Rate of true recurrent implantation failure is low: results of three successive frozen euploid single embryo transfers

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Objective: To study the true prevalence of recurrent implantation failure.
Design: Retrospective cohort study.
Setting: A private assisted reproductive technology center.
Patient(s): Women (n = 4,429) with anatomically normal uterus who underwent up to three consecutive frozen euploid single embryo transfers (FE-SETs) were included in the study. Cycles with donor eggs or gestational carriers were excluded.
Intervention(s): None.
Main Outcome Measure(s): Cumulative outcomes from these cycles were analyzed. A logistic regression model was used to assess the differences of outcomes between first, second, and third FE-SET and a Kaplan-Meier curve as used to analyze cumulative implantation rate.
Result(s): The mean age of the patients included in the study was of 35.4 years. The sustained implantation rates of the first, second, and third FE-SET were 69.9%, 59.8%, and 60.3% per transfer, respectively. The cumulative sustained implantation rate after up to three consecutive FE-SET was 95.2%. The live birth rates after the first, second, and third FE-SET were 64.8%, 54.4%, and 54.1% per transfer, respectively. The miscarriage rate after observing a positive heartbeat was not different between the first (7.2%), second (8.8%), and third (12.7%) FE-SET.
Conclusion(s): Our findings suggest that true recurrent implantation failure is rare. For those patients with the ability to make euploid blastocysts, <5% would fail to achieve a clinical pregnancy with three embryos transferred. It remains to be further investigated whether this threshold identifies a truly recalcitrant group or simply a statistical certainty based on random variation. (Fertil Steril® 2021;115:45–53. ©2020 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Recurrent implantation failure, frozen embryo transfer, euploid blastocysts, preimplantation genetic testing for aneuploidy

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The infertile population is a highly heterogeneous group who’s widely varying pathologies result in their inability to conceive and deliver a healthy child. With some diagnoses, directed treatments provide an effective means to attaining excellent clinical outcomes (e.g., ovulation induction for anovulation), but in many others, a specific etiology may not be evident or a directed treatment may not be available. In the latter circumstance, assisted reproductive technology (ART)—formally known as in vitro fertilization—are now widely used to optimize clinical outcomes.

The goal of ART for most couples is to overcome or bypass the factors impairing their fertility by attaining chromosomally and morphologically normal embryos and transferring them under optimal conditions. This approach has been generally effective, but a recalcitrant group of patients who fail to deliver remains. The question is whether or not this recalcitrant group is refractory to the contemporary

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approach to care, or present an endometrial receptivity problem requiring additional diagnostic evaluation or an alternative treatment regimen to attain optimal outcomes.

This group has been described as having recurrent implantation failure (RIF). Despite numerous publications regarding RIF (1, 2) there is as yet no universally accepted definition. Most investigators have used as definition a given number of transferred embryos that failed to implant and deliver. In the past investigators proposed that RIF should refer to failure to achieve a clinical pregnancy after ≥10 embryos had been transferred (3). At that time, it was likely that many women with repetitive failures had high levels of chromosomally abnormal or aneuploid embryos. Those cases may now be identified before transfer through preimplantation genetic testing for aneuploidy (PGT-A) and are thus no longer part of the RIF population.

As embryo quality, screening, and selection have improved, it is rightfully expected that success would be attained more quickly and that insights into an especially recalcitrant group might be identified after a lower threshold of transfers. Investigators have recently proposed to define RIF as failure to achieve a clinical pregnancy after transfer of at least four good-quality embryos (based on morphological assessment) in a minimum of three fresh or frozen cycles in a woman <40 years of age (4).

With the elimination of many embryonic and synchrony related failures, attention has shifted toward uterine aspects of implantation and early gestational development. This may be true even when the uterus is morphologically normal as defined per ultrasound and/or hysteroscopy findings. Numerous investigators have identified a number of putative functional alterations of the endometrium in an otherwise morphologically normal uterus that can hamper the capacity of embryos to implant. In these circumstances, endometrial receptivity is considered impaired. The range of functional alterations purported for explaining implantation failures include, as follows: immunologic factors and notably, endometrial natural killer cell concentration (5–9) or cytokine imbalance in helper T lymphocytes (10); thrombophilic conditions including the antiphospholipid antibody syndrome (3, 11–17); endometriosis–associated impairment of endometrial receptivity (18–22); and discordance between the timing of progesterone-driven endometrial changes and embryo development leading to misalignment of the elective period of window of endometrial receptivity (7, 8, 23).

