on the outcome of the first according to the iGenomix protocol), and embryo transfer timing was guided in the HRT cycle according to ERA results. For sampling, patients received an HRT cycle comprising 10–12 days of $E_2$ administration, and after endometrial thickness evaluation, 5 days of progesterone administration. An endometrial biopsy was collected under sterile conditions from the uterine fundus using a catheter. After the biopsy, endometrial tissue was transferred to a cryotube containing 1.5 mL of RNAlater and kept at 4 °C or on ice for at least 4 hours according to iGenomix recommendations for sample processing before shipment. Results were reported as receptive, prereceptive, or postreceptive with an associated diagnostic probability (Supplemental Figure 1, available online). On the basis of ERA results, patients received a recommendation for pET on days P+3, P+4, P+5, P+6, or P+7. For prereceptive or postreceptive patients, the ERA test was repeated with a fresh endometrial biopsy to confirm receptive status on the day indicated by the first test.

## Endometrial Preparation for FET and pET

The endometrial preparation protocol was described previously (27). Briefly, women with ovarian function were first down-regulated in the luteal phase with a single dose of GnRH agonist depot. Oral or transcutaneous estradiol valerate was used, and endometrial thickness was evaluated by ultrasound after 8–10 days of endometrial preparation. Progesterone and $E_2$ levels were assessed on the day of the ultrasound. For patients with trilaminar pattern and endometrial thickness >7 mm, micronized progesterone (800 $\mu$g/d) was administered vaginally at the dosage and route used by the participating physician/clinic for 5 days (P+5 or 120 hours, approximately) for FET or according to the ERA for pET.

## Outcome Measures

The main outcomes measured were LBR calculated per embryo transfer (percentage of deliveries with at least 1 infant

born) at the first embryo transfer and all consecutive transfers from each patient and CLBR (percentage of deliveries with at least 1 infant born after the subsequent embryo transfer, for each transfer) per patient, only considering transfers that were the same type (FET or fsET) as the first embryo transfer the patient received.

Secondary outcomes were pregnancy rate, defined as the percentage of embryo transfers resulting in a detectable pregnancy ($\beta$-hCG positive); implantation rate, defined as the percentage of embryos that successfully implanted assessed on the basis of the number of gestational sacs observed by vaginal ultrasound at the 5th week of pregnancy; and clinical miscarriage rate, defined as a fetal loss before the 20th week of gestation, either at the first embryo transfer or considering all emryo transfers.

### Statistical Analyses

Data are presented as means or proportions with corresponding standard deviations or 95% confidence intervals (CI). To ensure that the populations in each group were clinically similar, given the retrospective nature of the study, means and proportions of the most relevant clinical variables were compared with analysis of variance and chi squared tests, respectively. Parameters found to differ among the 3 groups as well as clinically relevant variables related to the main outcomes were later used to statistically control for potential biases.

To compare the main outcome measures between the pET, fsET, and FET groups, univariant and multivariant analyses were used, as appropriate, with the addition of relevant control variables in the model to reduce the risk of bias because of the confounding factors. Data were evaluated in the first embryo transfer using logistic regressions to estimate the corresponding odds ratio between groups, establishing the fsET group as the reference.

Data were also evaluated considering all subsequent embryo transfers, of the same type as the first transfer, for a given patient using generalized estimating equations during multivariant analysis, given the lack of data independence.

The variables considered as potential confounders were type of stimulation, FSH and human menopausal gonadotropin dose, patient age, donor age, BMI, number of aspirated oocytes, number of embryos transferred, day of embryo transfer, and type of insemination and trigger.

Two additional sensitivity analyses were performed. In the first, the cohort was divided into 2 study groups according to the origin of oocytes, either autologous or donated. In the second, we subdivided the sample on the basis of oocyte origin and whether PGT-A had been performed. Multivariable regression analysis was used as described previously, to address the same main outcome measures. The CLBRs were computed to estimate and compare time-to-event (i.e., live birth) using Kaplan-Meier estimates and Cox regression considering only subsequent transfers within the same patient. Cumulative hazard integrates (instantaneous) hazard rate over ages or time, similar to summing up probabilities, but because $\Delta t \Delta t$ is very small, these probabilities are also small numbers (e.g., hazard rate of dying may be around 0.004 at ages around 30). Hazard rate is conditional on not having experienced the event before t, so for a population it may sum $>1$.

SPSS version 26 (IBM, Chicago, IL, USA) was used for statistical analyses. A $P$ value $<.05$ was considered statistically significant.

## RESULTS

Data from 5,372 embryo transfers were included in the study, divided according to oocyte source and the presence or absence of PGT-A (Table 1). Among 3,239 autologous cycles (regardless of PGT-A status), 7.9% were ERA-guided pET; 34.6% were fsET; and 57.4% were FET. Among 2,133 donated cycles, 14.9% were ERA-guided pET; 55.1% were fsET; and 30% were FET. In Supplemental Figure 2 (available online), the number of embryo transfers included in the study were reported, including the first embryo transfer after a single previous failed transfer.

In autologous cycles, patient mean age $\pm$ standard deviation was 36.79 $\pm$ 3.5 for pET, 36.3 $\pm$ 3.41 for fsET, and 35.95 $\pm$ 3.82 for FET. In donor cycles, patient mean age was 41.13 $\pm$ 4.19 for pET, 40.42 $\pm$ 4.17 for fsET, and 42.16 $\pm$ 4.01 for FET.

Mean patient BMI (kg/m$^2$) for patients using autologous oocytes was 23.06 $\pm$ 3.96, 23.35 $\pm$ 4.23, and 22.87 $\pm$ 3.7 for pET, fsET, and FET, respectively. The mean number of years of infertility was 2.17 $\pm$ 1.69, 2.21 $\pm$ 1.72, and 2.44 $\pm$ 1.73 for pET, fsET, and FET, respectively. For patients receiving oocyte donation, mean BMI (kg/m$^2$) was 23.71 $\pm$ 4.1 for pET, 23.40 $\pm$ 3.93 for fsET, and 23.88 $\pm$ 4.3 for FET. The mean years of infertility for pET, fsET, and FET reported were 2.76 $\pm$ 2.36, 3.32 $\pm$ 2.92, and 3.67 $\pm$ 2.85, respectively.

Characteristics of the main stimulation cycles by PGT-A availability for all patients included in the study are summarized in Supplemental Table 1 (available online). Several statistical differences among groups were accounted for in the subsequent statistical modeling to avoid potential biases. These differences include the type of stimulation and triggering protocol, doses, the number of oocytes retrieved and number of fertilized insemination procedures, and the number of embryos transferred.

