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A new definition of recurrent implantation failure on the basis of anticipated blastocyst aneuploidy rates across female age

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Objective: To present a definition of recurrent implantation failure that accounts for the effects of female age and anticipated blastocyst euploidy rates on cumulative implantation rates.

Design: Mathematical modeling.

Setting: Not applicable.

Patient(s): Not applicable.

Intervention(s): Mathematical modeling of cumulative implantation probability on the basis of published blastocyst euploidy rates across categories of female age.

Main Outcome Measure(s): The number of blastocysts required to achieve 95% cumulative implantation probability under the assumption of the absence of any other factor affecting implantation.

Result(s): When the euploidy status of the transferred embryo is unknown (i.e., not subjected to preimplantation genetic testing for aneuploidies), our simulation shows that no age category reaches 95% cumulative probability of implantation of at least one embryo until after transfer of seven blastocysts. The number of blastocysts required to reach the same threshold is higher for older patients. For example, women older than 38 years require transfer of more than 10 untested blastocysts for the upper range of predictive probability to meet the threshold of 95%. On the other hand, if the implantation rate for a euploid blastocyst is assumed to be 55%, then 4 blastocysts are enough to reach a cumulative probability rate greater than 95%, regardless of age.

Conclusion(s): The term "recurrent implantation failure" should be a functional term guiding further management. We suggest that recurrent implantation failure should not be called until implantation failure becomes reasonably likely to be caused by factors other than embryo aneuploidy, the leading cause of implantation failure. We propose a new definition that factors in anticipated blastocyst euploidy rates across categories of female age, euploid blastocyst implantation rate, and a specified threshold of cumulative probability of implantation. (Fertil Steril® 2021;116:1320–7. ©2021 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: ART failure, aneuploidy, euploid embryo, genetic diagnosis, miscarriage, preimplantation

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An assisted reproductive technology (ART) cycle has four components: ovarian stimulation to provide multiple gametes, laboratory procedures for fertilization and embryo development, embryo transfer, and luteal phase support. Suboptimal performance at any step decreases the chances of implantation and live birth. Although a poor response to ovarian stimulation is most often caused by decreased ovarian reserve or, less commonly, by inadequate stimulation, there are many possible reasons for failure in the remaining steps (Table 1) (1). Among these, embryo aneuploidy (EA) stands out as the most common cause of ART failure. Embryo aneuploidy is the leading cause of embryo developmental arrest, implantation failure, and miscarriage (2).

It is unrealistic to expect every transferred embryo to implant and reach live birth, even in the absence

TABLE 1

Possible causes of implantation failure other than embryo aneuploidy.

Cause	Causal relationship	Diagnostic method	Can be diagnosed before RIF?	Evidence-based treatment	Can be addressed before first ART cycle?	RIF alters management?
Lifestyle factors						
Smoking	Plausible	History	Yes	Quitting	Yes	No
Alcohol	Plausible	History	Yes	Quitting	Yes	No
Obesity	Plausible	Weight and height	Yes	Weight loss	Yes	No
Gamete quality						
Oocyte	Plausible	None	N/A	N/A	Not required outside research setting	No
Spermatozoa	Plausible	None	N/A	N/A	Not required outside research setting	No
Uterine factors						
Uterine septum	Controversial	Ultrasound/HSG	Yes	Hysteroscopic resection[a]	Yes, if deemed necessary	Maybe[b]
Submucosal fibroids/polyps	Plausible	Ultrasound/HSG	Yes	Hysteroscopic resection[a]	Yes	Maybe[b]
Intramural fibroids	Plausible	Ultrasound	Yes	Surgery	Yes	Maybe[b]
Intrauterine adhesions	Plausible	Ultrasound /HSG	Yes	Hysteroscopy	Yes	No
Adenomyosis	Controversial	Ultrasound	Yes	Suppression/surgery[a]	Yes	Maybe[b]
Impaired receptivity	Controversial	Receptivity arrays	Not required outside research setting	N/A		No
Adnexal pathology						
Hydrosalpinx	Plausible	Ultrasound /HSG /Hy-Co-Sy[c]	Yes[c]	Salpingectomy/proximal tubal occlusion	Yes	No
Endometriosis	Controversial	Ultrasound	Yes	Suppression/surgery[a]	Yes	Maybe[b]
Other						
Thrombophilia	Controversial	Blood tests	No[d]	N/A	Not required outside research setting	No

Note: Modified from Somigliana et al. (1)

ART = assisted reproductive technology; HSG = hysterosalpingography; Hy-Co-Sy = hysterosalpingo-contrast-sonography; N/A = not applicable; RIF = recurrent implantation failure.