Whether alterations of the endometrial function are responsible for a sizable proportion of implantation failures—including RIF—of genetically normal embryos remains unknown. Although there are a number of publications on the various endometrial alterations, compelling proof of their actual role in implantation failures has not been elucidated nor have the efficacy of the measures recommended. Hence, our team was interested in studying this group of recalcitrant patients, but first it was important to determine their true prevalence in the ART population. This study seeks to determine the cumulative outcomes after up to three successive frozen euploid single embryo transfers (FE-SETs), anticipating that those patients with three consecutive single embryo transfers, which fail to deliver, would be considered to have RIF and be suitable for further investigation.

**MATERIALS AND METHODS**

**Study Population**

We conducted a retrospective study on all patients with up to three consecutive FE-SETs. This study spans January 2012 to July 2018 at a private ART center (Reproductive Medicine Associates of New Jersey, Basking Ridge, New Jersey). The first cycle of each patient was included as their first cycle in the study. All included patients were between the age of 18 and 45 years, had a body mass index (BMI) of >18 kg/m² and <40 kg/m², and a morphologically normal uterus on saline sonography and/or hysteroscopy. Patients undergoing egg donation, gestational carriers, patients using preimplantation genetic testing for monogenic diseases were excluded from the study. In addition, women with congenital uterine abnormalities, and whose endometrium thickness was <7 mm after estrogenization were excluded.

Women, who failed a FE-SET, had subsequent FE-SETs (up to a total of 3,) using either remaining frozen euploid blastocysts or embryos obtained from new ART treatments. Not all women who had a sustained implantation, determined by the presence of a gestational sac with fetal cardiac activity, had a live birth as some miscarried. Hence, some of women underwent a new FE-SET. Biochemical pregnancies were excluded. At each FE-SET, the embryo with the best morphology as determined by Gardner scale, were transferred first. Cumulative results for sustained implantation rate (SIR) and live birth rate (LBR) were calculated after three FE-SETs.

All embryos underwent PGT-A at the blastocyst stage using quantitative real-time polymerase chain reaction (24) or next generation sequencing-based platforms (25). All embryos were vitrified at the blastocyst stage after the trophectoderm biopsy was performed. Endometrial preparation was achieved with oral estradiol and intramuscular progesterone supplementation. The transfer of a single euploid blastocyst was performed on the sixth day of progesterone exposure only after obtaining at least 7 mm of endometrial thickness.

**Ethical Approval**

No embryos were biopsied specifically for the purpose of this study. Given the retrospective nature of this study, the access and processing of patient data was approved by the Advarra Institutional Review Board under a protocol for retrospective studies—protocol number Pro00027158.

**Patient Treatment**

**Ovarian stimulation.** The ART treatment followed routine protocols. Ovarian stimulation (OS) was achieved using highly purified urinary gonadotropins: recombinant follicle-stimulating hormone (FSH), urinary FSH, and/or metrotropins. For OS, individually set doses of hormones were used, ranging from 150–450 IU/d of FSH in an antagonist protocol. Development of ovarian follicles was monitored by transvaginal ultrasonography beginning on the sixth day of OS. If required, hormonal doses were adjusted to generate an
optimal response. The gonadotropin-releasing hormone (GnRH) antagonist was introduced as soon as one follicle reached 14 mm in diameter. Final oocyte maturation was typically induced with 5,000–10,000 IU of human chorionic gonadotropin or with GnRH agonist (2 mg Lupron), according to physician preference when three or more mature follicles of ≥18 mm were confirmed by vaginal ultrasound. Transvaginal oocyte retrieval (TVOR) was performed 36 hours after human chorionic gonadotropin and or GnRH agonist administration. When GnRH agonist was used, a second dose of Lupron (2 mg) was administered 12 hours after the first trigger.