### Reproductive Outcomes at the First Embryo Transfer Using Autologous Oocytes

Among autologous cycles, the implantation and biochemical pregnancy rates at the first embryo transfer were significantly higher in the FET and fsET groups than in the pET group when PGT-A was not performed. Only the pregnancy rate was higher in FET and fsET groups than in the pET group when PGT-A was used.

In addition, LBRs were higher in the FET (+17%) and fsET (+16.3%) groups than in the pET group ($P$=.005) among autologous cycles without PGT-A. In cases with PGT-A, the differences were +10.4% for FET and +13.6% for fsET groups relative to the pET group ($P$=.02).

Using the non PGT-A fsET group as a reference, and considering potential confounders, the adjusted odds ratio (AOR) for pregnancy rate in the FET group was 0.95 (95% CI, 0.72–1.24), which was not significantly different. Similar

## TABLE 1

**Reproductive outcomes at the first embryo transfer using autologous and donated oocytes after a previous failed in vitro fertilization transfer.**

| | | Autologous cycles | | | | Donated cycles | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Term | fsET | FET | pET (ERA) | *P* value | fsET | FET | pET (ERA) | *P* value |
| No PGT | N | 1,037 | 1,049 | 88 | | 1,167 | 538 | 303 | |
| | Single embryo transfer[a] (%) | 418 (40.31) | 611 (58.25) | 75 (85.23) | 9.31e-25 | 620 (53.13) | 448 (83.27) | 277 (91.42) | 1.677e-54 |
| | Day 3 embryo transfer (%) | 458 (44.17) | 139 (13.25) | 1 (1.14) | < .001 | 156 (13.37) | 13 (2.42) | 1 (0.33) | < .001 |
| | Day 5 embryo transfer (%) | 579 (55.83) | 910 (86.75) | 87 (98.86) | | 1,011 (86.63) | 525 (97.58) | 302 (99.67) | — |
| | Implantation rate | 32.79 ± 41.1 | 39.7 ± 45.02 | 30.68 ± 45.13 | 6.32e-04 | 52.96 ± 46.28 | 41.17 ± 49.59 | 34.49 ± 47.52 | 5.726e-11 |
| | Biochemical pregnancy rate (%) | 543 (52.36) | 602 (57.39) | 36 (40.91) | .00253 | 811 (69.49) | 277 (51.49) | 141 (46.53) | 1.138e-18 |
| | Biochemical miscarriage rate[b] (%) | 91 (16.76) | 105 (17.44) | 8 (22.22) | .694 | 105 (12.95) | 51 (18.41) | 36 (25.53) | .0002558 |
| | Clinical pregnancy rate (%) | 446 (43.01) | 489 (46.62) | 28 (31.82) | .014 | 698 (59.81) | 223 (41.45) | 102 (33.66) | 8.931e-21 |
| | Clinical miscarriage rate[b] (%) | 89 (16.39) | 118 (19.6) | 11 (30.56) | .0619 | 109 (13.44) | 58 (20.94) | 28 (19.86) | .004997 |
| | Ongoing pregnancy rate (%) | 357 (34.43) | 371 (35.37) | 17 (19.32) | .00954 | 589 (50.47) | 165 (30.67) | 74 (24.42) | 1.05e-22 |
| | Live birth rate[c] (%) | 357 (34.43) | 369 (35.18) | 16 (18.18) | .00523 | 588 (50.39) | 164 (30.48) | 74 (24.42) | 9.569e-23 |
| | Number of live births | 414 (0.4 ± 0.59) | 427 (0.41 ± 0.59) | 16 (0.18 ± 0.39) | .327 | 725 (0.62 ± 0.69) | 179 (0.33 ± 0.53) | 78 (0.26 ± 0.47) | 2.401e-09 |
| PGT | N | 85 | 813 | 167 | | 8 | 101 | 16 | |
| | Single embryo transfer[a] (%) | 56 (65.88) | 735 (90.41) | 158 (94.61) | 2.01e-12 | 4 (50) | 91 (90.1) | 16 (100) | .0007853 |
| | Day 3 embryo transfer (%) | 0 | 0 | 0 | < .001 | 0 | 0 | 0 | .106 |
| | Day 5 embryo transfer (%) | 85 (100) | 813 (100) | 167 (100) | | 8 (100) | 101 (100) | 16 (100) | — |
| | Implantation rate | 45.88 ± 50.13 | 49.57 ± 50.7 | 41.02 ± 49.79 | .128 | 43.75 ± 49.55 | 55.45 ± 50.45 | 25 ± 44.72 | .07295 |
| | Biochemical pregnancy rate (%) | 51 (60) | 475 (58.43) | 80 (47.9) | .0366 | 4 (50) | 63 (62.38) | 7 (43.75) | .3193 |
| | Biochemical miscarriage rate[b] (%) | 9 (17.65) | 69 (14.53) | 11 (13.75) | .81 | 1 (25) | 6 (9.52) | 3 (42.86) | .03942 |
| | Clinical pregnancy rate (%) | 42 (49.41) | 399 (49.08) | 68 (40.72) | .137 | 3 (37.5) | 57 (56.44) | 4 (25) | .04725 |
| | Clinical miscarriage rate[b] (%) | 5 (9.8) | 69 (14.53) | 18 (22.5) | .0987 | 0 | 10 (15.87) | 2 (28.57) | .457 |
| | Ongoing pregnancy rate (%) | 37 (43.53) | 330 (40.59) | 50 (29.94) | .0255 | 3 (37.5) | 47 (46.53) | 2 (12.5) | .03607 |
| | Live birth rate[c] (%) | 37 (43.53) | 328 (40.34) | 50 (29.94) | .0285 | 2 (25) | 46 (45.54) | 2 (12.5) | .02894 |
| | Number of live births | 49 (0.58 ± 0.73) | 337 (0.41 ± 0.51) | 50 (0.3 ± 0.46) | .0565 | 2 (0.25 ± 0.46) | 50 (0.5 ± 0.58) | 2 (0.12 ± 0.34) | .5755 |

*Note:* Data represent means or proportions with their corresponding SDs.
Computed *P* values of the Pearson's chi squared test for comparing proportions in 3 groups.
Computed *P* values of the analysis of variance (after the F-test for equal variance) in 3 groups. PGT = preimplantation genetic testing, fsET = fresh embryo transfer, FET = frozen embryo transfer, pET = personalized embryo transfer, ERA = endometrial receptivity array.
[a] Percentage of single embryo transfers over the total number of embryos.
[b] Percentage over the number of pregnancies.
[c] Percentage calculated by the number of transfers minus the number of pregnancies without reported delivery.

