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Assisted Reproductive Technologies (ART) Failures: Is It the Seed or the Soil?

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ABSTRACT

Assisted reproductive technologies (ART) have accomplished spectacular progresses over the last few years, leading to sustained implantation rates (sIR) ≥60% following euploid blastocyst transfers. These results raise new challenges for infertility specialists, notably the ability to care for infertile couples who fail ART, sometimes recurrently.

ART failures may be due to disorders residing in the endometrium (the soil) or embryo (seed). To simplify the review of this dilemma and limit variables, we focused our research on the outcome of euploid blastocysts transfers conducted in E2 and i.m. progesterone replacement cycles. This methodological choice for our research should not be confused with a therapeutic recommendation in case of ART failures. The sum of the data collected indicates that if recurrent implantation failure (RIF) exists, it is extremely rare, affecting only ≤5% of ART couples.

Keywords: Assisted Reproductive Technologies (ART); In Vitro Fertilization (IVF); Embryo Implantation; Euploid Blastocyst; IVF—ART Failure; Recurrent Implantation Failure (RIF).

ABSTRACT
[IN NATIVE LANGUAGE – KHMER]

សេចក្តីសង្ខេប៖ បច្ចេកវិទ្យាជំនួយការបង្កកំណើត (ART) សម្រេចបាននូវឧឡារភាពគួរឲ្យកត់សំគាល់នៅក្នុងរយៈពេលប៉ុន្មានឆ្នាំចុងក្រោយនេះ ដែលនាំឲ្យអត្រានៃការតោងជាប់ឈានដល់លើសពី៦០% បន្ទាប់ពីការបញ្ចូលអំប្រ៊ីយ៉ុងដែលមានក្រូម៉ូសូមប្រក្រតី (euploid blastocyst) ។ ទោះបីយ៉ាងនេះក្តី លទ្ធផលទាំងអស់នេះ បណ្តាលឲ្យមានបញ្ហាប្រឈមថ្មីៗផ្សេងទៀត ក្នុងការប្រើប្រាស់បច្ចេកវិទ្យាជំនួយការបង្កកំណើត (ART) សម្រាប់អ្នកឯកទេសផ្នែកលំបាកមានកូនជាពិសេសលទ្ធភាពក្នុងការគ្រប់គ្រងព្យាបាលគូស្វាមីភរិយាដែលបរាជ័យ ហើយគូខ្លះបរាជ័យជាបន្តបន្ទាប់ច្រើនដង។ បរាជ័យនៃបច្ចេកវិទ្យាជំនួយការបង្កកំណើត (ART) អាចបណ្តាលមកពីបញ្ហាដែលកើតនៅលើស្រទាប់រដូវ (ដី) ឬអំប្រ៊ីយ៉ុង (គ្រាប់ពូជ) ។ ដើម្បីបន្ថយភាពស្មុគស្មាញនៃចំណោទបញ្ហានេះ និងដើម្បីដាក់ដៃនកំណត់លើកត្តាអថេរពាក់ព័ន្ធផ្សេងៗ យើងបានផ្តោតការសិក្សាស្រាវជ្រាវនេះ លើលទ្ធផលនៃការដាក់បញ្ចូលអំប្រ៊ីយ៉ុងដែលមានក្រូម៉ូសូមប្រក្រតី ដោយជ្រើសរើសតែករណីនៃវដ្តព្យាបាលទាំងឡាយណា ដែលប្រើប្រាស់នូវអ័រម៉ូនអ៊ីស្ត្រាឌីយ៉ូល និងប្រូហ្សេស្តេរ៉ូន (E2 & i.m. Progesterone)។ ជម្រើសយកវិធីសាស្ត្រសិក្សាស្រាវជ្រាវបែបនេះ មានភាពដាច់ដោយឡែក មិនរួមបញ្ចូលនឹងនីតិវិធីណែនាំព្យាបាលពេលមានករណីបរាជ័យ ART

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នោះទេ។ ទិន្នន័យប្រមូលបានពីការសិក្សាស្រាវជ្រាវ បង្ហាញថា ទោះបីជា បរាជ័យនៃការតោងជាប់របស់អំប្រ៊ីយ៉ុង អាចកើតមានបន្តបន្ទាប់ច្រើនដងពិតមែន បញ្ហានេះជាករណីកម្រ ដែលអាចកើតមានត្រឹមតែ៥%ប៉ុណ្ណោះ ក្នុងចំណោមចំនួនគូស្វាមីភរិយាដែលទទួលការព្យាបាលតាមបច្ចេកវិទ្យាជំនួយការបង្កកំណើត ។

