Recurrent implantation failure: reality or a statistical mirage?

Consensus statement from the July 1, 2022 Lugano Workshop on recurrent implantation failure

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Importance: To date, recurrent implantation failure (RIF) has no clear definition and no clearly identified impaired function. Hence, the term RIF is currently used somewhat haphazardly, on the basis of clinicians' judgment.
Objective: International experts in reproductive medicine met on July 1, 2022, in Lugano, Switzerland, to review the different facets of RIF and define the diagnosis and its appropriate management.
Evidence Review: A systematic review without meta-analysis of studies published in English from January 2015 to May 2022.
Findings: Data indicated that RIF has been largely overevaluated, overdiagnosed, and overtreated without sufficient critical assessment of its true nature. Our analyses show that true RIF is extremely uncommon—occurring in <5% of couples with infertility—and that reassurance and continued conventional therapies are warranted in most cases of assisted reproductive technology (ART) failure. Although the true biologic determinants of RIF may exist in a small subset of people with infertility, they elude the currently available tools for assessment. Without identification of the true underlying etiology(ies), it is reasonable not to assign this diagnosis to a patient until she has failed at least 3 euploid blastocyst transfers (or the equivalent number of unscreened embryo transfers, adjusted to the patient's age and corresponding euploidy rate). In addition, other factors should be ruled out that may contribute to her reduced odds of sustained implantation. In such cases, implantation failure should not be the only issue considered in case of ART failure because this may result from multiple other factors that are not necessarily repetitive or persistent. In reality, RIF impacting the probability of further ART success is a very rare occurrence.
Conclusion: True RIF is extremely uncommon, occurring in <5% of couples with infertility. Reassurance and continued conventional therapies are warranted in most cases. It would seem reasonable not to assign this diagnosis to a patient until she has failed at least 3 euploid embryo transfers (or the equivalent number of unscreened embryos, adjusted to her age).
Relevance: Given the number of internationally recognized experts in the field present at the Lugano meeting 2022, our publication constitutes a consensus statement. (Fertil Steril® 2023;120:45–59. ©2023 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Recurrent implantation failure (RIF), endometrial receptivity, IVF failure, FET, frozen embryo transfer, PGT-A, preimplantation genetic testing for aneuploidy

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The success rates of assisted reproductive technologies (ARTs) have improved steadily since the first live birth (LB) from in vitro fertilization (IVF) in 1978. The implantation rates (IRs) of <10% in the early years have now increased to as high as 65% in several IVF programs with transfer of euploid blastocysts (1). However, 35% of euploid embryos transferred to an anatomically normal uterus still fail to implant, leaving patients worried that something has been overlooked in the management of their infertility.

Defining failure after multiple ART cycles—commonly referred to as recurrent implantation failure (RIF)—has been estimated on the basis of cumulative ART results (2). In the absence of consensus on the diagnostic criteria for RIF, this presumptive diagnosis is used somewhat haphazardly, on the basis of an individual clinician's judgment (3). Complicating the assessment of implantation failure is the recognition that there are several factors that contribute to the establishment of a successful pregnancy after ART. More confusion stems from the fact ART failure is defined in a multitude of ways, including by the absence of an LB, lack of sustained implantation with fetal heart activity (4) or no detectable beta-human chorionic gonadotropin in the serum after embryo transfer (ET) (5). The lack of consensus on the definition of RIF leads to the risk of overdiagnosing and overtreating the condition (3). The uncertainties and confusion regarding the diagnosis of RIF, an important clinical topic, were the primary motivation for organizing the Lugano Workshop. The members of the Lugano Workshop decided to study RIF as being the repeated failure to establish a sustained implantation after ART. To limit, as much as possible, the role of the embryo in implantation failures, this group also decided to primarily focus on the outcome of euploid blastocyst transfers conducted in hormone replacement–primed cycles using intramuscular (IM) progesterone.

A particular feature of the Lugano RIF Workshop was that it included representative specialists practicing reproductive medicine in both the United States and Europe. Hence, the Lugano Workshop aimed to merge any transatlantic variation in the clinical concept and management of RIF. Given the number of recognized experts in the field present in this meeting and their broad origin, we believe that this publication constitutes a consensus statement.

MATERIALS AND METHODS

The Workshop and the Working Group

The 2022 Lugano RIF Workshop received an unconditional grant from IBSA for covering the cost of this meeting. Although the financial support was an unconditional grant, it is worth mentioning that one of IBSA's products, a subcutaneous progesterone preparation (Prolutex; IBSA, Lugano, Switzerland), is mentioned in the discussion of this manuscript. However, this is just one of the progesterone preparations available.

The members of the workshop comprised a panel of international experts (n = 27) who met in Lugano, Switzerland, on July 1, 2022. Experts were selected on the basis of their overall research activities and their publications on the subject. Each member of the working group received a defined topic and the searches to be covered. Topics included the definition(s) of RIF, its clinical characteristics, correct uterine assessment before ART, and the soundness of diagnostic means and therapeutic measures, commonly proposed after 1 or several ART failures.

Literature Search and Consensus Building

A literature search through PubMed and Cochrane was performed using the following key terms: "recurrent embryo implantation failure," "recurrent reproductive failure," "RIF," "successive euploid embryo transfer," and "euploid embryo transfer." All titles and abstracts, written in English and published from January 2015 to May 2022, were screened to identify relevant studies, for which full-text articles were collected and summarized. Scientific data were reviewed regarding the success rates for serial transfers with euploid embryos, and the success rates and mathematical models were derived on the basis of age (with and without genetic evaluation of the embryo). To assess implantation failure, our working group started with an assumption of good-quality embryos to limit the impact of the many factors that affect the quality of gametes and embryos.