*Cozzolino. ERA-guided pET after failed transfer. Fertil Steril 2022.*

results were reached for pET relative to fsET, the AOR was 0.51 (95% CI, 0.30–0.89), a statistically significant difference. For the PGT-A cases, there were no significant differences in AOR of the FET and pET groups relative to the fsET reference group.

There was a statistically significant increase in the clinical miscarriage rate when comparing the non PGT-A fsET reference and pET groups (AOR, 3.36; 95% CI, 1.34–8.42), ($P<.05$), without difference between pET and FET. When PGT-A was performed, miscarriage rates were comparable among all groups with or without adjustment.

Concerning the main outcome measure, i.e., LBR per embryo transfer, the pET group generally performed more poorly than the other transfer groups regardless of PGT-A status, both before and after adjusting for potential confounders. Using fsET as the reference group, the AOR was 0.85 (95% CI, 0.63–1.14) for FET in non PGT-A cases and 1.20 (95% CI, 0.58–2.48) for PGT-A cases, neither of which represented a significant difference. For PGT-A cases of pET, the AOR was 0.55 (95% CI, 0.32–0.95, not significantly different). In contrast, for non PGT-A cases of pET vs. fsET, the AOR of the LBR was significantly low at 0.39 (95%CI, 0.19–1.79; $P<.05$).

This analysis was repeated by assessing only embryos transferred to the blastocyst stage as shown in Supplemental Table 2 (available online). In this subgroup analysis, pET again had worse IVF outcomes than fsET and FET.

## Reproductive Outcomes at the First Embryo Transfer Using Donated Oocytes

The implantation and pregnancy rates at the first embryo transfer in patients receiving donated oocytes without PGT-A were higher in the FET and fsET than in the pET group ($P<.0001$). Biochemical and clinical miscarriage rates were lower in the fsET group than in the FET and pET groups ($P<.0001$). In addition, LBRs were higher in the fsET (+26%) and FET (+6.1%) groups than in the pET group ($P<.0001$).

Pregnancy rates in the FET and pET groups were statistically lower than that in the fsET reference; the AORs were 0.55 (95% CI, 0.44–0.70) and 0.46 (95% CI, 0.35–0.61), respectively. Biochemical and clinical miscarriage rates were significantly higher in the pET group than in the fsET and FET group, resulting in an AOR of 1.70 (95% CI, 1.07–2.69) and 1.70 (95% CI, 1.02–2.82), respectively. Ultimately, these differences reduced the resulting delivery per embryo transfer in the FET (AOR, 0.48; 95% CI, 0.37–0.61) and pET groups (AOR, 0.37; 95% CI, 0.27–0.50), with all differences statistically significant.

Patients receiving donated oocytes with PGT-A exhibited no significant differences in biochemical and clinical pregnancy rates, but the low number of cases and increased percentage of biochemical miscarriages in the pET group resulted in an LBR lower than that of the FET (+33%) and fsET (+12.5%) groups ($P=.03$) (Table 1). This difference was not statistically significant after adjusting for the most relevant variables.

## Reproductive Outcomes at all Consecutive Embryo Transfers with Autologous Oocytes

Table 2 shows the outcome measures considering all transfers analyzed in this study. For a given patient, multiple transfers were considered only if they matched the type used in the first attempt (after the initial failed transfer). For transfers using autologous oocytes without PGT-A, the LBR with at least 1 live infant was significantly lower (by approximately 15%; $P=.002$) in the pET group than in the FET and fsET groups. Clinical pregnancy rates appeared similar among groups, but the pET vs. fsET (AOR,0.62; 95% CI, 0.39–1.00; $P<.001$) indicated a significant reduction. The clinical miscarriage rate was significantly higher in the pET group (AOR, 2.83; 95% CI, 1.32–6.06; $P<.001$), and the LBR was significantly lower after adjustment (AOR, 0.45; 95% CI, 0.24–0.82; $P<.001$).

In the pET group, LBR was also significantly lower than that in the FET and fsET groups in autologous cycles with PGT-A. In the pET to fsET reference group comparison, the pET group had a significantly lower pregnancy rate resulting in significantly lower LBR. However, after adjusting for the selected covariates, there were no statistically significant differences in pregnancy rate (AOR, 1.51; 95% CI, 0.74–3.10) or LBR (AOR, 1.08; 95% CI, 0.51–2.29).

This analysis was repeated by assessing only embryos transferred to the blastocyst stage as shown in Supplemental Table 2. In this subgroup analysis, pET again had worse IVF outcomes than fsET and FET.

## Reproductive Outcomes at all Consecutive Embryo Transfers with Donated Oocytes

In embryo transfers with donated oocytes not undergoing PGT-A, LBR was significantly higher, by approximately 20% and 25% in the fsET and FET groups, respectively ($P<.001$ [Table 2]) compared with the pET group. Pregnancy rates were significantly lower in the FET and pET groups than the fsET group, with AOR of 0.53 (95% CI, 0.43–0.65) and 0.47 (95% CI, 0.37–0.60), respectively. Clinical miscarriage rates were also higher in both the FET (AOR, 1.54; 95% CI, 1.09–2.17) and pET groups (AOR, 1.62; 95% CI, 1.06–2.47).

These differences resulted in CLBRs that were significantly lower in the FET and pET groups than the fsET group, with AOR of 0.51 (95% CI, 0.42–0.63) and 0.39 (95% CI, 0.30–0.51), respectively. In embryo transfers with donated oocytes undergoing PGT-A, there were no significant between-group differences in pregnancy, miscarriage, or resulting LBRs (Table 2). These comparable results were maintained even after adjusting for potential confounders.

## Cumulative Live Birth Rates Per Embryo Transfer Number

The CLBRs after 3 embryo transfers, analyzed through a survival analysis and time-to-event approach, for patients undergoing autologous oocyte transfer without PGT-A were 52.59% (95% CI, 45.06–59.10) for fsET, 51.87% (95% CI, 47.16–56.16) for FET, and 33.16% (95% CI, 14.03–48.03) for