[a] Not proven effective by well-designed studies.

[b] Despite the lack of evidence of effectiveness, recurrent implantation failure can lead to consideration of surgical (or medical for adenomyosis and endometriosis) treatment if these pathologies were present and not treated before the initial ART cycles.

[c] Most of the women would have undergone a tubal patency assessment even before the first ART cycle.

[d] Thrombophilia screening is not expected to be done before ART.

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TABLE 2

Blastocyst euploidy rates with comprehensive chromosome analysis according to female partner's age.

Study	< 35 y	35–37 y	38–40 y	41–42 y	> 42 y
Ata et al. 2012 (4)[a]	60%–63%	51%–55%	36%–39%	21%–25%	13%–17%
Demko et al. 2016 (6)[b,c]	60%	55%	45%	35%	20%
Barash et al. 2017 (3)[c]	62%	57%	44%	30%	
Hong et al. 2019 (7)[d]	74%	65%	47%	29%	15%
Irani et al. (5) 2020	55%	45%	32%	18%	8%

Note: [a] Published and unpublished data.
[b] Figures for only day five embryos.
[c] Based on approximations from the published figures and graphs in the original publications.
[d] Only women who underwent ovarian stimulation are included in the table.

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of any other factor adversely affecting the process, because almost half of blastocysts are aneuploid, even in women under 35 years of age (3–7). Thus, implantation failure should become a concern after several embryos fail to reach live birth. But how many transferred embryos should have failed to implant to make a diagnosis of recurrent implantation failure (RIF)?

Recurrent implantation failure should be a functional term guiding further management. Recurrent implantation failure should mark the point where additional investigations and/or a change in treatment plans should be considered. We suggest that RIF should be diagnosed when implantation failure becomes unlikely to be caused by EA, the most common reason. Because female age is the strongest determinant of EA rate (4), any definition of RIF that does not take the euploidy status of transferred embryos or female age at the time of oocyte collection into account will be incomplete and inaccurate. EA rates at different female ages have been published and seem to be fairly consistent across studies, with some variation possibly because of several factors, including the platform used to assess euploidy status and indications for preimplantation genetic testing for aneuploidies (PGT-A) (Table 2) (3–7). Thus, one can calculate how many embryos should have failed to implant in a woman before reasonably ascribing implantation failure to another etiology than EA at a given female age.

We present a method for calculation of the total number of blastocysts transferred to a woman that would be required to provide a predefined cumulative probability of implantation under the assumption that all implantation failures would be solely because of EA.

MATERIALS AND METHODS

This study used simulations derived from published data and did not require approval from a human research ethics committee.

Selection of a Threshold for Anticipated Cumulative Implantation Probability to Assume that Implantation Failure Can Be Because of Another Etiology than EA

In analogy to clinical studies, to test the hypothesis that implantation failure is caused by another factor than EA, the null hypothesis (H_0) would be that implantation failure