Consensus conclusions were stated on the basis of this literature search and the expert opinions of the working group. At the end of the meeting, key points were established, and conclusions were reached.

Preparation of the Manuscript

The writing group prepared successive drafts of recommendations that were shared among the work group experts for feedback and suggestions. The feedback received was discussed online. The list of experts who contributed to the consensus is included at the beginning of the manuscript.

COMMENTARY WITH RESULTS

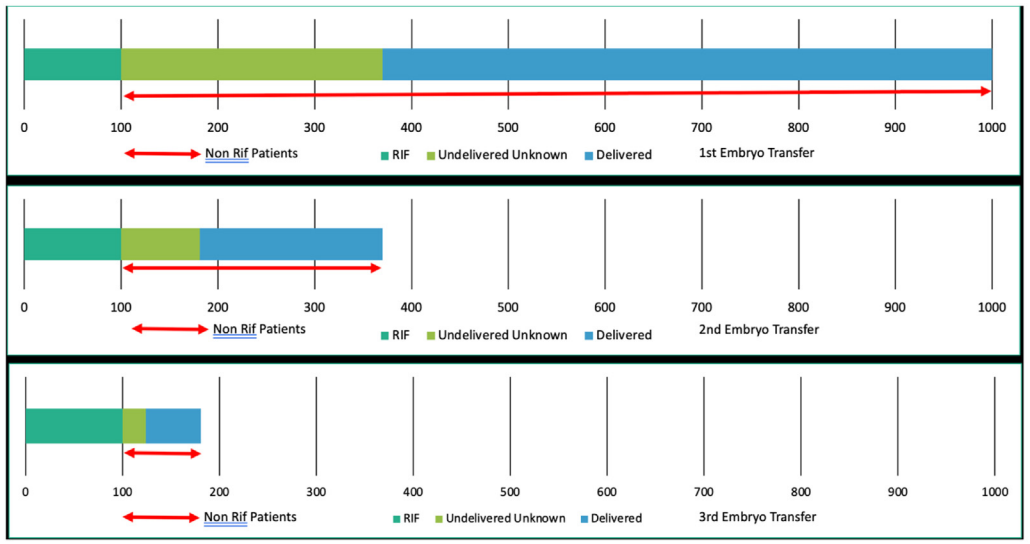
Defining RIF

A recent Views and Reviews in *Fertility and Sterility* on RIF was summarized by Hill (6) with the following comment: "evidence based medicine is wanted for the evidence component that so vitally informs its practice." Evidence is certainly lacking to inform us regarding what constitutes a diagnosis of RIF. The definition, which has drifted enormously over the last several decades, has been complicated by improvements in sustained IRs and by changes in ART practice, especially by decreasing the number of embryos transferred.

The consensus reached by our group was that consideration of an RIF diagnosis should focus on failure to achieve "sustained" implantation (defined as a gestational sac identified on ultrasound [US]). This definition does not literally follow the concept of "implantation failure," but neither clinicians nor patients consider a biochemical pregnancy an ART success. Furthermore, this definition allows differentiation from recurrent pregnancy loss.

Today's high IRs result from a variety of factors that are now routine in IVF: improved embryo culture; blastocyst transfer; US-guided ET; and, in several cases, preimplantation genetic testing for aneuploidy. Therefore, RIF refers to the lack

FIGURE 1



The most effective way to estimate the number of patients with recurrent implantation failure (RIF) in a typical assisted reproductive technology population was to model the decline in the pregnancy rates over successive euploid embryo transfers (ETs). This model could then be compared with the actual clinical data to determine whether the estimated prevalence was similar. Given a population with a 10% prevalence of RIF undergoing euploid ET, at the first transfer, 100 had RIF, and 900 had some chance at implantation. If the RIF was 70%, a total of 630 (63%) would deliver. At the second transfer, a total of 370 patients would remain undelivered—100 with RIF and 270 without. Applying the 70% sustained implantation rates for euploid ET to the receptive patients, 189 would deliver. At third transfer, 100 still had RIF, and 81 normal patients remain. This provided a live birth rate of 31% (57 of 181) for the third ET. The population of patients with RIF was enriched with each successive ET. *Undelivered unknown—all those patients without RIF who did not deliver after the ET including the following: no pregnancy; biochemical pregnancies; and miscarriage.

Recurrent implantation failure. Fertil Steril 2023.

of sustained implantation after the transfer of good-quality embryos in a uterus that is morphologically normal (as per US, saline infusion sonography, and/or hysteroscopy). Importantly, there are many sporadic reasons why a good-quality embryo may not implant. Not every ET is identical because some may be technically difficult because of anatomical challenges, which could affect the success rates. These technical difficulties in performing ET may not necessarily be encountered on every occasion. Moreover, implantation failure of the approximately 35% of euploid blastocysts may be due to 1 or multiple factors and not necessarily the same factor each time.

Several definitions of RIF have been proposed, and most have focused on the number of ET failures. Historically, RIF was defined as the transfer of >10 embryos of high quality (by morphology) (7–9). Today, the various proposed definitions rather refer to the number of failed ETs a patient has had, with a common number being 3 (10). Still, others count the cumulative number of high-quality embryos that have been transferred along with female age, the primary factor of aneuploidy risk (11), as reviewed by Macklon (12).