ពាក្យគន្លឹះ បច្ចេកវិទ្យាជំនួយការបង្កកំណើត; ការបង្កកំណើតក្រៅ; ការតោងជាប់របស់អំប្រ៊ីយ៉ុង; អំប្រ៊ីយ៉ុងដែលមានក្រូម៉ូសូមប្រក្រតី; បរាជ័យនៃការប្រើប្រាស់បច្ចេកវិទ្យាជំនួយការបង្កកំណើតក្រៅ; បរាជ័យនៃការតោងជាប់របស់អំប្រ៊ីយ៉ុងជាបន្តបន្ទាប់

INTRODUCTION

In the early days of ART—then called IVF—implantation rates (IR) were miserable, commonly hovering around 10% at best. Logically, all was done to improve those meager results, including opting for multiple embryo transfers (ET) having for consequence, a high risk of multiple pregnancies.

The recent years however have seen spectacular improvements in ART results through series of technical improvements. These notably include: (a) ovarian stimulation protocols that allow the retrieval of large numbers of oocytes without fearing anymore the risk of ovarian hyperstimulation syndrome (OHSS) or decreased embryo quality, (b) better laboratory conditions—single chamber incubators, proper gas mixtures, and so on—allowing the development of embryos to the blastocyst stage (day 5–7), (c) improved cryopreservation techniques through vitrification, and (d) last but not least, the possibility to determine the genetic status of embryos through preimplantation genetic testing for aneuploidy (PGT-A). The latter allows to exclude embryos that have no development potential and thereby avoid transfers with no chance of success or worst, leading to miscarriages (Scott et al., 2022; Tiegs et al., 2021). Through these achievements, sustained implantation rates (sIR) with positive fetal heart activity following euploid ET are commonly reaching today 50%–65% per transfer (Pirtea et al., 2021). This allows to most often revert to single ET, which markedly reduces multiple pregnancy rates (Forman et al., 2013).

Achieving such a remarkable ART outcome—high sIR—raises a new challenge for those caring for infertile couples being capable to deal with ART failures. Commonly, a woman undergoing ET is told by the biologist: "Madame, we are transferring you a beautiful embryo." Logically, therefore, if implantation fails, the infertile patient will be inclined to blame herself for the failure: "If they transferred me a 'beautiful embryo' then, the failure has to come from me." "It has to be my uterus that is not capable of allowing the implantation of that embryo." This feeling of distress that commonly affects patients who fail ART is the starting point for initiating all kind of measures—diagnostic and therapeutic—after one or multiple ART failures. These measures are collectively known as ART "add-ons." None, however, has any recognized value (Braga et al., 2022; Glatthorn and Decherney, 2022; Lensen et al., 2019). ART failures have to be identified as extremely strenuous for infertile couples. Hence, they require counseling and support rather than simply, if not automatically, reverting to using any unproven "add-on," which may be both very expensive and ineffective for the next attempts.

METHOD

A literature search through PubMed and Embase was conducted using the following terms: ART-IVF failure (n = 1,402 hits), recurrent embryo implantation failure (n = 589 hits), recurrent ART-IVF failure (n = 366 hits), euploid ET (n = 563 hits), and failed euploid E (n = 38 hits). All titles and abstracts, written in English and published from January 2015 to May 2023, were screened to identify relevant studies. Ultimately, 35 of these references were judged pertinent for the topic addressed here.

The present narrative review follows an invited presentation made at the annual Fertility Society of Australia and New Zealand (FSANZ) held on the Gold Coast (Queensland) on June 3–6, 2023.