was because of EA. To reject the null hypothesis, a type 1 error rate of 0.05 (implantation failure being indeed because of EA while observations suggest otherwise) is required by convention. This line of reasoning raises the question "What should be the total number of embryos transferred to a woman to expect a 95% (i.e., 1–0.05) cumulative probability of implantation at a given female age if EA were the sole reason for implantation failure?"
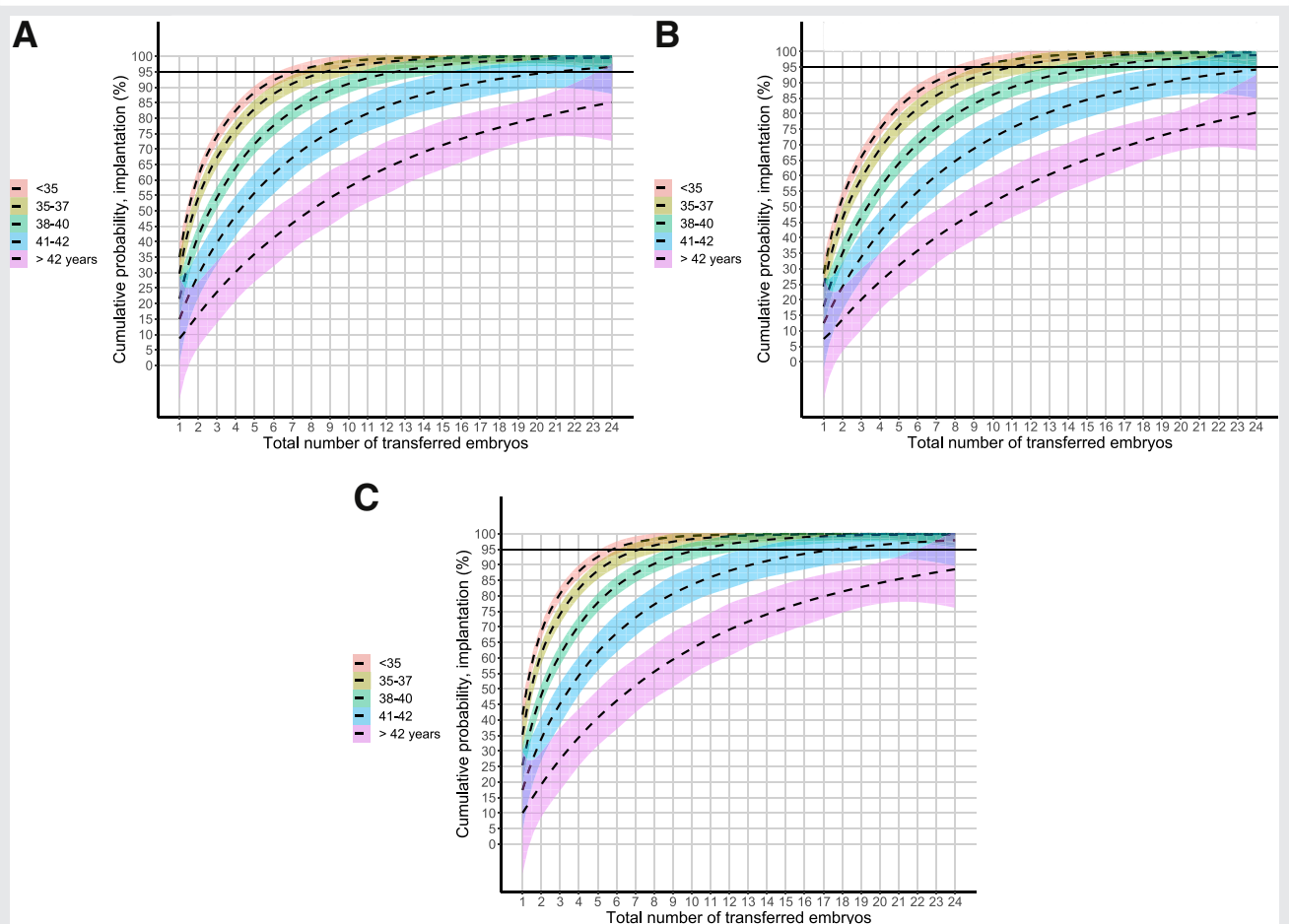
Calculation of the Number of Embryos That Fail to Implant Across Female Age Required to Make a Diagnosis of RIF