In a survey including a total of 735 clinicians and 300 ART biologists, more than two thirds of the participants also took lifestyle factors into account (e.g., medications, smoking, and body mass index [BMI]), and overall, the study found a profound lack of agreement on the definition of RIF (13). These investigators concluded that the definition of RIF is blurred by a "profusion of confusion and may, in their eyes, simply be an illusion" (14).

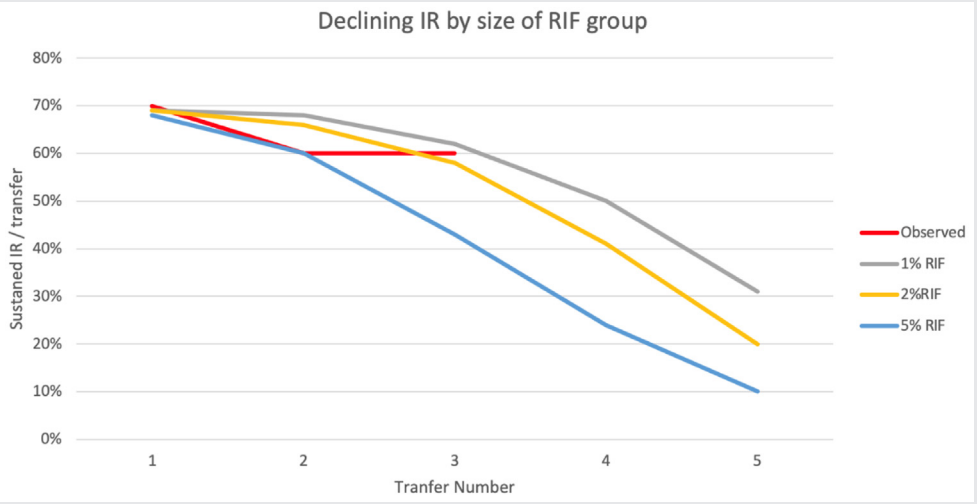
Perhaps, the first task in defining RIF is to ask what it would look like clinically. When performing clinical ART, the population would consist of 2 groups: those patients with a realistic probability to conceive and deliver and those with RIF, who have a biologic resistance to sustained implantation, and are, therefore, unlikely to conceive and deliver.

Some have proposed that RIF is likely very rare because the chance of implantation is high with the first ET and remains relatively high with successive ETs (6). Indeed, Pirtea et al. (4) demonstrated that the initial sustained IR was 69.9% and remained high at 59.8% and 60.3% with the second and third euploid frozen ETs (FETs), respectively. The cumulative sustained IR was 95.5% with 3 consecutive euploid single ETs. This suggests that the upper limit of the RIF group is 4.5% because 95.5% were successful by the third transfer (4). It is notable as well that the sample size was not sufficient to evaluate the success of a fourth euploid ET, begging the following questions: after how many ETs does the odds of success per transfer go down, and is there even such a number?

ESTIMATING THE SIZE OF THE RIF COHORT (SUSTAINED IMPLANTATION FAILURE DECLINE OVER SUCCESSIVE ETS)

Estimating the true size of the RIF group can be assessed by the rate at which sustained IRs decline over successive ETs. Because, conceptually, patients with true RIF would be

FIGURE 2



Calculated implantation rates (IRs) assuming IRs of 70% and recurrent implantation failure (RIF) prevalence rates of 1%, 2%, and 5% in the initial group, compared with the rates observed in the study by Pirtea et al. (4), suggesting a true incidence of RIF of between 1% and 5%. Using this model, the estimated prevalence would be <1%.

Recurrent implantation failure. Fertil Steril 2023.

expected to very rarely achieve sustained implantation, they will remain in the group who fail after multiple transfers, thereby "enriching" the pool in later ETs. Figure 1 illustrates, in detail, this concept. If 10% of routine ART patients were to experience RIF, they would constitute 10% of the first transfers but 27% and 55% of the second and third ETs, respectively. This level of enrichment (as would be evidenced by rapidly dropping sustained IRs with successive ETs) is not observed in clinical practice. Figure 2 illustrates, in detail, the variable rates of RIF in the population who would be anticipated to impact sustained IRs in successive high-quality ETs. Comparing these curves to the Pirtea dataset (4) suggests that the true rate of RIF is likely to be in the range of 1%–5% (15).

Other datasets corroborate this estimate. The Society for Reproductive Technology (SART) (16) publishes annual national data on most US ART programs. On the basis of the SART 2020 data, among women aged <35 years having a single euploid blastocyst transferred, a total of 62.5% of the first ETs implant (n = 17,890), and 55.5% of the second or subsequent ETs implant (n = 9,474), reporting only a 7.0% decline.

Pirtea et al. (4) reported results—for sustained IRs and live birth rates (LBRs)—after successive euploid FETs. In case of euploid FETs, implantation chances are high with the first euploid transfer (69.9%) and remain relatively high with the second (59.8%) and third (60.3%) ETs (4). The cumulative sustained IR was 95.5% after 3 consecutive single euploid FETs (4).

A study using the National Assisted Reproductive Technology Surveillance System data (17) of 44,750 women aged 20–35 years who have ≥4 embryos cryopreserved used a novel modified dynamical model (18) to assess the change in IRs over successive transfers to calculate the size of the "inherent fertility." Estimates were 91.7% among FETs and 90.0% among fresh ETs (17), implying that the size of the RIF group would be 9.2%. However, notably, this study did not control for ploidy status (17).

Taken together, a decline in the IRs of between 7% and 10% would occur when an RIF subgroup of 2%–5% exists in the initial cohort. We, therefore, estimate that 2%–5% of patients pursuing ART treatment may have RIF.