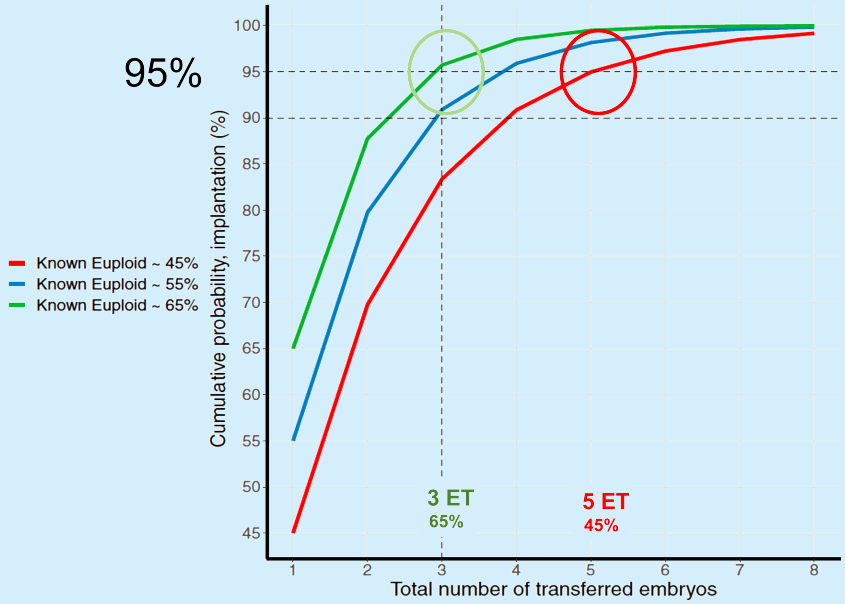
DEFINITION OF RECURRENT IMPLANTATION FAILURE (RIF)

Schematically, ART failures can result from two types of causes, sporadic events—not inclined to repeat themselves—and recurrent issues, which will affect all future ART attempts. An example of a sporadic cause of ART failure are problems encountered at the time of ET. Indeed, not all transfers are easy, but the causes of possible difficulties are by essence variable and likely to not be repetitive. The strain encountered during ET may result from a high degree of anterior or posterior curve of the uterus, which will likely differ at the time of the next ET, maybe because of a different degree of bladder filling or other reasons. Also, Nabothian cysts, which may exist in the cervical canal, can interfere with the smooth passage of the catheter on one occasion and less on another one for reasons linked to luck alone. This may make one transfer difficult and thus, more prone to failure. On a different occasion, however, by sheer luck or other reasons, the transfer in the same patient may end up being easier and thus more prone to success. Furthermore, certain transferers may be more skillful than others and generally have a better outcome. As transferers are commonly different for each transfer, the impact of the transferer is likely to not be recurrent.

Conversely, a recurrent cause of ART failure could, for example, emanate from a persistent alteration of endometrial receptivity. In this case, defective receptivity would reduce implantation chances at each subsequent ET. Hence, an impairment of endometrial receptivity would have a progressive impact on the outcome of successive ETs by selecting out individuals affected by a receptivity disorder in the failed ART group. For example, if an impairment of endometrial receptivity affected, say, 10% of routine ART patients, the sIR would be decreased by 10% at the first ART attempt. But the affected non-receptive individuals being segregated in the failed ART group would accumulate when further ETs are performed. In the example given, an original incidence of impaired receptivity of 10% would end up altering receptivity by 27% and 55%—above normal failure rates—in the second and third ET, respectively. Hence, an incidence of just 10% of impaired receptivity would result in markedly dropping sIR during successive ART attempts. Clinically,

Fig. 1. Number of euploid embryo transfers necessary to achieve a cumulative implantation rate of 95%, depending on euploid embryo implantation rates.

Adapted from Somigliana et al. (2022) and Ata et al. (2021)



there is evidence (as discussed below) that this is not the case. As we will see, a recurrent cause of implantation failure may indeed exist in ART, but if it does, available data indicate that it is extremely rare, affecting ≤5% of infertile women.

THE 2022 LUGANO-RIF WORKSHOP

A workshop mustered experts in ART and endometrial receptivity from both the United States and Europe in Lugano, Switzerland on July 1, 2022. The workshop objectives were to define the conditions that allow to identify RIF, delineate its possible causes, and possible therapeutic measures. The consensus that emanated from the 2022 Lugano-RIF workshop was recently published (Pirtea et al., 2022).

First, the members of the workshop focused on defining, what in their eyes, best constitutes an implantation failure. The consensus reached was that ART failure—and by extension, RIF—was the failure(s) to achieve "sustained" implantation (defined as a gestational sac with positive fetal heart activity identified on ultrasound [US]). This definition does not literally follow the concept of "implantation failure," as biochemical pregnancies have undergone the very early steps of implantation. Yet one easily convenes that neither clinicians nor patients consider a biochemical pregnancy as an ART success. Also, defining ART failure as the lack of sustained implantation allows to distinguish RIF from early pregnancy losses, let alone recurrent pregnancy losses (RPL), which are different pathologies altogether.