We estimated the cumulative implantation rate over n blastocysts with the probability of implantation per blastocyst transferred (p). The range of euploidy rates of blastocysts for each age category was taken from studies that reported euploidy rates in relation to female age (3–7). The probability of implantation of a euploid blastocyst is reported to be independent of female age and ranges between 45% and 65% (8–10). We assumed that the probability of euploidy of each blastocyst would depend on the woman's age and the implantation rate would depend on euploidy status. We assumed that each blastocyst was an independent unit and that the probability of implantation of a blastocyst followed the Bernoulli distribution. Therefore, the probability of implantation over n blastocysts transferred would follow the binomial distribution. The cumulative implantation rates for each age category (i.e., categories used by the Society of Assisted Reproduction) were calculated with the following probability mass function: $\Pr(X > k) = \sum_{i=k-1}^{n} \binom{n}{i} p^i (1-p)^{n-i}$, where k is the number of desired implantations, i.e., at least one, p is the joint probability of implantation, and n is the number of blastocysts transferred. The joint probability of implantation (p) was calculated as the euploidy rate for the corresponding age category times the implantation rate of a euploid embryo plus a 1% probability for aneuploid embryos ($p = p_{aneuploid} \times 0.01 + p_{euploid} \times p_i$) (2). The results were simulated for implantation rates of 45%, 55%, and 65% for a euploid blastocyst. Different euploidy rates derived from the literature were used for each age category to reflect the variance. The association between transferred embryos and

FIGURE 1

Association between number of transferred blastocysts without preimplantation genetic testing for aneuploidies and cumulative implantation probability simulated for anticipated euploidy rate and euploid embryo implantation rates of 55% (**A**), 45% (**B**), and 65% (**C**). *Dashed lines* are fitted with locally estimated scatterplot smoothing polynomial regression using highest and lowest reported euploidy rates for given female age. *Shaded areas* show the 95% confidence intervals. Age categories are depicted in *color*.

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implantation was plotted with the use of locally estimated scatterplot smoothing (LOESS) polynomial regression lines with 95% confidence intervals.
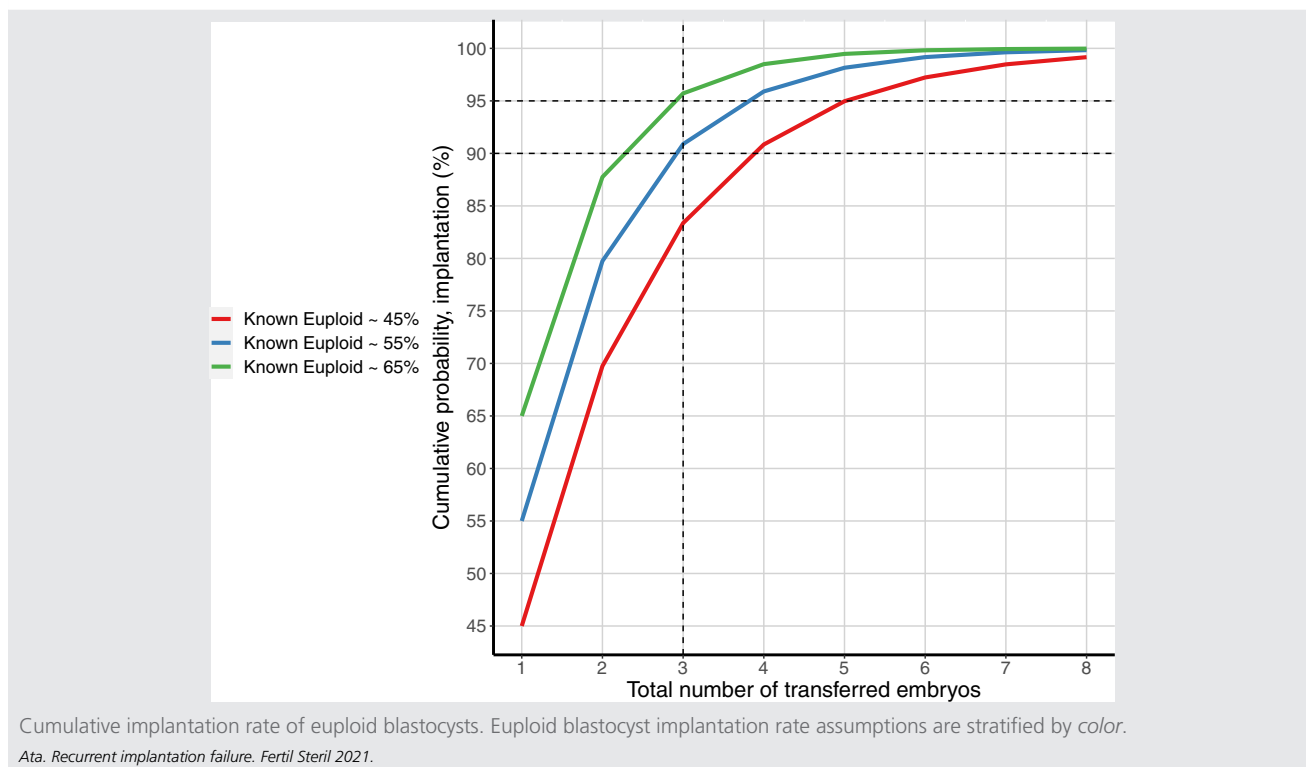
RESULTS