## TABLE 2

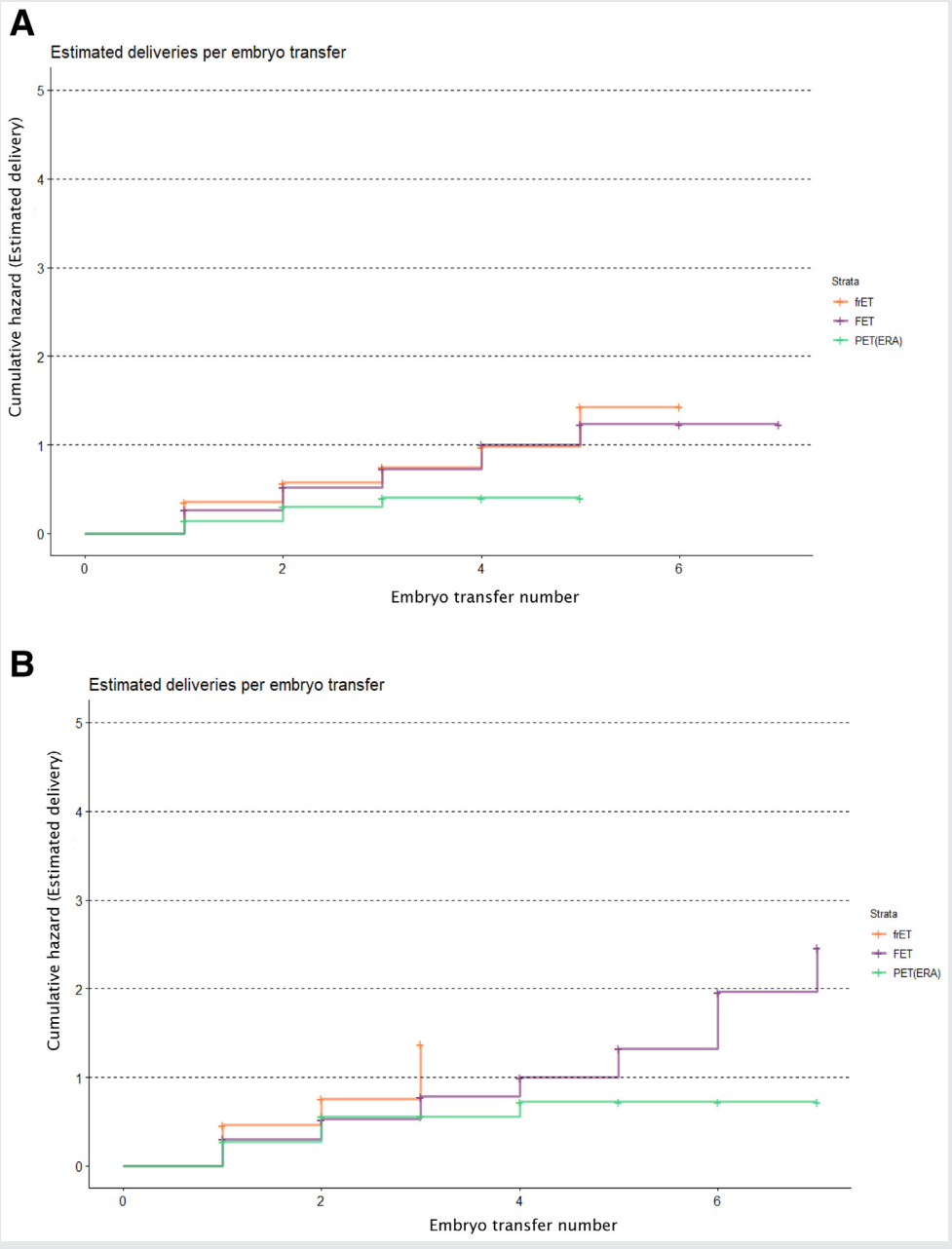
**Reproductive outcomes after all embryo transfers using autologous and donated oocytes after a previous failed in vitro fertilization cycle.**

| | | Autologous cycles | | | | Donated cycles | | | |
|---|---|---|---|---|---|---|---|---|---|
| **PGT** | **Term** | **fsET** | **FET** | **pET(ERA)** | ***P* value** | **fsET** | **FET** | **pET (ERA)** | ***P* value** |
| No PGT | N | 1,190 | 1,570 | 121 | | 1,324 | 800 | 449 | |
| | Day 3 embryo transfer (%) | 510 (42.86) | 174 (11.08) | 1 (0.83) | < .001 | 165 (12.46) | 15 (1.88) | 1 (0.22) | < .001 |
| | Day 5 embryo transfer (%) | 680 (57.14) | 1,396 (88.92) | 120 (99.17) | | 1,159 (87.54) | 785 (98.12) | 448 (99.78) | |
| | Biochemical pregnancy rate (%) | 612 (51.43) | 852 (54.27) | 52 (42.98) | .03172* | 922 (69.64) | 403 (50.38) | 207 (46.1) | 2.924e-26*** |
| | Clinical pregnancy rate (%) | 506 (42.52) | 696 (44.33) | 39 (32.23) | .03078* | 792 (59.82) | 324 (40.5) | 153 (34.08) | 7.088e-28*** |
| | Ongoing pregnancy rate (%) | 400 (33.61) | 533 (33.95) | 23 (19.01) | .003215** | 663 (50.08) | 247 (30.88) | 110 (24.5) | 9.896e-29*** |
| | Live birth rate[a] (%) | 400 (33.61) | 530 (33.76) | 22 (18.18) | .001822** | 662 (50) | 246 (30.75) | 110 (24.5) | 1.015e-28*** |
| | Number of live births | 460 (0.39 ± 0.58) | 608 (0.39 ± 0.58) | 22 (0.18 ± 0.39) | .2579 | 818 (0.62 ± 0.69) | 266 (0.33 ± 0.52) | 114 (0.25 ± 0.46) | 9.003e-13*** |
| PGT | N | 100 | 1,249 | 207 | | 10 | 148 | 25 | |
| | Day 3 embryo transfer (%) | 0 | 0 | 0 | < .001 | 0 | 0 | 0 | .01 |
| | Day 5 embryo transfer (%) | 100 (100) | 1,249 (100) | 207 (100) | | 10 (100%) | 148 (100) | 25 (100) | |
| | Biochemical pregnancy rate (%) | 59 (59) | 728 (58.29) | 97 (46.86) | .007994** | 6 (60) | 84 (56.76) | 13 (52) | .8798 |
| | Clinical pregnancy rate (%) | 49 (49) | 600 (48.04) | 82 (39.61) | .07298* | 5 (50) | 76 (51.35) | 9 (36) | .3643 |
| | Ongoing pregnancy rate (%) | 44 (44) | 484 (38.75) | 62 (29.95) | .02328* | 4 (40) | 60 (40.54) | 7 (28) | .4909 |
| | Live birth rate[a] (%) | 44 (44) | 482 (38.59) | 61 (29.47) | .01759* | 3 (30) | 59 (39.86) | 7 (28) | .4609 |
| | Number of live births | 57 (0.57 ± 0.71) | 501 (0.4 ± 0.52) | 61 (0.29 ± 0.46) | .03252* | 3 (0.3 ± 0.48) | 63 (0.43 ±0.55) | 7 (0.28 ± 0.46) | .75 |

*Note:* Data represent means or proportions with their corresponding SDs.
Computed P values of the Pearson's chi squared test for comparing proportions in 3 groups.
Computed P values of the Analysis of variance (after the F-test for equal variance) in 3 groups. PGT = preimplantation genetic testing, fsET = fresh embryo transfer, FET = frozen embryo transfer, pET = personalized embryo transfer, ERA = endometrial receptivity array.
[a] Percentage calculated by the number of transfers minus the number of pregnancies without reported delivery.
* $P < .05$; ** $P < .001$; *** $P < .001$.