Defining RIF by Assessing Success After Transfer of Euploid Embryos

The consensus of the group was to assess ART results observed after transfers of genetically tested embryos conducted in hormonally controlled conditions, using FET in hormone replacement treatment (HRT) regimens to minimize confounding factors from other causes of failure. Indeed, the risk of implantation failure increases with age (19) in parallel with the age-related increase in the aneuploidy rates (20), indicating that embryo aneuploidy is a primary cause of age-related ART failure. Conversely, the effect of maternal age on implantation of euploid blastocysts appears small (21), and paternal age has limited impact (22). Moreover, the chances of obtaining euploid blastocysts are not affected by prior ART cycles yielding only aneuploid embryos (23). Finally, trophectoderm biopsy has limited adverse impact on sustained implantation (24). This suggests that the 35% of cases in which a euploid embryo does not implant fail for reasons other than aneuploidy (25). Although some see a possible cause in the cytoplasmic properties of the embryo—mitochondria (23)—this issue remains puzzling, may be multifactorial, and awaits data from further research.

Given that embryo aneuploidy is the primary cause of ART failure (20), Pagidas et al. (19) investigated the outcome of euploid ET conducted in patients clinically diagnosed with

TABLE 1

Sustained implantation rate after embryo transfer with or without preimplantation genetic testing for aneuploidy by age in the 2020 Society for Reproductive Technology national outcomes report (18).

Type of ART cycle	<35y	35–37y	38–40y	41–42 y	≥43y
PGT-A cycles	62.5%	60.8%	58.7%	53.7%	48.3%
Non-PGT-A cycles	46.8%	41.1%	34.7%	25.5%	16.7%

PGT-A = preimplantation genetic testing for aneuploidy.

Recurrent implantation failure. Fertil Steril 2023.

RIF. According to their findings, the availability of euploid embryos in a patient with a history of RIF was associated with high ongoing pregnancy rates and IRs (19). In a retrospective study, Cimadomo et al. (26) analyzed the factors that affect euploidy and implantation in 2,676 patients undergoing 8,151 euploid blastocysts transfers. As shown by others (25), these investigators observed that the euploidy rates sharply decreased with increasing maternal age (26). However, this age-related decrease in the euploidy rate was not affected by previous LB (1 or >1), miscarriage (1, 2, or >2) or past ART cycles with no euploid blastocysts (26). The fact that a prior lack of obtaining euploid embryos does not impact the further chances of having euploid embryos has also been shown by others (23). Together, these findings indicate that studying the outcome of euploid ET is most likely the best method for analyzing the prevalence of RIF.

Assessing sustained IRs of euploid blastocysts for studying RIF is supported by Ata et al. (27). Indeed, these investigators proffer that one should not talk of RIF until after one can ascertain that implantation failure is reasonably likely caused by factors other than embryo aneuploidy, the leading cause of implantation failure. Therefore, these investigators propose that the definition of RIF should consider the anticipated blastocyst euploidy rates across categories of female age to predict cumulative probability of implantation (27). The expected sustained IRs after euploid and nontested embryos as in the SART age groups reported in US 2020 national outcome report are depicted in Table 1. An estimation model of the number of unscreened embryos needed to be equivalent to 3 euploid ETs and achieve a 95% chance of a sustained implantation is presented in Table 2.

Defining RIF on the Basis of Defining a Statistical Outlier

A commonly used method to establish diagnostic criteria for a given clinical entity is the application of the 95% confidence interval (i.e., 2 standard deviations) of the mean. This method may be used in 1 of 2 ways: first, it can be in a sample of adequate size of diagnosed cases of a particular entity from which the mean and 2 standard deviations are calculated. This method may carry the chance of declaring some false-negative cases, thereby lowering its positive predictive value. Second, this method may be performed on a sample of known negative cases. In this case, the upper limit of its 95% confidence interval may be taken as the cutoff value. If a patient's value is greater than this cutoff value, it may be considered positive (diseased). This approach may carry a chance of declaring some false-positive cases, thus lowering its negative predictive value. Yet, the use of a 95% threshold for defining RIF has benefits when no diagnostic test exists for the entity. Notably, using a 5% cutoff is also similar to the rate of failure of 3 euploid FETs (4).

Definitions on the basis of normal distributions have limitations. There is always someone whose outcomes will fall outside of 2 standard deviations or 3. If the definition of RIF is not based on pathology, it will not predict diminished outcomes in future attempts. A probabilistic definition of RIF may lead to overdiagnosis with the potential to generate incorrect diagnoses, unnecessary testing, and altered clinical management without evidence of benefit.

PUTATIVE CAUSES UNDERLYING RIF

Oocyte Cohort Effect

One question regarding RIF is the possibility of variation due to a cohort effect in oocyte/embryo quality on the basis of ovarian stimulation and oocyte harvests between cycles. Several aspects of laboratory performance suggest that this is the case. One of the earliest factors to be identified to vary from cycle-to-cycle in the same couple was fertilization. In the days before intracytoplasmic sperm injection (ICSI), excluding severe male factor, failed fertilization in a single cycle was associated with a <30% risk of recurrence in a subsequent cycle (28). Although this may be thought to be due to sperm quality, a suggestion that the oocyte equally contributes to this is supported by the observation that the fertilization rate (with either ICSI or conventional IVF) is correlated with the IR (29). Additionally, abnormal fertilization (triploidy with ICSI) lowers the IRs of the entire normally fertilized cohort, again suggesting an oocyte issue in the cohort (30). Another aspect of the cohort is the presence of excess embryos for freezing and whether transfer was at the cleavage (31) or blastocyst stage (32, 33). Availability of excess embryos was associated with higher IRs even with equivalent embryo grade at transfer. Thus, the definition of RIF should not be considered on the basis of only 1 cohort of embryos but rather on the basis of the number of euploid blastocyst transferred or the number of transfers adjusted to patients' age.