When the euploidy status of transferred embryos is unknown (i.e., untested by PGT-A), our simulation shows that no age category reaches a 95% cumulative probability of implantation of at least one embryo with a total of three blastocyst transfers for all assumptions of euploid embryo implantation rates (Fig. 1A to C). Women under 35 years of age reached a 95% cumulative probability of implantation of at least one blastocyst after transfer of seven blastocysts for euploid embryo implantation rates between 45% and 55% (Fig. 1A and B) and after transfer of six blastocysts for a euploid blastocyst implantation rate of 65% (Fig. 1C). The number of blastocysts required to reach the same threshold is higher for older patients. For example, women older than 38 years require more than 10 blastocysts transferred for the upper range of

probability to meet the threshold of 95%, while the number is impractically large for women older than 42 across all implantation rate assumptions (Fig. 1).

If the implantation rate of a euploid embryo were 45% or 65%, using the lower and upper ranges reported in the literature, the number of blastocysts required to reach a 95% cumulative probability of implantation would be within ±1 of the calculated number for women aged <38 years and within ±2–3 of the calculated number for older women with an implantation rate of 55% (Fig. 1B and C for 45% and 65%, respectively).

These numbers dramatically change when we assume that embryos are known to be euploid. If the implantation rate of a euploid blastocyst is assumed to be 55%, then 3 and 4 blastocysts are enough to reach cumulative probability rates greater than 90% and 95%, respectively (Fig. 2). These numbers are consistent with the findings of Pirtea et al. (2), who suggested that three euploid embryo transfers is enough for most women to achieve a 95% cumulative implantation rate.

FIGURE 2

Cumulative implantation rate of euploid blastocysts. Euploid blastocyst implantation rate assumptions are stratified by *color*.

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We present a calculator that can be used by each center on the basis of its own figures (Supplementary Material, available online). The center can input the blastocyst euploidy rate observed in each age bracket, the euploid blastocyst implantation rate observed in its setting, and the threshold for cumulative implantation probability over which it wants to diagnose RIF and calculate the number of blastocysts required to meet that threshold in its own population and setting.

DISCUSSION

We present a statistical model on the basis of blastocyst euploidy rates in relation to female age for calculation of the required number of blastocysts transferred to a woman to achieve a predefined cumulative probability of implantation under the assumption that EA is the sole reason for implantation failure. The figures suggested by the model are higher than the currently suggested threshold of four blastocysts to call RIF, across the range of euploid blastocyst implantation rates in the literature (11).

Our assumptions are subject to limitations and may not adequately describe all clinical realities. We assumed age to be the sole factor for EA status and implantation rate to be constant for consecutive trials. More complex assumptions can be made to explain the variance in EA status, and an increasing number of failed attempts are likely to correspond to a lower implantation rate. However, such factors are unlikely to significantly change the number of blastocysts required to reach a similar threshold of cumulative implantation

probability. Another limitation of our model is the omission of cleavage-stage embryo transfers. However, comprehensive chromosomal screening results are not available for cleavage-stage embryos, thus precluding such a calculation.

When Should Other Factors Affecting Implantation Be Searched for? Diagnostic (Ir)relevance of the Term "Recurrent Implantation Failure"

Ideally, all factors that can decrease the implantation potential of an embryo should be ruled out or diagnosed and treated before embarking on an ART cycle. However, the cost and inconvenience of required tests should be weighed against the probability of diagnosing and effectively treating a particular factor. If the prevalence of a sought-for factor is considered to be too low to justify screening before the initial ART cycle, and there is no patently effective treatment for it, the test can be deferred until the couple is considered to experience RIF, when the prevalence of the condition would become higher. One example is testing for parental chromosomal abnormalities; the likelihood of a couple having a chromosomal abnormality increases with the number of failed ART cycles (12). Thus, screening every couple for chromosomal abnormalities before the first ART cycle, in the absence of any other indication, is of moderate clinical interest and is unlikely to be cost-effective.