*Cozzolino. ERA-guided pET after failed transfer. Fertil Steril 2022.*

## FIGURE 1



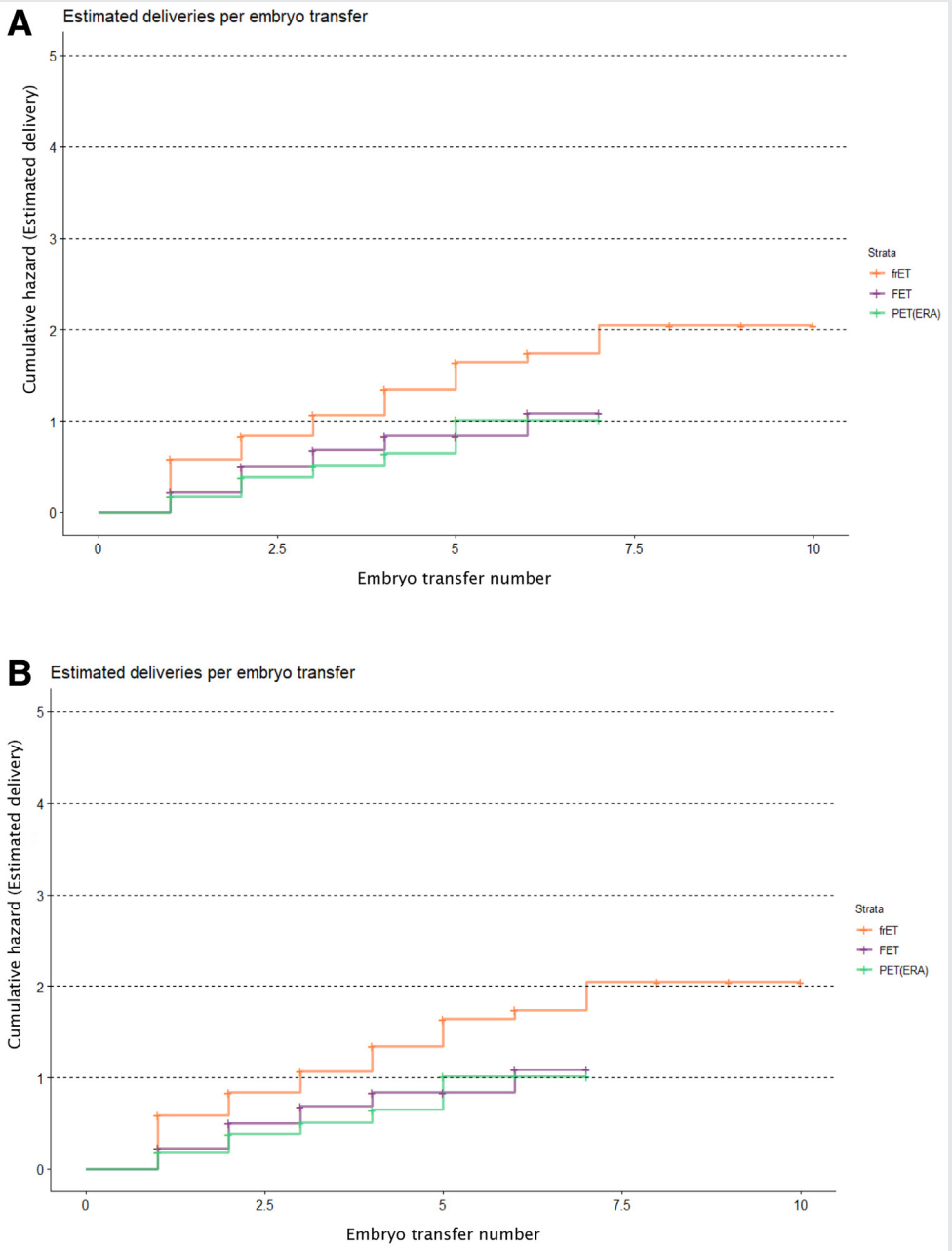

Cumulative delivery rates per embryo transfer and cumulative delivery rate in autologous cycles without preimplantation genetic testing for aneuploidy **(A)**, with preimplantation genetic testing for aneuploidy **(B).** frET = fresh embryo transfer, FET = frozen embryo transfer, pET (ERA) = personalized embryo transfer guided by endometrial receptivity array.

*Cozzolino. ERA-guided pET after failed transfer. Fertil Steril 2022.*

pET ($P<.0001$) (Fig. 1A and Supplemental Table 3[available online]). For patients with autologous oocytes undergoing PGT-A, CLBRs after 3 embryo transfers were 74.69% (95% CI, 44.78–88.40) for fsET, 54.13% (95% CI, 57.25–68.18) for FET, and 51.61% (95% CI, 29.31–66.88) for pET ($P=.01$) (Fig. 1B and Supplemental Table 4 [available online]).

In addition, CLBRs after 5 embryo transfers, for patients receiving donor oocytes without PGT-A, were 80.59% (95% CI, 73.25–85.92) for fsET, 66.33% (95% CI, 42.99–80.11) for FET, and 63.71% (95% CI, 36.28–79.33) for pET (both $P<.0001$) (Fig. 2A and Supplemental Table 5 [available online]). In patients with donor oocyte cycles undergoing PGT-A, the CLBRs after 2 embryo transfers were 70.21% (95% CI, 18.00–95.89) for fsET, 44.05% (95% CI, 33.38–53.02) for FET, and 46.60% (95% CI, 7.20–69.27) for pET ($P=.68$) (Fig. 2B and Supplemental Table 6 [available online]).

## FIGURE 2




Cumulative delivery rates per embryo transfer and cumulative rates in oocyte donor cycles without preimplantation genetic testing for aneuploidy **(A)**, with preimplantation genetic testing for aneuploidy **(B)** frET = fresh embryo transfer, FET = frozen embryo transfer, pET (ERA) = endometrial receptivity array-guided personalized embryo transfer.