Theoretically implantation failures, and hence RIF, can find their cause in a problem residing in either the embryo, or the endometrium. In the objective of limiting possible variables, the members of the 2022 Lugano-RIF Workshop decided to primarily focus on studying the fate of euploid ET. De facto, studying the fate of euploid embryos implies that these were vitrified and their transfer conducted in programmed E2 and i.m. progesterone cycles.

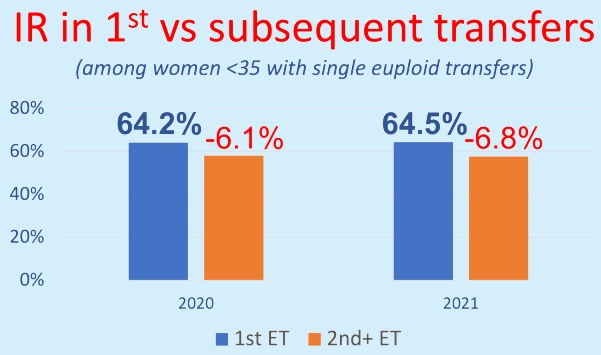
Somigliana et al. constructed a model to study the number of transfers necessary for achieving a cumulative IR of 95%, provided that the cause of the implantation failure would be primarily in the embryo (Somigliana et al., 2022). As illustrated in Fig. 1, we see that if the euploid embryo sIR is 65%, it takes three ETs to achieve a cumulative sIR of 95%. If, however, the euploid embryo IR is 45%, it would need five ETs for achieving a similar 95% sIR (Ata et al., 2021; Somigliana et al., 2022).

Rozen et al. formulated an algorithm to personalize the diagnostic of RIF based on theoretical cumulative IR, irrespective of whether PGT-A was performed or not (Rozen et al., 2021). This latter approach offers a useful practical tool, as it allows couples to predict the number of ET needed to achieve optimal cumulative chances based on the expected IR, itself dependent primarily on age (Rozen et al., 2021). According to the Rozen Model, a theoretical sIR of 50% provides an estimated cumulative sIR of ≥85% after three ETs. These numbers are practically similar to those proposed by Somigliana et al. (2022). If, however, sIR is 30% (instead of 50%), it would take five ETs to achieve a similar outcome. Finally, if sIR is 10%—a proper estimate for untested embryos in women of more than 40 years of age—it would take 16 ETs to achieve a similar cumulative outcome (Rozen et al., 2021).

The numbers offered in the Rozen Model actually fit with success rates obtained with frozen euploid blastocyst transfers, taking into account the losses due to aneuploidy (Rozen et al., 2021). Indeed, if endometrial receptivity was affected in a fraction of patients, non-receptive individuals would accumulate in the first ART failed group. In the hypothetical situation proposed—"non-receptive" individuals constituting 10% of the original population—the concentration of non-receptive women would increase to 27% and 55% in the second and third ART attempt. This would obviously drastically reduce the ART outcome of the second and third attempt. But the reality

Fig. 2. Society for Assisted Reproductive Technology. SART national IVF results (https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx reporting Year. 2020. Accessed April 19, 2023).

Adapted from Society for Assisted Reproductive Technology. SART national IVF results. Available at: https://www.sartcorsonline.com/rptCSR_Public Multi Year, reportingYear.2020. Accessed April 19, 2023.



is different, and these marked decreases in pregnancy rates with successive ART attempts are not seen.

In the United States, the Society for Assisted Reproductive Technology (SART) reported the outcome observed after one and two euploid blastocyst transfers in 2020 and 2021, the last dates available in 2023 (https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear.2020, accessed on April 19, 2023). As illustrated in Fig. 2, one sees that there is only a slight decrease in IR after the second euploid blastocyst transfer of −6.1% and 6.8% in 2020 and 2021, respectively. These results clearly speak for only a minimal decrease in sIR after successive transfers of euploid blastocysts. Hence, these results indicate that the number of persistent endometrial receptivity problems is very small, if any—particularly considering that SART data are biased by the fact that the best morphologic blastocysts were transferred first.