TABLE 2

Estimation model for of the number of unscreened good-quality embryos needed to be equivalent to 3 successive euploid embryo transfers and achieve a 95% chance of sustained implantation on the basis of the observed aneuploidy rate (20).

Age (y)	Observed aneuploidy rate	No. of untested blastocysts to achieve a 95% chance of sustained implantation
<35	20%	4
35–37	30%	5
38–40	50%	7
41–42	70%	13
≥43	85%	27

Recurrent implantation failure. Fertil Steril 2023.

Uterine Factors

Uterine/endometrial factors can certainly cause infertility by impairing embryo implantation. However, these possible causes of ART failure ought to be ruled out before undertaking ART, not after an unspecified number of ART failures. Notably, it has been well demonstrated that communicating hydrosalpinges significantly reduce the odds of sustained IRs (34–38), as do various uterine cavity distorting anatomical lesions (39–45), and that surgical management can improve success. Therefore, such possible uterine causes should be ruled out before initial planned ET to a patient with infertility. Saline infusion sonohysterography paired with hysterosalpingo-contrast sonography can accomplish both goals in experienced hands (46–49). Given its excellent diagnostic accuracy and tolerability, saline infusion sonography has emerged as the initial method of choice for evaluating the uterine cavity (50–54). Of note, randomized clinical trial (RCT) data indicate that the routine use of diagnostic hysteroscopy either before the initial ET or after multiple ETs does not improve the odds of sustained IRs (55, 56). A hysterosalpingogram can be used to exclude the presence of hydrosalpinx(ges) in settings where hysterosalpingo-contrast sonography with 3-dimensional rendering and high-frequency Doppler are not available (57). Although plain transvaginal US without contrast instillation has high specificity for a diagnosis of hydrosalpinx, the test lacks sensitivity (58, 59).

In the absence of abnormal uterine bleeding and with a normal size uterus on US, further uterine examination in search of possible adenomyosis is not warranted. Indeed, recent data indicate that the impact of asymptomatic adenomyosis on implantation after FET is doubtful (60–62).

Endometrial Receptivity and Factors

The concept that the endometrium is receptive only during a short-lasting window of receptivity (WOR) emanates from early experience with donor oocyte ART. The early cycles were conducted using estradiol (E2) and progesterone—IM injections—in programed or "HRT" cycles in women who experienced complete premature ovarian failure (63, 64). The remarkable successes of donor egg ART led to adopt a similar approach, using E2 and progesterone, for priming FETs (65). In women whose ovaries are functional, this was conducted with (65), and later without (66, 67), ovarian suppression with a gonadotropin-releasing hormone agonist. The alternative is to perform FET in natural or modified natural cycles. In an RCT, Groenewoud et al. (68) demonstrated that ETs timed in natural, modified natural, or E2 and progesterone programed cycles had similar outcomes. Although this observation has been confirmed in meta-analyses (69–71), some investigators suggest that true natural cycles have better results (72).

The WOR is controlled by the duration of progesterone exposure after sufficient E2 priming, as clearly defined in HRT cycles (64, 73). The exact duration of the WOR has been a matter of debate. Van de Vijver et al. (74, 75) have studied this issue by conducting 2 RCTs in E2 and progesterone programed cycles. These investigators reported similar LBR after the transfer of cleavage-stage embryos on the third or fifth day (74) and blastocysts on the fifth or seventh day of progesterone treatment (75).

Receptivity Assays

Over the last 2 decades, tests were developed for assessing endometrial receptivity. The most widely used of these tests is the endometrial receptivity assay (ERA), which requires a biopsy performed in a cycle before the transfer cycle (76, 77). The results provided by ERA indicate whether the endometrium is receptive, prereceptive, or postreceptive on the anticipated WOR. The recommendation is to transfer on the calculated, also known as personalized, period of receptivity, which can be either during, after, or before the anticipated WOR (78). The ERA test was heavily marketed well before any proof of validation was provided, and several recent studies have shown that "personalized" ETs on the basis of ERA data do not improve outcomes (79–82) compared with ETs on the basis of conventional timing (83).

Another functional endometrial assay investigated possible overexpression of B-cell lymphoma 6 protein expression in the endometrium (84). This assay marketed under the name of Receptiva (85) is proposed as a marker of endometrial alterations encountered in endometriosis and notably, endometrial resistance to progesterone. Although the value of the test as a diagnostic tool for endometriosis is not questioned here, its ability to predict endometrial receptivity was not properly validated in an appropriately designed study or an RCT. Of note, the outcome of euploid FET in E2 and progesterone programed cycles was not different between patients with and without endometriosis (86). Klimczak et al. (87) reported that the proportion of patients with B-cell lymphoma 6 positivity did not significantly differ between those who achieved LB and those who did not. Finally, other endometrial receptivity tests have been proposed for assessing endometrial receptivity; however, none of these have been properly validated in an RCT (88, 89).

In summary, the current tests of endometrial receptively should not be used to characterize or justify treatment of women with suspected RIF.

Endometrial Thickness

Large registry and retrospective studies suggest decreased pregnancy rates and LBRs in case of a "thin" endometrium at the time of ET (90), and the existence of a threshold below which results start to compromise is an ongoing discussion (91).