*Cozzolino. ERA-guided pET after failed transfer. Fertil Steril 2022.*

## DISCUSSION

Although retrospective, this study is the largest to date and the first to include CLBR to assess the effect of ERA-guided pET in consecutive embryo transfers. This study also is the only one to include donor cycles, a widely-used technique with a clinical performance different from the conventional IVF, with autologous oocytes. Our findings demonstrate worse LBR for pET compared with fsET and FET in women with a previous failed embryo transfer for both autologous and donor cycles. In the subgroup analysis, considering only embryo transferred at the blastocyst stage, again pET demonstrated worse outcomes than fsET and FET. For fsET and FET relative to pET for autologous cycles, CLBRs were high; in donor cycles, the CLBR was increased in these groups

only when considering cycles without PGT-A. Thus, rather than improving reproductive outcomes, these findings indicate that timing the transfer day according to ERA results worsens the outcomes.

Data from an RCT on an unselected population undergoing euploid embryo transfers were recently presented (23). In that study, 767 subjects were randomized; 381 received ERA-guided pET and 386 were assigned to the control group with progesterone exposure of 123 ± 3 hours. Their results indicated that ERA-guided pET did not improve the ongoing pregnancy rate for euploid single embryo transfers (23). Similarly, we found no benefit of pET after 1 previous failed transfer. These results align with those of other studies assessing the outcomes after first embryo transfer, although the previous studies did not calculate CLBR (24, 25).

Our study did assess CLBR as an important indicator of reproductive success in IVF. According to Pirtea et al. (1), CLBR is approximately 95% after 3 consecutive frozen euploid embryo transfers, but LBR per transfer is approximately 50%–60% (1). Moreover, they described that a high percentage of patients receiving euploid embryos does not achieve pregnancy. These outcomes could indicate a possible defect in the interaction between blastocyst and endometrium. Notably, our study did not find a similar CLBR to that reported by Pirtea et al. (1). This difference could stem from differences in the inclusion criteria because we included patients who had experienced 1 failed transfer whereas the previous study included patients with no previous cycles.

Our study was designed to add important information on the clinical outcomes of pET guided by ERA results. The ERA was the first molecular assay test created to assess endometrial receptivity in RIF (10), but its usefulness has not been validated (17, 19). Several studies with small sample sizes detected consistent transcriptomic profiles cycle-by-cycle (6, 28), but inconsistencies are reported for the ERA in the same patient, indicating some month-to-month variation (29, 30). Further, studies endorsing the use of ERA for personalized medicine did not consider the euploid status of the embryo, which may have influenced their findings (10, 15). The ERA-guided pET failed to improve the pregnancy outcomes for patients with at least 1 failed euploid embryo transfer in our study and those experiencing 2 failed donor embryo transfers (31). In addition, euploid embryo transfers yielded similar implantation rates, ongoing pregnancy rates, and LBRs in patients with receptive or nonreceptive results after ERA (16).

Most importantly, an RCT (21) showed that the CLBR after a 12-month follow-up was significantly higher for ERA-guided pET received at the first appointment than for FET and fsET. In contrast, our study, which analyzed CLBR using survival analysis depending on the number of embryo transfers, indicated that CLBR was lower for the pET group than the FET and fsET groups, both for autologous and donor cycles and independent of PGT-A performance. In the RCT, no statistical differences were reported in the LBRs of women receiving either pET, FET, or fsET (56.2%, 42.4%, or 45.7%, respectively; pET vs. FET, $P=.09$; pET vs. fsET, $P=.17$) after the first embryo transfer, although the percentage of live births was higher in the pET group (21). The results of the RCT appear interesting, but the data quality and analysis had several limitations, which made it difficult to translate findings to clinical practice. Further, the study had an unexpectedly high drop-out rate, and the analysis was not conducted after the intention to treat (22). Although the ERA signature is an accurate endometrial dating tool for detecting the WOI, in our study, the use of ERA-guided pET did not seem to benefit autologous or donor cycles, even when considering CLBR.

It is possible that the use of ERA-based pET in IVF cycles may not be realized simply by adjusting the progesterone administration time. Although progesterone is essential for guaranteeing normal embryo implantation, no existing clinical evidence indicates that specific routes, dosages, or duration of progesterone administration in IVF or intracytoplasmic sperm injection cycles favors outcomes (14, 32–37). On the other hand, although the midsecretory endometrium achieves a sufficient intratissue level of progesterone, this seems insufficient to achieve pregnancy. In addition, the proportion of nonreceptive ERA cases that achieved a live birth after an adjusted progesterone exposure, i.e., personalized FET, was lower in women with 3 previous failed transfers than in those with 1 previous failed transfer (19). This suggests that additional factors, such as the underlying etiology of infertility (11) or differences in ovarian function, are involved in the implantation failure beyond an adjustment in progesterone exposure (33).

Further, no association is documented between serum progesterone and ERA-based endometrial maturation (14). Although predictive of ongoing pregnancy, progesterone is a poor indirect marker of endometrial function (20). This finding was confirmed in a case–control trial, in which 46 women were randomized to receive increasing doses of intramuscular progesterone before undergoing an endometrial biopsy. The results revealed that normal histologic development can occur at well-below normal levels of progesterone, in contrast to the detrimental effects of low progesterone observed at the level of endometrial gene expression (38). We cannot rule out the possibility that the detection of timing for progesterone administration may benefit a subgroup of patients, but this parameter appears unhelpful for patients undergoing their first FET.

Interestingly, we found that patients who underwent pET had worse results compared with those receiving either FETs or frETs. Many studies debate whether biopsy has a positive effect on reproductive outcomes. In our study, assuming that changing progesterone does not have any relevant clinical effect, the biopsy produced worse results. This outcome may be attributable to the effects of HRT, which could alter the complex interaction between embryo and endometrium, and that high serum $E_2$ levels could damage the endometrium, shorten the available WOI, and inhibit embryo implantation. Patients undergoing pET received HRT, whereas some patients undergoing FET had natural cycles. Natural cycles seem to have better IVF outcomes than HRT in frozen cycles.

Nonetheless, our results further underscore that the endometrial factor remains an unsolved problem. Although ERA results inform on endometrial status, ERA-guided pET did not improve reproductive outcomes. The use of ERA is not generalizable to the entire population pursuing embryo transfer, and in clinical practice, the results are controversial enough to preclude pET by changing the day of transfer. However, there remains a need for methods to assess the endometrium to improve the pregnancy rate per transfer.

Further studies should clarify which patient populations, if any, might benefit from pET. In this vein, Sebastian-Leon et al. (11) applied transcriptomic and artificial intelligence algorithms to consider 2 possible molecular causes of endometrial problems: a displaced and/or a dysfunctional endometrium. In this clinical algorithm, only patients with a displaced but healthy endometrium would benefit from pET according to endometrial dating. Patients with dysfunctional endometria should be diagnosed, and their treatment would require development of new therapies (11).