Fertilization was achieved with intracytoplasmic sperm injection given the intent to perform PGT-A. Normally fertilized zygotes were cultured in cleavage medium in a low oxygen (5%) tension environment. On day 3 of embryo development, all cleaved embryos underwent laser-assisted hatching of the zona pellucida. All embryos were then placed in extended culture regardless of the size or quality of the cohort. Blastocysts were considered usable if suitable for biopsy and vitrification for future use. Embryo morphology assessment was performed by using a modified Gardner scale. All usable expanded blastocysts with an inner cell mass and trophectoderm grade C or better underwent PGT-A [26].

Embryo genetic testing. Preimplantation genetic testing for aneuploidy was performed at the blastocyst stage and involved sampling and testing of 5–10 trophectoderm cells [27]. The PGT-A was performed at the Foundation for Embryonic Competence, New Jersey, using well–validated platforms for quantitative real–time polymerase chain reaction [24, 28–30] and next generation sequencing [25, 31]. Mosaic embryos were not transferred.

Endometrial preparation for embryo transfer. In a subsequent cycle, patients were administered hormones for endometrial preparation before embryo transfer. Patients began oral estrogen (2 mg twice daily estradiol) for the first 4–6 days and three times a day thereafter to induce endometrial proliferation yet suppressing follicular development. The duration of estrogen only therapy ranged from a minimum of 12 to 25 days.

Endometrial thickness was monitored on transvaginal ultrasonography, whereas serum estradiol and progesterone were assessed to rule out premature ovulation before initiation of progesterone supplementation. Progesterone was administered by intramuscular injections of 50 mg once daily starting 5 days before FE-SET. On the sixth day of progesterone administration, a warmed euploid blastocyst was transferred. When more than one embryo were available, the choice was made based on morphological grading following the modified Gardner scale. The FE-SET was performed under transabdominal ultrasound guidance using a soft catheter.

Daily estrogen and progesterone administration were continued until the pregnancy test. If pregnancy was achieved, hormone administration was continued until the expected luteoeplacental shift, at 8 to 9 weeks of gestation.

Statistical Analysis
For the demographics of patients, the numeric data from first TVOR cycle is used if the patient transferred embryos from multiple TVOR cycles. Means and standard deviations are used for demographic parameters. For pregnancy outcome, two end points were used. The primary end point was implantation rate (IR), as determined by the presence of a gestational sac with fetal cardiac activity. The secondary end point was LBR. To compare success rate between first, second, and third transfer cycles, logistic regression on pregnancy outcome is used with oocyte age adjusted. Pairwise comparisons between first, second, and third transfer outcomes were conducted using Tukey’s HSD by R package multcomp (version 1.4-8; R Foundation). Survival analysis was used to analyze cumulative success rate. Kaplan–Meier estimates and confidence intervals were estimated using R package survival (version 2.43–3). All statistical analyses were done in R (version 3.5.0).

RESULTS
Patient Characteristics
A total of 4,429 women who met the inclusion criteria were included in the study. Among them, 4,111 used embryo(s) from a single TVOR cycle, 297 patients used embryos from 2 different TVORs, and 21 patients used embryos from 3 TVORs. The TVOR dates span (time span between first and last TVOR) are, as follows: 0–1 year, 287 patients; 1–2 years, 29 patients; >2 years, 2 patients.

The average patient age in the study cohort was 35.4 ± 4.2 years and the average BMI was 25.46 ± 5.36 kg/m². Other demographic information and markers of ovarian reserve were collected, including age (in years), BMI, minimum antimüllerian hormone level (in nanograms per milliliter), and maximum day 3 FSH level (in milli-international units per milliliter). Cycle response including number of oocytes retrieved, fertilization rates, blastulation rates, euploidy rates are illustrated in Table 1.

Implantation Rate
Results for the primary outcome—SIR—as determined by the presence of a gestational sac with fetal cardiac activity after