Pirtea et al. reported a large retrospective study analyzing sIR following one, two, and three euploid blastocysts transfers in E2 and i.m. progesterone cycles, which also demonstrate a very small reduction of sIR after successive ETs (Pirtea et al., 2021). These authors' results show that sIR was of 69.9%, 59.8%, and 60.3% after the first, second, and third euploid blastocyst transfers, respectively. Taken together, these findings amount to an incidence of RIF of 5% for the first-to-the-second attempt and approximately 1% for the second-to-the-third attempt, amounting in total to <5%, as illustrated in Fig. 3 (Pirtea et al., 2023). Considering that the morphologically best embryos were transferred first, this indicates that overall, the incidence of RIF due to endometrial receptivity is in fact even lower. Hence, the participants in the 2022 Lugano-RIF consensus workshop (Pirtea et al., 2023) concluded based on available data on frozen euploid blastocysts transfers that RIF may indeed exist, but if it does, it only affects a very small number of women ≤5%. These conclusions are in agreement with the observation of Bishop et al. that endometriosis, which has a prevalence of 20%–40% in infertile women, does not affect frozen euploid blastocysts transfers (Bishop et al., 2021).

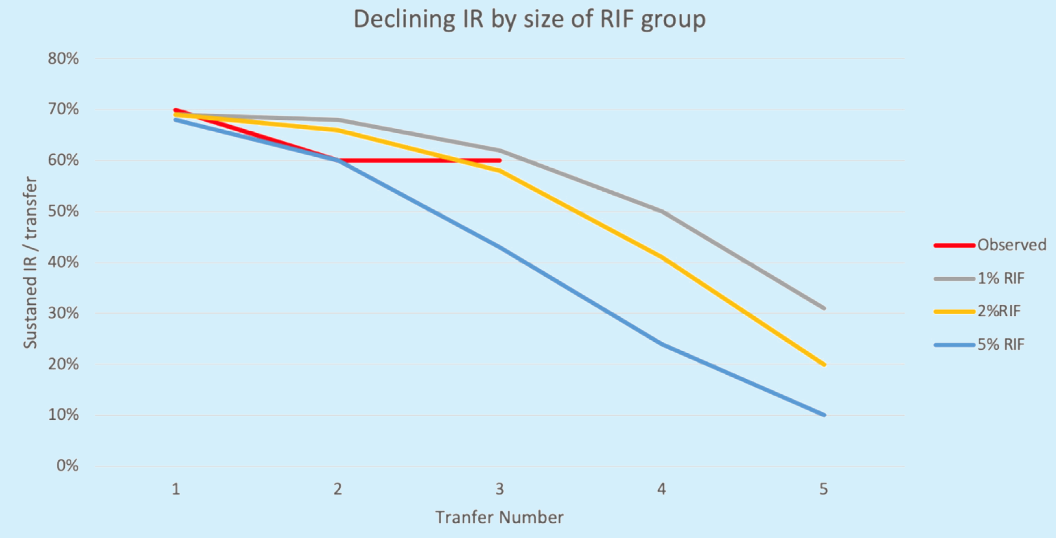
EUPLOID EMBRYOS TRANSFERRED IN E2 AND I.M. PROGESTERONE CYCLES

As indicated above, our quest to assess the true incidence of RIF led us to focus on reports of successive euploid ET in order to limit the variability of embryo quality. Similar calculations can be conducted for untested ET, adjusting the expected sIR according to the known age-related decrease in embryo euploidy (Cimadomo et al., 2021; Treff et al., 2012). This may notably be accomplished with the help of the "Rozen Model," which offers the advantage of not relying on PGTA, an approach challenged by some (Rozen et al., 2021).

Endometrial receptivity issues could be generated by ovarian stimulation (OS) and the characteristically elevated levels of E2

Fig. 3. Successive sustained implantation rates (sIR) following up to three euploid blastocyst transfers compared to theoretical RIF incidences of 1%–5% from Pirtea et al. (2023).