The strengths of our study include its large sample size and consideration of patients with infertility after 1 previous failed embryo transfer even with euploid embryos, thereby selecting a patient population that may benefit from endometrial factor consideration. The large sample size allows for the detection of even small differences between the different treatments. An additional strength is that we controlled for all variables that might bias the analysis. However, the retrospective design is a limitation of this study, as is the variability in progesterone protocols used. The study covers a long period, in few cases embryo biopsy for PGT-A was performed at cleavage stage with embryos transferred at blastocyst stage. In addition, this is a nonrandomized, retrospective study; it is possible that there is a bias introduced by clinicians who allocated patients to the treatment. Varying luteal support protocols can differentially affect the endometrial gene signature; therefore, the inconsistency of progesterone protocols used in our cohort may have influenced our results (39). This study included cases assessed with ERA using the array technology and Next Generation Sequencing model predictor, which was based on the current approach offered by iGenomix; in contrast, the RCT by Simon et al. (21) started in 2015 included patients assessed with both the original and the improved model because of a transition in the method over time. Lastly, the study included a small sample size of patients in donor cycles undergoing PGT-A.

Currently, ERA-guided pET increases the cost and delays IVF treatment because endometrial gene expression must be analyzed in the cycle before embryo transfer. This may be unnecessary in patients with 1 previous failed embryo transfer and for most of the patients undergoing IVF.

## CONCLUSIONS

In summary, our results suggest that ERA-guided pET does not improve the reproductive outcomes of patients with 1 previous implantation failure either in autologous and donor cycles or even after euploid embryo transfer. Conversely, worse outcomes were detected with pET guided by ERA. A new procedure for endometrial evaluation associated with fertility status is needed to improve IVF cycles.


**DIALOG:** You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/34383

## REFERENCES


1. Pirtea P, De Ziegler D, Tao X, Sun L, Zhan Y, Ayyub JM, et al. Rate of true recurrent implantation failure is low: results of three successive frozen euploid single embryo transfers. Fertil Steril 2021;115:45–53.
2. Scott RT Jr, Upham KM, Forman EJ, Hong KH, Scott KL, Taylor D, et al. Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial. Fertil Steril 2013;100:697–703.
3. Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. N Engl J Med 1999;340:1796–9.
4. Navot D, Scott RT, Droesch K, Veeck LL, Liu HC, Rosenwaks Z. The window of embryo transfer and the efficiency of human conception in vitro. Fertil Steril 1991;55:114–8.
5. Karizbodagh MP, Rashidi B, Sahebkar A, Masoudifar A, Mirzaei H. Implantation window and angiogenesis. J Cell Biochem 2017;118:4141–51.
6. Díaz-Gimeno P, Ruiz-Alonso M, Blesa D, Bosch N, Martínez-Conejero JA, Alamá P, et al. The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity. Fertil Steril 2013;99:508–17.
7. Coutifaris C, Myers ER, Guzick DS, Diamond MP, Carson SA, Legro RS, et al. Histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertil Steril 2004;82:1264–72.
8. Murray MJ, Meyer WR, Zaino RJ, Lessey BA, Novotny DB, Ireland K, et al. A critical analysis of the accuracy, reproducibility, and clinical utility of histologic endometrial dating in fertile women. Fertil Steril 2004;81:1333–43.
9. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Am J Obstet Gynecol 1975;122:262–3.
10. Ruiz-Alonso M, Blesa D, Díaz-Gimeno P, Gómez E, Fernández-Sánchez M, Carranza F, et al. The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. Fertil Steril 2013;100:818–24.
11. Sebastian-Leon P, Garrido N, Remohi J, Pellicer A, Díaz-Gimeno P. Asynchronous and pathological windows of implantation: two causes of recurrent implantation failure. Hum Reprod 2018;33:626–35.
12. Díaz-Gimeno P, Sebastian-Leon P, Sanchez-Reyes JM, Spath K, Aleman A, Vidal C, et al. Identifying and optimizing human endometrial gene expression signatures for endometrial dating. Hum Reprod 2022;37:284–96.
13. Díaz-Gimeno P, Ruiz-Alonso M, Sebastian-Leon P, Pellicer A, Valbuena D, Simón C. Window of implantation transcriptomic stratification reveals different endometrial subsignatures associated with live birth and biochemical pregnancy. Fertil Steril 2017;108:703–10.e3.
14. Labarta E, Sebastian-Leon P, Devesa-Peiro A, Celada P, Vidal C, Giles J, et al. Analysis of serum and endometrial progesterone in determining endometrial receptivity. Hum Reprod 2021;36:2861–70.
15. Patel JA, Patel AJ, Banker JM, Shah SI, Banker MR. Personalized embryo transfer helps in improving in vitro fertilization/ICSI outcomes in patients with recurrent implantation failure. J Hum Reprod Sci 2019;12:59–66.
16. Tan J, Kan A, Hitkari J, Taylor B, Tallon N, Warraich G, et al. The role of the endometrial receptivity array (ERA) in patients who have failed euploid embryo transfers. J Assist Reprod Genet 2018;35:683–92.
17. Cozzolino M, Diaz-Gimeno P, Pellicer A, Garrido N. Evaluation of the endometrial receptivity assay and the preimplantation genetic test for aneuploidy in overcoming recurrent implantation failure. J Assist Reprod Genet 2020;37:2989–97.
18. Cohen AM, Ye XY, Colgan TJ, Greenblatt EM, Chan C. Comparing endometrial receptivity array to histologic dating of the endometrium in