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient demographics and treatment cycle characteristics.</th>
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<tbody>
<tr>
<td>Variable</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age at first TVOR (y)</td>
<td>35.39 (4.20)</td>
</tr>
<tr>
<td>BMI closest to first TVOR (kg/m²)</td>
<td>25.47 (5.36)</td>
</tr>
<tr>
<td>Minimum antimüllerian hormone value (ng/mL)</td>
<td>3.01 (3.40)</td>
</tr>
<tr>
<td>Day 3 FSH value (mIU/mL)</td>
<td>8.70 (3.76)</td>
</tr>
<tr>
<td>MII rate from the first TVOR</td>
<td>12.51 (8.21)</td>
</tr>
<tr>
<td>2PN rate from the first TVOR</td>
<td>10.50 (7.10)</td>
</tr>
<tr>
<td>Biopsy rate from the first TVOR</td>
<td>5.45 (4.16)</td>
</tr>
<tr>
<td>Euploidy rate from the first TVOR</td>
<td>3.54 (3.04)</td>
</tr>
<tr>
<td>Noneuploidy rate from the first TVOR</td>
<td>1.84 (1.92)</td>
</tr>
</tbody>
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Note: BMI = body mass index; FSH = follicle-stimulating hormone; MII = meiosis II; 2PN = pronuclei; SD = standard deviation; TVOR = transvaginal oocyte retrieval. Pirtea. True rate of recurrent implantation failure. Fertil Steril 2020.
the first, second, and third FE-SET were 69.9%, 59.8%, and 60.3% per transfer, respectively (Fig. 1A, B). Of those who failed to achieve implantation after the first FE-SET (n = 1,335), 764 (57.22%) underwent a second FE-SET. Of those who failed to achieve implantation after the second FE-SET (n = 324), 141 (43.51%) patients underwent a third FE-SET. Furthermore, our logistic regression model showed that the second FE-SET resulted in slightly decreased SIRs compared with the first FE-SET (odds ratio [OR], 0.641; 95% confidence interval [CI] 0.547–0.752), as was also the case for third FE-SET (OR, 0.649; 95% CI 0.455–0.932). There were, however, no differences in SIR between the second and third SE-FETs. These findings were confirmed after adjusting for multiple comparisons (Fig. 1B).

We also asked whether the mean age of patients who failed to achieve implantation after three FE-SETs (n = 52) was different from those who had implantation after the first, second, or third attempt (n = 3,630). There was no age difference (age at first embryo transfer, 35.16 ± 4.57 vs. 35.14 ± 4.15 years; P = .975).

Live Birth Rate

The distribution of patients was slightly different when comparing for the secondary outcome LBR, as some patients who had a positive implantation miscarried and underwent a new FE-SET. They were, therefore, not counted in the first group. The patients who underwent a new ART cycle after a miscarriage were not included in the LBR study group. The
LBR results after the first, second, and third FE-SET were 64.8%, 54.4%, and 54.1% per transfer, respectively (Fig. 2A,B). Of those women who failed to achieve a live birth after the first FE-SET (n = 1,335), 885 (56.8%) underwent a second FE-SET. Of those women who failed to achieve a live birth after the second FE-SET (n = 404), 170 (42.7%) patients underwent a third FE-SET. The transfer cycle is shown on the horizontal axis (Tukey’s range test, *P = .01, **P < .001). (B) The LBRs after the first, second, and third cycles. The transfer cycle is shown on the horizontal axis (Tukey’s range test, *P = .01, **P < .001). (C) The cumulative LBR after up to three consecutive FE-SET was 92.6% (95% CI 92.6%–93.9%) as illustrated by Kaplan-Meier estimates. The cumulative LBR after the first (64.8%; 95% CI 63.4%–66.2%) and after the second (83.9%; 95% CI 82.6%–89.0%) FE-SET were also Kaplan-Meier estimates. The number of embryo transfers is shown on the horizontal axis. 


Cumulative SIR and LBR

The cumulative SIR after up to three consecutive FE-SETs was 95.2% (95% CI 94.0%–96.2%) as illustrated by Kaplan-Meier estimates reporting also cumulative SIR results after the first (69.9% with 95% CI 68.5%–71.2%) and after the second (87.9% with 95% CI 86.7%–89.0%) FE-SET (Fig. 1C). The cumulative LBR after up to three consecutive FE-SETs was 92.6% (95% CI 91.2%–93.9%). Kaplan-Meier estimates for multiple comparisons (Fig. 2B). Similarly to what we observed for implantation, the mean age of patients who failed to achieve a live birth after three FE-SETs (n = 78) was not different from those who had a live birth after the first, second, or third attempt (n = 3,443) (age at first embryo transfer, 35.48 ± 4.48 years vs. 35.09 ± 4.14 years; P = .446).
The miscarriage rate reported was 7.2% (95% confidence interval [CI] 6.4%–8.2%) after the first frozen euploid single embryo transfer (FE-SET), 8.8% (95% CI 6.3%–11.7%) after the second FE-SET, and 12.7% (95% CI 6.2%–22.0%) after the third FE-SET. When we compared the miscarriage rate results after the first, second, and third FE-SET, no significant difference was observed according to logistic regression adjusted for age (P = .143). The transfer cycle is shown on the horizontal axis.