A negative association between endometrial thickness/pattern and pregnancy rates has also been reported in FETs and natural cycles (92, 93). However, numerous studies, with or without stratification according to somewhat arbitrarily chosen cutoff values, for example, <6, <7, and <8 mm, have provided contradictory conclusions (90, 94–98). Interestingly, however, prospective and retrospective studies in which transfers were performed irrespective of endometrial thickness suggested that endometrial thickness does not impact ART outcome (91, 94–96, 98). Women with an endometrial thickness of <5 mm after E2 preparation are rare, and it is difficult to draw definitive conclusions. However, whether endometrial thickness per se affects implantation once an intracavitary pathology has been ruled out is controversial. Conversely, a hyperechogenic appearance of the endometrium reflects premature progesterone exposure, which shifts the WOR and can affect sustained IRs (94, 95, 99). Finally, it is important to underscore that the study on repeated euploid blastocyst transfers quoted earlier was conducted in women whose endometrial thickness was ≥7 mm (4).

Certain studies have emphasized the importance of the timing of endometrial thickness measurement. Haas et al. (100) and Zilberberg et al. (101) reported that a decrease in endometrial thickness after exposure to progesterone—a phenomenon identified as "compaction"—was associated with optimal outcome. Conversely, Bu et al. (102) reported opposite findings with optimal results achieved when the endometrial thickness on the day of ET increased or remained unchanged compared with that on the first day of progesterone administration. An additional study indicated that endometrial compaction did not predict ART outcome (103). Taken together, available evidence indicates that a clear role of endometrial compaction in response to progesterone treatment and its association with outcome awaits further data.

It is crucial to mention that most prior studies on endometrial thickness did not account for embryo ploidy status or morphologic grade of embryos, another major determinant of implantation potential (90, 95, 98). Thus, it would be fair to suggest that more studies that control for embryo ploidy status are needed to bring further light on this issue.

Endometrial Microbiome

Recent interest has been focused on the endometrial microbiome. Numerous publications have demonstrated that the endometrial cavity is not sterile but rather the resident site of various microorganisms (104). Some have claimed that the nature of the endometrial microbiome impacts endometrial receptivity (105, 106), whereas others have not found such a correlation (107). The most common vaginal dysbiosis is bacterial vaginosis. A recent systematic review including 17 studies did not report a significant decline in ART outcome in women with bacterial vaginosis (105). A recent study employed ribonucleic acid sequencing, rather than the previously used deoxyribonucleic acid sequencing, to identify live active microbiota in the endometrial cavity from 7 healthy women (108). With this methodology change, the investigators reported that the lactobacillus represented only <1% of the "live" endometrial microbiota (108), whereas its presence was taken as a sign of receptive endometrium by those claiming that the endometrial microbiome affects endometrial receptivity (105, 106). In view of the existing divergence of results and new methodological issues (108), further study is needed to define whether the microbiome plays a role in the probability of implantation.

Endometrial Inflammatory Factors

Numerous publications have highlighted the presence of endometrial alterations within the eutopic endometrium, notably in women with endometriosis. The characteristic feature of these effects is an endometrial resistance to progesterone (109, 110). The impact of these endometrial changes is minimized by ovarian suppression using either a gonadotropin-releasing hormone agonist (111) or the oral contraceptive pill (112). Recently, normal IRs have been reported after FETs in E2 and progesterone (IM) replacement cycles (88). In a large donor oocyte study, the success rates were not altered in recipients affected by endometriosis (113). Recent data indicate that when embryos are transferred to patients with endometriosis in HRT cycles, serum progesterone mattered (114) with higher LBRs when the serum progesterone levels were >37.1 ng/mL. Moreover, endometriosis does not affect oocyte quality, as evidenced by unaltered fertilization, blastulation, and blastocyst euploidy rates (115, 116). Adenomyosis has been claimed to affect IRs (60) but not in the morphologically normal uterus (61).

Chronic endometritis (CE) is a persistent inflammatory condition of the endometrium. Contrary to acute forms of endometritis, CE is characterized by a paucity of symptoms that may include abnormal uterine bleeding and some degree of pelvic pain (117). The diagnostic criteria of CE have been debated. Commonly, the diagnosis is made using hysteroscopy with identification of micropolyps (118) or the presence of immune-stained plasmocytes either on endometrial biopsies (119) or in endometrial cultures (120). Interestingly, the incidence of CE is increased in patients with endometriosis, a factor which may play a role in the genesis of this disease (121). Unfortunately, the diagnosis of CE is said to lack clarity and specificity (122, 123), and given the inconsistencies in available evidence, the issue on CE diagnosis is still far from being resolved, and the role of this disease in reproductive failure deserves further investigation (124, 125). The most common therapy proposed is antibiotic treatment (126). Recent data indicate that CE does not impair ART outcome after euploid FET. Indeed, Herlihy et al. (127) who investigated the

sustained IRs of euploid FETs did not find the differences in the presence of CD138 cell in endometrial biopsies at any concentration. These recent data, therefore, indicate that CE, which likely plays a role in the pathophysiology of endometriosis, may fail to directly impact ART outcome, as assessed by sustained IRs after euploid FET in E2 and progesterone cycles (121).