Adapted from Pirtea et al. (2023)



(Montoya-Botero and Polyzos, 2019). Hence, following our quest of limiting the number of variables when studying RIF, the experts who attended the Lugano-RIF workshop decided to also limit their analysis to FETs programmed in E2 and i.m. progesterone cycles. Today, numerous reports have indicated that pregnancy rates are equivalent following transfers in programmed and natural or modified natural cycles, the latter possibly having lesser obstetrical complications (Pakes et al., 2020). Yet, considering the number of alterations described in the eutopic endometrium in case of endometriosis (Bulun et al., 2023), it remains to be established that endometrial receptivity is not altered in natural-cycle FETs, as it has been demonstrated in programmed cycles (Bishop et al., 2021).

The limitations chosen for studying RIF—studying results of euploid ETs conducted in E2 and progesterone cycles—do not mean that this approach constitutes any form of suggested cure for women suspected of suffering from RIF.

WHY NOT ALL EUPLOID EMBRYO IMPLANT

Despite selecting genetically normal embryos through PGT-A, 35% of euploid ET conducted in an anatomically normal uterus still fail to implant. As said earlier, these failures can result from sporadic factors such as those related to the performance of the ET procedure itself or from other disorders affecting genetically normal embryos. In a recent analysis, Cimadomo et al. assessed the morphologic characteristics of euploid blastocysts that implant and those that do not (Cimadomo et al., 2023). They observed that the grading characteristics of both the inner cell mass and trophectoderm, as well as the development speed, impact on sIR chances of these euploid blastocyst transfers (Cimadomo et al., 2023). It is therefore conceivable that future work—possibly using AI—may actually improve the capability to predict euploid blastocyst implantation potential.

TESTING ENDOMETRIAL RECEPTIVITY

In the early days of ART, research on endometrial receptivity stemmed from work conducted in donor-egg ART. The objective was to refine the endometrial preparation regimens proposed to women whose ovaries were not functioning. This early work—now classical—demonstrated that an E2 priming course of 10–30 days followed by the addition of progesterone sufficed for securing optimal endometrial receptivity (Lütjen et al., 1985; Navot et al., 1986, 1989). It was also shown that the E2 to progesterone ratio had no impact on endometrial morphology and receptivity (de Ziegler et al., 1991, 1992). Recent work showed that the receptive period—the window on endometrial receptivity—is fairly wide, lasting at least 2 days. Indeed, a RCT concluded that IR are equal following transfers of cleaving stage embryos (day 3) on the third or fifth day of progesterone administration (van de Vijver et al., 2016). For blastocyst transfers, likewise, evidence indicates that there is no difference between transfers done on the fifth or seventh day of progesterone administration (Roelens et al., 2020).

Approximately 20 years ago, several groups have attempted to define endometrial receptivity according to the genic expression of endometrial epithelial and stromal cells. This was conducted on endometrial tissue sampled with an endometrial biopsy performed in a study cycle performed prior to the actual ET cycle (Díaz-Gimeno et al., 2011; Horcajadas et al., 2007; Ruiz-Alonso et al., 2013). The most known of these models is the endometrial receptivity array (ERA) test. Results from endometrial aspiration conducted during the theoretical window of receptivity are defined as being either receptive, pre-receptive or post-receptive (Díaz-Gimeno et al., 2011). The recommendations made based on the results obtained in the study cycle call to adjust the date of ET (days of progesterone) accordingly. This ERA-based approach has been identified as a "personalized embryo transfer" strategy (Ruiz-Alonso et al., 2013). The ERA test has been extensively used worldwide due to intense marketing efforts. Unfortunately, however, several recent studies have concluded that the results of the ERA test are of no practical value for timing ET (Cozzolino et al., 2022). Ultimately, a large RCT funded in part by the manufacturers of the ERA test itself observed that IR are similar in women whose biopsy was read as receptive or non-receptive (Doyle et al., 2022). Furthermore, a post hoc analysis of the above data led to conclude that in case of non-receptive findings on ERA, adjustments performed according to the personalized transfer recommendations were actually detrimental (Richter and Richter, 2023).

Other laboratories have proposed a slightly different mode of endometrial genic analysis for determining the timing of endometrial receptivity (Haouzi et al., 2009). These authors likewise proposed to adjust the timing of ETs according to the biopsy results. Unfortunately, however, this latter approach has never been appropriately tested with a RCT and is likely to not be more effective than the ERA test (Haouzi et al., 2021). Finally, overexpression of B-cell lymphoma 6 (BCL-6) in endometrial tissue obtained by aspiration—the Receptiva® test—has been claimed to represent a characteristic of endometriosis (Sansone et al., 2021) and a predictor of reduced ART outcome (Almquist et al., 2017). Yet recently, the group of Richard Scott found that the expression of BCL-6—elevated or not—is not associated with live birth rates in normal ART responder (Klimczak et al., 2022).