On the other hand, detailed history-taking, focused physical examination, and proper assessment of uterine anatomy,

preferably with three-dimensional transvaginal ultrasound and a test of tubal patency, will ensure diagnosis of almost all other factors known to affect the chances of implantation before the initial ART cycle. Commonly used screening methods for such factors and whether they can be implemented before the first ART cycle are presented in Table 1.

How Should Treatment Plans Be Altered in Case of RIF? Therapeutic (Ir)relevance of the Term "Recurrent Implantation Failure"

As a functional term, RIF should lead to consideration of the treatment of factors that are known to affect the implantation process but that are without proven effective treatment. For example, treatments that have not been proven effective include removal of intramural fibroids that are not encroaching on the endometrial cavity. Although good-quality observational studies suggest decreased chances of pregnancy and increased risks of miscarriage in women who have intramural fibroids, there is no convincing evidence that myomectomy improves these outcomes (13, 14). Thus, if a woman with intramural fibroids experiences multiple implantation failures that become less likely to be explained by EA, she can choose to embrace the probability of benefit from myomectomy, since whether and when an answer from well-designed studies will become available is unknown. She may prefer the risk of an intervention being ineffective, because EA has become less likely to be an explanation for her prior failures. Perhaps a similar argument can be made for surgical treatment of adenomyosis and hysteroscopic correction of a subseptate or dysmorphic uterus. The data on the effects of these abnormalities and their treatment on reproductive potential are inconclusive (15). Similar to intramural fibroids, their treatment can be discussed and considered when implantation failure becomes less likely to be caused by EA alone. However, whether these interventions will prove beneficial is currently unknown from an evidence-based medicine standpoint.

A premature diagnosis of RIF can lead to unjustified interventions that consume morale and funds that could be directed toward further ART cycles and that in addition carry some risk of harm, such as risks associated with interventions, which can decrease the success of future ART cycles. Thus, before embarking on such an intervention, it would be prudent to wait until implantation failure is unlikely to be because of EA and the effectiveness and safety of the intervention have been proven by sound research.

Given the high numbers of untested blastocysts required to reach 95% (or even as low as 80%) cumulative probability of implantation for women over 38 years of age, perhaps an argument can be made in favor of starting with PGT-A to identify implantation failures that would not be because of EA and consider other factors, as mentioned above.

Perils of Arbitrary "RIF" Definitions for Research

The success of a clinical research project depends on a well-defined study population, among other factors. The study population should include adequate numbers of participants with the particular condition to be addressed with the experimental intervention. Otherwise, false negativity, i.e., failure to demonstrate the effectiveness of the intervention when it is indeed effective, becomes a risk. Clearly, failure to exclude women who are likely to have experienced implantation failure because of EA will dilute the number of women with other abnormalities and any effect of an intervention that aims to address another putative mechanism affecting implantation.

The risk of conducting research on a heterogeneous population is not limited to false negativity. Numerous RIF studies have been published involving greatly heterogeneous populations, e.g., women who have had two or three failed embryo transfers regardless of age and the number of embryos transferred, or women who have had implantation failure after the transfer of an arbitrary number of embryos regardless of age. Since the probability of a random finding of effectiveness increases with multiple hypothesis tests in a single study or over multiple studies, "statistically significant" improvements that have been claimed in some of these studies can be expected to be due purely to chance associated with multiple testing rather than genuine effectiveness. These false positive findings lead to many couples undergoing ineffective interventions around the world, consuming their morale, time, and money, under the guise of being on the basis of scientific findings and publications even in credible journals.

Thus, an accurate definition of RIF that takes into account the probability of previous implantation failures being because of EA is of paramount importance for research on the subject. Such a definition will enable recruitment of couples who are likely to have experienced RIF because of other causes than EA and will decrease the risks of false negativity in a particular study and false positivity in the literature in general. This approach can be expected to increase the quality of research and expedite discovery of other factors affecting the implantation process and effective treatments for them. The current approach has so far resulted in a mixture of conflicting findings, confusing professionals and couples and possibly misleading us altogether.