DISCUSSION

Recurrent implantation failure is an important clinical entity with no universally established definition. The incidence of RIF is unknown, and the true relevance of numerous factors that have been implicated in its pathogenesis, remains to be determined. In the current study we sought to establish the incidence of RIF in women who have an anatomically normal uterus and are undergoing consecutive euploid single embryo transfers. In a total of 4,229 women who underwent up to three successive FE-SETs, we found a cumulative SIR of 95.2%. In light of these numbers, RIF rates after three FE-SETs seems to have an incidence of <5%. Our findings challenge the publications (3, 9, 11–14, 17, 32) claiming various uterine causes for RIF and suggest that it is of uterine origin not is a common entity in women whose uterus appears normal on saline sonography and/or hysteroscopy.

The investigators who point at various causes of endometrial alterations as putative explanation(s) for implantation failures in ART, and possibly RIF, also offer specific testing methods and therapies. Ledee et al. (33) propose to test endometrial immune function by measuring natural killer cells and other inflammation markers in end-luteal phase endometrial biopsies. Excessive or insufficient immune responses, as assessed by biopsies, are given as explanations for implantation failures (34–36). These investigators propose various therapeutic options for treating dysregulation of the uterine immune response ranging from increasing the vaginal progesterone dose to intralipid administration and corticoid therapies. Other investigators claim that thrombophilic conditions cause implantation failures and suggest numerous empirical interventions (3). Reports (37) have pointed at alteration of endometrial function in case of endometriosis, with investigators reporting excessive endometrial expression of BCL6 in such cases and altered endometrial receptivity. Ever since the precise timing of endometrial changes taking place in the luteal phase has been described by Noyes et al. (38), claims have been made that endometrial transformations may be delayed or out of phase thereby impairing endometrial receptivity. In recent years, the timing of progesterone-led endometrial changes has been assessed by panels of gene expressions in endometrial tissue (34–36) rather than histologic changes. Gene assessments made in midluteal endometrial findings are reported as either prereceptive, receptive, or postreceptive. The recommendations made by the proponent of these tests is that adjustments need to be made in the timing of embryo transfers to achieve a synchronous window of implantation (39, 40). Most recently, the endometrial assessment strategies based solely on hormonal changes of the endometrium have been challenged, recognizing that the endometrium might simply be pathological (or disrupted) (41).

Our study further calls into question the use of receptivity tests (34–40) and various therapies offered to women who failed to implant after ART treatment. These tests include endometrial immunology testing (5–7, 9), markers of endometrial alterations in endometriosis (18), and window of implantation testing for potential adjustments (18, 19, 36, 42). Our results suggest that RIF observed after untested embryo transfers is likely due to an embryonic factor, and do not support the broad deployment of clinical measures targeting the endometrium—ranging from immunologic to hormonal treatments (33, 43, 44), and personalized transfers (35, 43).

In addition, finding a <5% incidence of RIF after three consecutive euploid embryo transfers, our study supports the concept that RIF due to a pathology inherent to the endometrium is rare. We found SIR to only decrease from 69.9% in the first cycle to 59.8% in the second cycle, and remained the same at 60.3% in the third cycle. This indicates that failed implantation after a FE-SET does not select out women with overt receptivity disorders. Considering that the first FE-SETs were morphologically selected, it is reasonable to estimate that the difference between the first and the second SIR—69.9% and 59.8%, respectively—is in part the reflection of embryo selection for the first transfer. In addition, miscarriage rates after the first to the third FE-SET were low, between 7.2% and 12.7%, and did not differ significantly.
Although spontaneous miscarriages are not included in the definition of RIF, this finding does not support the presence of an inherent pathology in these patients, selecting for endometrial dysfunction or loss.