Progesterone Effects

Progesterone levels and implantation Labarta et al. (128) were first to report that in women receiving vaginal progesterone in programed FET cycles, ART outcome was decreased in women whose progesterone levels were low on the day of ET. These findings were later confirmed in a meta-analysis showing poorer outcome when serum progesterone levels were <10 to 20 ng/mL (129). These shortcomings encountered in case of low progesterone levels on the day of transfer could be corrected by the addition of exogenous supplementation using subcutaneous progesterone 25 mg/day (Prolutex; IBSA) (130–132). This led some to propose individualizing progesterone administration with supplementing women whose serum progesterone levels are <10 to 20 ng/mL (133). However, others, opted for supplementing all women receiving vaginal progesterone with subcutaneous progesterone 25 mg/day for the sake of simplicity (134). Subcutaneous progesterone alone was also effective at the dose of 25 mg twice a day in FETs (135, 136). Hence, assuring that proper progesterone supplementation is achieved in HRT cycles for FET appears crucial to optimize ART outcome because inadequate progesterone supplementation is a possible cause of ART failure. The reported "optimal" serum progesterone levels apply only to vaginal progesterone (128), and it is difficult to extrapolate to IM progesterone cycles. It is worth mentioning that vaginal progesterone use in HRT FET has been found inferior to IM progesterone in a multicenter RCT by Devine et al. (137). In this RCT including a total of 1,060 FETs, the LBR was significantly lower in women who received only vaginal progesterone (27%) than in those who received IM progesterone (44%) or combination treatment (46%). Fifty percent of pregnancies in women who received only vaginal progesterone ended in miscarriage (137).

Progesterone supplementation in programed cycles Data reported by Pirtea et al. (4) were obtained after euploid FET in E2 primed cycles, which used IM progesterone (50 mg/day). A prospective RCT reported lower LBRs when using vaginal progesterone than when using IM progesterone in HRT-based FETs (138). Of note, IM progesterone has been reported recently as consistent practice by a comprehensive survey conducted in 13 high-performing US fertility clinics (139).

Metabolic Factors

In a recent clinical practice survey, metabolic factors were related to RIF by 82 % of medical providers (13). Although diabetes was not addressed in specialized guidelines, BMI was considered relevant to RIF and has been recognized as a high-risk factor for reproductive health. Although obesity has long been known to exert various deleterious effects on female fertility, the underlying mechanisms, especially the roles of lipid metabolism in endometrial receptivity, remain largely elusive (140). In addition, whether the association between obesity and chronic inflammation and oxidative stress (141) decreases endometrial receptivity (by displacing the WOR) (142, 143) remains to be clarified. Further studies need to clarify these gaps in knowledge and help inform how obesity may need to be factored into a definition of RIF in this unique patient population (144).

Male Factor

The possible contribution of male gametes in RIF remains incompletely understood. There are data suggesting that sperm quality—notably, the deoxyribonucleic acid fragmentation level—contributes to ART failures and, possibly, to RIF (145). The mechanism whereby sperm may affect embryo implantation is still unclear, and results are controversial (146–148). Likewise, sperm quality has been implicated as a possible cause of miscarriage (149).

Therapeutic Measures Commonly Proposed After Several ART Failures and Place of ART "Add-Ons"

Couples who repeatedly fail to conceive after ART inevitably will look for possible explanations. Couples with infertility become even more vulnerable and fall prey to accepting and/or seeking all kinds of recipes, treatments, and various measures that they may hear about to increase their chances of conception. Possible therapeutic options are often presented by word of mouth, the Internet, and other means. Current evidence shows no known effective treatment for RIF. Collectively, these therapeutic options proposed after failed ART attempts—or, sometimes, up front—are regrouped under the name of ART "add-ons." Among these add-ons, we notably highlight the following.

Immunologic, thrombophilia testing and treatments. Reports associating RIF with inherited thrombophilic conditions are multiple. A recent meta-analysis including 7 articles reported no difference in ART outcome in case of factor V Leiden mutation, prothrombin gene, methylenetetrahydrofolate reductase, and activated protein C resistance mutation (150, 151). Acquired thrombophilias, specifically antiphospholipid syndrome, are significantly associated with recurrent pregnancy loss and obstetric complications (152). However, evidence is conflicting regarding their association with RIF (153–155).

Consequently, testing for inherited or acquired thrombophilia in patients with ART failures is not recommended because of insufficient evidence regarding a positive association with ART outcome (156).

The hypothetical role of cytokines and uterine natural lymphocyte killer cells led to proposals for the use of glucocorticoids (157, 158). However, several RCTs have shown no clinical improvements (159–162), and the American Society for Reproductive Medicine guidelines (157) currently

recommend against the use of glucocorticoids to improve ART outcome.

Similarly, other immunomodulators, such as intravenous immunoglobulin and intralipids, have been considered but without proof of efficacy (157, 163, 164).

Endometrial scratching. Intentional injury of the endometrium, known as endometrial "scratching," has been proposed but with no proven efficacy (138). A recent study was stopped when interim evaluation showed that endometrial scratching had harmful effects (165).

Other potential add-ons, such as intrauterine infusion of intravenous immunoglobulin (166, 167), granulocyte colony-stimulating factor, intrauterine perfusion of autologous platelet-rich plasma (168, 169), intrauterine autologous peripheral blood mononuclear cell infusion (167, 170), or human chorionic gonadotropin (167, 171), have been reviewed and discussed; however, given the lack of comprehensive data and heterogeneity of the studies reported, the working group decided not to include them for recommendation.

DISCUSSION

A Way Forward

We acknowledge the limitations of this consensus document and the shortfall of a systematic review without meta-analysis. Nevertheless, a common definition of RIF is needed to harmonize and interpret ongoing and future research of this condition. In addition, a stricter estimate of the prevalence of RIF offers the added benefit of avoiding overdiagnosis and, thereby, unnecessary treatments, such as ART add-ons.