Several studies have described the presence of chronic endometritis (CE)—a subclinical inflammation of the endometrium—in a fraction of infertile women (Vitagliano et al., 2022). Interestingly, the incidence of CE is markedly increased in case of endometriosis (Racca et al., 2023), which opens interesting new views for the genesis of this disease. While CE has been claimed to alter endometrial receptivity, more recent data on IR of euploid blastocysts in E2 and i.m. progesterone cycles contradicted this claim (Herlihy et al., 2022). Indeed, no differences in success rates were observed irrespective of the number of plasma cells taken as a cutoff value (Herlihy et al., 2022). That the presence of CE does not seem to impact on ART outcome does not mean that CE is of no clinical importance. Indeed, CE and the resulting inflammation of the endometrium may play a role in the genesis of endometriosis (Racca et al., 2023). The failure of all receptivity prediction tests (Doyle et al., 2022; Klimczak et al., 2022; Richter and Richter, 2023) goes along with our observation that if true RIF exists, it's a very rare phenomenon that only affects ≤5% of ART participants (Pirtea et al., 2023).

THE ROLE OF PROGESTERONE

Progesterone induces endometrial changes—antimitotic and secretory effects—that are both indispensable for priming endometrial receptivity to embryo implantation, as demonstrated by the early donor egg experience (Lütjen et al., 1985; Navot et al., 1986). In regular fresh-transfer ART, the need for luteal phase support has been amply demonstrated (Penzias et al., 2002). In their review, Penzias et al. indicate that in fresh-ART cycles, progesterone support beyond the positive serum pregnancy test may not be needed (Penzias et al., 2002). Furthermore, in fresh cycles, pregnancy rates after vaginal and i.m. progesterone support are comparable.

Progesterone needs following frozen embryo transfers (FET) are drastically different however. Indeed, none of the progesterone preparations currently available on the market has been approved—and formally tested—in hormone replacement regimens for FET. As the number of FETs has drastically increased with the advent of

vitrification, it became obvious that progesterone needs are different in FET compared to what has been established in fresh ART. The first evidence that vaginal progesterone is insufficient has been formally established in a RCT conducted by Devine et al. (2018). These authors showed that vaginal progesterone alone provided significantly lower LBR and higher miscarriage rates compared to transfers primed with i.m. progesterone or combined vaginal and i.m. progesterone (Devine et al., 2018). Other studies have shown that in the case of vaginal progesterone administration, measuring serum progesterone on the day of ET allows to single out women whose progesterone levels are insufficient and ART outcome lower (Labarta et al., 2021). In these women, it is possible to supplement progesterone with subcutaneous injections—Prolutex®, IBSA Switzerland, 25 mg/day—and correct the detrimental effects of low progesterone levels (Álvarez et al., 2021).

Taking into account the above-mentioned data on progesterone, one should always ascertain that any ART failure is not due to an inappropriate progesterone treatment. This is particularly important in non-US studies. Indeed, in these latter cases, vaginal progesterone is often the sole source of progesterone used thereby, throwing into questions the results of such studies.

CONCLUSION

Contrary to infertility, RIF is not an overt clinical entity. The diagnosis of infertility—the inability to conceive after one year of unprotected intercourses—is associated with a series of clinical findings. The latter include an increased incidence of tubal, male factor infertility, and endometriosis, just to name a few. Together, the increased prevalence of these disorders defines the clinical entity of infertility. On the contrary, RIF is not associated with any specific identifiable anomalies—as of now—other than having repetitively failed several ART attempts. RIF therefore is not a clinical entity identifiable by biomarkers, a fact that impairs the study of RIF pathophysiology.

To standardize the definition of RIF, the participants at the "2022 Lugano-RIF Workshop" opted for studying the incidence of sIR following transfers of euploid blastocysts in E2 and progesterone (i.m.) replacement cycles. This deliberate choice was made to limit the variability of this complex and still poorly defined entity called RIF. It should not be deduced, however, that proceeding to euploid blastocyst transfers in E2 and i.m. progesterone is in itself a therapy in case of failed ART attempts.