Our data suffer from the weakness of the retrospective nature of its design. Data analyzed were, however, prospectively acquired. Furthermore, the large size of the cohort studied and its extensive nature—all FE-SETs during 7 years—partially compensates for the weakness of the design. A potential limitation of the study could be represented by some successive FE-SETs that came from different ART cycles. However, when we calculated the IR of the two subgroups after the second FE-SET we noticed similar results, 59.2% for those using remaining embryos and 61.2% for those using embryos from new ART treatments. Also, some patients who failed their first or second cycle dropped out. None of the patients who dropped out had remaining euploid embryos available for transfer. Some of these patients underwent non-PGT-A procedures or reverted to donor egg, or lastly, ran out of funds for conducting further FE-SET with PGT-A-tested embryos. Important, the patients who dropped out were assigned exactly the same (lower) SIR and LBR associated with the second and third cycles, which were calculated for patients who completed all cycles. As a result, if all patients who dropped out were excluded, calculated SIR and LBR after three euploid transfers would be unchanged. Finally, the impact of potential confounders, such as obesity or smoking, was also not evaluated, and although psychological support was available to all patients, a standardized assessment or intervention was not part of the study.

Our series is the largest reported of sequential FE-SETs, which confers its strength. Hence, the nature of the data allows to reliably call into question the role of uterine factors in RIF. Further studies are needed to investigate the outcome of approximately 5% of women who have RIF after three consecutive FE-SETs and determine whether they have endometrial pathologies.

In conclusion our study of a large cohort of repeated FE-SETs in women whose endometrium was sonographically normal, seriously questions the existence of RIF due to endometrial effects. Likewise, our results challenge the soundness of the sometimes expensive endometrial testing and ensuing therapies that have been broadly deployed for diagnosing and treating RIF of endometrial origin. On the contrary, our results suggest that most RIFs are of embryonic origin, which can be minimized by transferring euploid embryos.

REFERENCES


La tasa real de Fallo de Implantación Recurrente es baja: resultados tras tres transferencias embrionarias consecutivas de un único embrión euploide.

Objetivo: Estudiar la prevalencia real de fallo de implantación recurrente.

Diseño: Estudio de cohorte retrospectivo.

Escenario: Centro privado de reproducción asistida.

Paciente(s): Se incluyeron en el estudio mujeres (n = 4,429) con un útero anatómicamente normal que realizaron consecutivamente hasta tres transferencias embrionarias únicas, mediante el uso de un embrión euploide congelado en estadio de blastocisto (FE-SETs). Los ciclos realizados a partir de ovocitos donados o en receptoras fueron excluidos del estudio.

Intervención(es): Ninguna.

Variables principales: Tasa de éxito acumulado. Mediante un modelo de regresión logística se evaluaron de las diferencias observadas en los resultados obtenidos en la primera, segunda y tercera transferencia embrionaria. La tasa de implantación acumulada se analizó mediante una curva de Kalplan-Meier.

Resultado(s): La edad media de las pacientes incluidas en el estudio fue de 35.4 años. La tasa de implantación sostenida o continuada de la primera, segunda y tercera transferencia embrionarias fue de 69.9%, 59.8%, y 60.3% (por transferencia), respectivamente. La tasa de implantación sostenida acumulada tras tres transferenciasembrionarias únicas consecutivas con blastocistos euploides fue del 95.2%. La tasa de recién nacido vivo tras la primera, segunda y tercera transferencia fue de 64.8%, 54.4%, and 54.1% (por transferencia), respectivamente. La tasa de recién nacido vivo acumulada tras tres transferencias embrionarias consecutivas fue del 92.6%. No se observaron diferencias en la tasa de aborto clínico (tras visualizar latido embrionario) en la primera (7.2%), segunda (8.8%), y tercera transferencia (12.7%).

Conclusión(es): Estos resultados sugieren que el verdadero fallo de implantación recurrente es raro. En pacientes que consiguen obtener embriones euploides, < 5% no conseguiría gestación tras tres transferencias embrionarias consecutivas. Sin embargo, se necesitan estudios adicionales para aclarar si este umbral o punto de corte identificaría a un grupo con riesgo incrementado de fallo de implantación certero o si estos resultados responden a una variación estadística meramente aleatoria.