women with a history of implantation failure. Syst Biol Reprod Med 2020; 66:347–54.
19. Eisman LE, Pisarska MD, Wertheimer S, Chan JL, Akopians AL, Surrey MW, et al. Clinical utility of the endometrial receptivity analysis in women with prior failed transfers. J Assist Reprod Genet 2021;38:645–50.
20. Saxtorph MH, Hallager T, Persson G, Petersen KB, Eriksen JO, Larsen LG, et al, Assessing endometrial receptivity after recurrent implantation failure: a prospective controlled cohort study. Reprod Biomed Online 2020;41:998–1006.
21. Simón C, Gómez C, Cabanillas S, Vladimirov I, Castillón G, Giles J, et al. A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF. Reprod Biomed Online 2020;41:402–15.
22. Lensen S, Wilkinson J, van Wely M, Farquhar C. Comments on the methodology of an endometrial receptivity array trial. Reprod Biomed Online 2021; 42:283.
23. Doyle N, Jahandideh S, Hill MJ, Widra EA, Levy M, Devine K, et al. Live birth after transfer of a single euploid vitrified-warmed blastocyst according to standard timing vs. timing as recommended by endometrial receptivity analysis. Fertil Steril 2022;118:314–21.
24. Bergin K, Eliner Y, Duvall DW, Roger S, Elguero S, Penzias AS, et al. The use of propensity score matching to assess the benefit of the endometrial receptivity analysis in frozen embryo transfers. Fertil Steril 2021;116:396–403.
25. Riestenberg C, Kroener L, Quinn M, Ching K, Ambartsumyan G. Routine endometrial receptivity array in first embryo transfer cycles does not improve live birth rate. Fertil Steril 2021;115:1001–6.
26. Garrido N, Zuzuarregui JL, Meseguer M, Simón C, Remohí J, Pellicer A. Sperm and oocyte donor selection and management: experience of a 10 year follow-up of more than 2100 candidates. Hum Reprod 2002;17: 3142–8.
27. Soares SR, Troncoso C, Bosch E, Serra V, Simón C, Remohí J, et al. Age and uterine receptiveness: predicting the outcome of oocyte donation cycles. J Clin Endocrinol Metab 2005;90:4399–404.
28. Evans GE, Phillipson GTM, Sykes PH, McNoe LA, Print CG, Evans JJ. Does the endometrial gene expression of fertile women vary within and between cycles? Hum Reprod 2018;33:452–63.
29. Dahan MH, Tan SL. Variations in the endometrial receptivity assay (ERA) may actually represent test error. J Assist Reprod Genet 2018;35:1923–4.
30. Cho K, Tan S, Buckett W, Dahan MH. Intra-patient variability in the endometrial receptivity assay (ERA) test. J Assist Reprod Genet 2018 May;35(5): 929–30.
31. Neves AR, Devesa M, Martínez F, Garcia-Martinez S, Rodriguez I, Polyzos NP, et al. What is the clinical impact of the endometrial receptivity array in PGT-A and oocyte donation cycles? J Assist Reprod Genet 2019; 36:1901–8.
32. Glujovsky D, Pesce R, Fiszbajn G, Sueldo C, Hart RJ, Ciapponi A. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. Cochrane Database Syst Rev 2010;20: CD006359.
33. Hirschberg CI, Blakemore JK, Fino E, Grifo JA. Prospective analysis of progesterone exposure in programmed single thawed euploid embryo transfer cycles and outcomes. J Assist Reprod Genet 2021;38:901–5.
34. Labarta E, Mariani G, Rodríguez-Varela C, Bosch E. Individualized luteal phase support normalizes live birth rate in women with low progesterone levels on the day of embryo transfer in artificial endometrial preparation cycles. Fertil Steril 2022;117:96–103.
35. Roelens C, Santos-Ribeiro S, Becu L, Mackens S, Van Landuyt L, Racca A, et al. Frozen-warmed blastocyst transfer after 6 or 7 days of progesterone administration: impact on live birth rate in hormone replacement therapy cycles. Fertil Steril 2020;114:125–32.
36. Theodorou E, Forman R. Live birth after blastocyst transfer following only 2 days of progesterone administration in an agonadal oocyte recipient. Reprod Biomed Online 2012;25:355–7.
37. van de Vijver A, Drakopoulos P, Polyzos NP, Van Landuyt L, Mackens S, Santos-Ribeiro S, et al. Vitrified-warmed blastocyst transfer on the 5th or 7th day of progesterone supplementation in an artificial cycle: a randomised controlled trial. Gynecol Endocrinol 2017;33:783–6.
38. Young SL, Savaris RF, Lessey BA, Sharkey AM, Balthazar U, Zaino RJ, et al. Effect of randomized serum progesterone concentration on secretory endometrial histologic development and gene expression. Hum Reprod 2017;32: 1903–14.
39. Bermejo A, Cerrillo M, Ruiz-Alonso M, Blesa D, Simon C, Pellicer A, et al. Impact of final oocyte maturation using gonadotropin-releasing hormone agonist triggering and different luteal support protocols on endometrial gene expression. Fertil Steril 2014;101:138–46.e3.

**El uso del ensayo de receptividad endometrial para guiar la transferencia embrionaria personalizada luego de un intento fallido de transferencia fue asociado con una menor tasa acumulativa y por transferencia de nacidos vivos durante ciclos de donantes y autólogos.**

**Objetivo:** Determinar si la transferencia embrionaria personalizada (pET) guiada por la prueba de ensayo de receptividad endometrial (ERA) mejora los resultados reproductivos para transferencias embrionarias en fresco (fsETs) o transferencias embrionarias de congelados (FETs) durante ciclos autólogos y de donantes en pacientes de clínicas IVIRMA.

**Diseño:** Un estudio de cohorte retrospectivo, observacional y multicéntrico.

**Lugar:** Centro de fertilización in vitro afiliado a la Universidad.

**Paciente (s):** El estudio incluyó pacientes con una sola transferencia previa fallida y produjo 3,239 transferencias autólogas y 2,133 transferencias de donantes. Entre las transferencias autólogas, 255 fueron pET guiadas por ERA; entre las transferencias autólogas no guiadas, 1,122 y 1,862 transferencias involucraron embriones frescos o previamente congelados, respectivamente. Entre las transferencias de donantes, 319 fueran guiadas-ERA; entre las transferencias de donantes no guiadas, 1,175 y 639 involucraron fsETs o FETs, respectivamente.

**Intervención (es):** Ninguna

**Principal (es) Medida (s) de Resultado (s):** Los resultados primarios fueron tasa de nacidos vivos por transferencia embrionaria y tasa acumulada de nacidos vivos en transferencias consecutivas hasta tener un nacido vivo o cese del embarazo. Los resultados secundarios fueron implantación, tasa de embarazo, tasa de embarazo clínico por transferencia embrionaria, y tasa de aborto espontáneo por embarazo.

**Resultado (s):** Durante ambas transferencias autólogas o de donantes, la tasa de nacidos vivos y la tasa acumulada de nacidos vivos fueron mayores en FET y fsET que en grupos pET, incluso con transferencias euploides. El análisis de regresión logística, considerando posibles factores de confusiones, indicaron que pacientes recibiendo pET tuvieron resultados más pobres que aquellas sometidas a FET y fsETs en ciclos autólogos y de donantes. Las tasas de implantación, embarazo, embarazo clínico fueron más bajas que en pacientes sometidas a pET.

**Conclusión (es):** El uso de ERA para guiar pET durante ciclos ya sea autólogos o de donates luego de un intento de transferencia fallido no mejoraron los resultados reproductivos. Por el contrario, fueron detectados peores resultados cuando se usó ERA.