Hazards of Inaccurate Definitions of RIF and an Unjustified Early Diagnosis of RIF for Couples

Most of the couples lack the biology background to truly understand the details of the reproductive process in humans. Failure of one ART cycle is frustrating and adds to the already existing stress because of the inability to comprehend the treatment process and the uncertainty of their prognosis. The financial burden of ART is another concern and a cause of distress for many couples around the world (16). These negative feelings increase with repeated failures, and being labeled with a vague diagnosis of RIF would increase stress and feelings of uncertainty. An early diagnosis of RIF may make a couple believe that they have an unknown, undiagnosable, and untreatable problem, decreasing their chances or even totally preventing them from having a child. They may simply decide that it is not worth the effort anymore

and drop out of treatment when they could have had a reasonable chance if they continued. On the flip side of the coin, they may seek and be offered interventions without any sound biologic rationale or scientific evidence of acceptable quality. These interventions can expose them to undue risks, e.g., side effects or complications associated with interventions that have not been properly assessed (17).

On the other hand, knowledge of the anticipated aneuploidy rate in a couple's embryos and related implantation and live birth rates per embryo transferred can facilitate the couple's understanding of the most probable reason for failure. Because each new embryo represents an additional chance of success, the couple may be empowered to make an informed choice to pursue further treatment on the basis of the female partner's age and the expected number of blastocysts on the basis of her ovarian response in previous cycles. In other words, explaining these issues to the couples could be more effective than the use of extravagant and unsupported tests or treatments (17).

In conclusion, we aimed to highlight that the definition of RIF should not be independent of female age and anticipated euploidy rates, because EA is the most common cause of implantation failure. Once other known reasons contributing to implantation failure are ruled out or diagnosed and treated before the first ART cycle, an early diagnosis of RIF on the basis of arbitrary definitions seems likely to cause more harm than benefit.

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Una nueva definición de fallo recurrente de implantación basado en tasas de aneuploidía de blastocisto anticipadas según la edad de la mujer.

Objetivo: Presentar una definición de fallo recurrente de implantación que tenga en cuenta los efectos de la edad de la mujer y las tasas anticipadas de euploidía de blastocisto sobre las tasas acumulativas de implantación.

Diseño: Modelo matemático.

Lugar: No aplicable.

Pacientes(s): No aplicable.

Intervención(es): Modelo matemático de probabilidad acumulativa de implantación basado en las tasas de euploidía de blastocisto publicadas según categorías de edad de la mujer.

Principal(es) medida(s) de resultado(s): El número de blastocistos requerido para obtener una probabilidad acumulativa de implantación del 95% asumiendo la ausencia de cualquier otro factor que afecte la implantación.

Resultado(s): Cuando es estado de euploidía del embrión transferido es desconocido (i.e., no sujeto a diagnóstico genético preimplantacional para aneuploidías), nuestra simulación demuestra que ninguna categoría de edad llega al 95% de probabilidad acumulativa de implantación de al menos un embrión hasta después de transferir siete blastocistos. El número de blastocistos requeridos para alcanzar el mismo nivel es mayor en pacientes mayores. Por ejemplo, las mujeres mayores de 38 años requieren transferencia de más de 10 blastocistos sin evaluar para que el rango superior de probabilidad predictiva alcance el nivel de 95%. Por otra parte, si la tasa de implantación de un blastocisto euploide se estima en 55%, entonces 4 blastocistos son suficientes para alcanzar una tasa de probabilidad acumulativa mayor del 95%, sin importar la edad.

Conclusión(es): El término "fallo recurrente de implantación" debería ser un término funcional para guiar el manejo posterior. Sugerimos que no debería llamarse fallo recurrente de implantación hasta que sea razonablemente probable que el fallo de implantación sea causado por otros factores además de la aneuploidía embrionaria, la principal causa de fallo de implantación. Proponemos una nueva definición que tenga en cuenta las tasas anticipadas de euploidía de blastocistos según categorías de edad de la mujer, tasa de implantación de blastocisto euploide y un nivel específico de probabilidad acumulativa de implantación.