It is possible that there are unidentifiable factors that contribute to RIF. However, this condition is rare and is likely present in <5% of women. Currently, this condition can only be identified by unexplained repetitive failure after transfer of good-quality embryos, a definition on the basis of probability instead of biology. With RIF, the decline in future IRs with each cycle fits more to an exponential decay curve rather than as a linear decrease. However, after repeated failure, the chance of having a biologic basis for failure becomes more likely, and investigation may be justified, depending on quality and cost of the test and the efficacy of the treatment. When a woman is found to meet these criteria, all aspects of the IVF process should be evaluated, not solely a focus on the endometrium.

A definition of RIF on the basis of normal distributions has limitations. There is always someone whose outcome will fall outside of 2 or even 3 standard deviations. Identification of occurrence does not amount to defining a pathology and does not automatically predict diminished outcomes in future attempts. In the absence of a biologic difference, the simple fact that someone has multiple failures does not justify new investigations or treatments. To be meaningful, the diagnosis of RIF must be on the basis of actual pathophysiological data. Further research is needed to identify male and female factors that may contribute to repetitive ART failure of pregnancy with good-quality embryos and should concentrate on the <5% of the population that failed 3 successive euploid blastocyst transfers (or the equivalent number of nontested embryos).

In conclusion, despite significant advances in ART success over the past decades, there are still couples who fail to conceive after multiple ART attempts. Some have proposed that these patients are diagnosed with RIF. However, whether these patients have an undetected biologic condition or have just been "unlucky so far" is a critical distinction when guiding future care for these patients. Given the existing data, it would seem reasonable not to assign this diagnosis to a patient until she has failed at least 3 euploid FETs (or the equivalent number of untested embryos, adjusted to the patient's age) and other factors have been ruled out that are known, or believed, to result in reduced odds of sustained implantation. Further diagnostic or therapeutic interventions should be limited to this group that comprises fewer than 5% of patients undergoing ART.

Contrary to infertility, RIF is not an overt clinical entity. Currently, RIF has no clear-cut definition or impairment-related function. Data on repeat euploid FET success after further ART attempts do not drastically differ from similarly characterized couples undertaking their first ART attempt (4). In women with an apparent anatomically and functionally normal uterus and with a normal BMI, RIF is a challenge (4). Assessments of couples who fail repeated ART attempts should involve the number of euploid transferred embryos and, if embryos were not tested, the number of FETs adjusted to the patient age accordingly.

Therefore, the consensus reached by the participants to the 2022 Lugano Workshop is that RIF has been overevaluated, overdiagnosed, and overtreated without sufficient critical evaluation of the presumed condition. In repeated euploid blastocyst transfers in HRT cycles using IM progesterone, RIF—not yet defined as a biologic entity—only occurs in <5% of cases. Our understanding of the determinants of implantation, both embryonic and uterine, remains limited, and further improvements in that knowledge will underpin future improvements in the success of modern ART.

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Fallo de implantación recurrente: ¿realidad o espejismo estadístico? Declaración de consenso del taller de Lugano del 1 de julio de 2022 sobre el fallo de implantación recurrente.

Importancia: Hasta la fecha, el fallo de implantación recurrente (RIF) no tiene una definición clara ni una función alterada claramente identificada. Por lo tanto, el término RIF actualmente se usa de manera un tanto aleatoria, según el juicio de los médicos.

Objetivo: Expertos internacionales en medicina reproductiva se reunieron el 1 de julio de 2022 en Lugano, Suiza, para revisar las diferentes facetas del RIF y definir el diagnóstico y su manejo adecuado.

Revisión de la evidencia: Una revisión sistemática sin meta-análisis de estudios publicados en inglés desde enero de 2015 hasta mayo de 2022.

Hallazgos: Los datos indicaron que el RIF ha sido sobrevaluado, sobrediagnosticado y sobretratado en gran medida sin una evaluación crítica suficiente de su verdadera naturaleza. Nuestros análisis muestran que el verdadero RIF es extremadamente poco común (ocurre en <5% de las parejas con infertilidad) y que la tranquilidad y los tratamientos convencionales continuos están justificados en la mayoría de los casos de fallo de los tratamientos de reproducción asistida (TRA). Aunque los verdaderos determinantes biológicos del RIF pueden existir en un pequeño subconjunto de personas con infertilidad, eluden las herramientas de evaluación actualmente disponibles. Sin la identificación de la(s) verdadera(s) etiología(s) subyacente(s), es razonable no asignar este diagnóstico a una paciente hasta que haya fallado al menos 3 transferencias de blastocistos euploides (o el número equivalente de transferencias de embriones no seleccionados, ajustadas a la edad de la paciente y la tasa de euploidía correspondiente). Además, se deben descartar otros factores que puedan contribuir a reducir las probabilidades de implantación sostenida. En tales casos, el fallo de la implantación no debe ser el único problema que se considere en caso de fracaso del TRA, ya que esto puede deberse a muchos otros factores que no son necesariamente repetitivos o persistentes. En realidad, el RIF que afecta la probabilidad de un mayor éxito del TRA es un suceso muy raro.

Conclusión(es): El verdadero RIF es extremadamente poco común y ocurre en <5% de las parejas con infertilidad. La tranquilidad y los tratamientos convencionales continuos están justificadas en la mayoría de los casos. Parecería razonable no asignar este diagnóstico a una paciente hasta que haya fallado al menos 3 transferencias de embriones euploides (o el número equivalente de embriones no seleccionados, ajustado a su edad).