As detailed above, the conclusion of multiple studies is that RIF—and possible endometrial receptivity impairment—may exist, but is extremely rare. Estimates from reviewing these studies indicate that RIF only affects ≤5% of cases, provided that the uterus is normal on ultrasound and/or hysteroscopy. Therefore, the diagnosis of RIF should not be assigned until a patient has failed at least three euploid FETs, or the equivalent number of untested ET, as per euploidy prevalence as a function of age.

In light of this, the 2022 Lugano-RIF Workshop concluded that disorders of endometrial receptivity are extremely rare in women whose uterus is normal on ultrasound and hysteroscopy. Consequently, endometrial receptivity assays are useless, and the recommendations made based on results are detrimental in the case of ERA (Doyle et al., 2022). Likewise, a large variety of "add-ons" is sometimes proposed in case of past ART failure. These are generally simply unnecessary and of no proven safety.

We however recommend that all workup measures (i.e., uterine ultrasound, saline infusion sonography, and/or hysteroscopy) are undertaken upfront, that is, before the first ART procedure rather than after one or several failures. Finally, and most importantly, couples should be prepared for the possibility of ART failure(s). In particular, couples should be made aware that their parenthood project may fail not just because of ART failure, but also because they may give up their treatment process altogether. Indeed, numerous couples abandon their project simply because ART procedures are emotionally strenuous, not just financially expansive. In France, for example, numerous couples forgo their project while their ART chances remain reasonable, despite the fact that in France ART is entirely covered by governmental insurance (Bourrion et al., 2022).

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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REFERENCES

Almquist LD, Likes CE, Stone B, et al. Endometrial BCL6 testing for the prediction of in vitro fertilization outcomes: a cohort study. Fertil Steril. 2017;108(6):1063–9.

Álvarez M, Gaggiotti-Marre S, Martínez F, et al. Individualised luteal phase support in artificially prepared frozen embryo transfer cycles based on serum progesterone levels: a prospective cohort study. Hum Reprod. 2021;36(6):1552–60.

Ata B, Kalafat E, Somigliana E. A new definition of recurrent implantation failure on the basis of anticipated blastocyst aneuploidy rates across female age. Fertil Steril. 2021;116(5):1320–7.

Bishop LA, Gunn J, Jahandideh S, Devine K, Decherney AH, Hill MJ. Endometriosis does not impact live-birth rates in frozen embryo transfers of euploid blastocysts. Fertil Steril. 2021;115(2):416–22.

Bourrion B, Panjo H, Bithorel PL, de La Rochebrochard E, François M, Pelletier-Fleury N. The economic burden of infertility treatment and distribution of expenditures overtime in France: a self-controlled pre-post study. BMC Health Serv Res. 2022;22(1):512.

Braga D, Setti AS, Borges E, Jr. Ethics and IVF add-ons: we need to talk about it. JBRA Assist Reprod. 2022;26(3):371–3.

Bulun SE, Yildiz S, Adli M, et al. Endometriosis and adenomyosis: shared pathophysiology. Fertil Steril. 2023;119(5):746–50.

Cimadomo D, Capalbo A, Dovere L, et al. Leave the past behind: women's reproductive history shows no association with blastocysts' euploidy and limited association with live birth rates after euploid embryo transfers. Hum Reprod. 2021;36(4):929–40.

Cimadomo D, Rienzi L, Conforti A, et al. Opening the black box: why do euploid blastocysts fail to implant? A systematic review and meta-analysis. Hum Reprod Update. 2023;38(Supplement_1).

Cozzolino M, Diáz-Gimeno P, Pellicer A, Garrido N. Use of the endometrial receptivity array to guide personalized embryo transfer after a failed transfer attempt was associated with a lower cumulative and per transfer live birth rate during donor and autologous cycles. Fertil Steril. 2022;118(4):724–36.

de Ziegler D, Bergeron C, Cornel C, et al. Effects of luteal estradiol on the secretory transformation of human endometrium and plasma gonadotropins. J Clin Endocrinol Metab. 1992;74(2):322–31.

de Ziegler D, Cornel C, Bergeron C, Hazout A, Bouchard P, Frydman R. Controlled preparation of the endometrium with exogenous estradiol and progesterone in women having functioning ovaries. Fertil Steril. 1991;56(5):851–5.

Devine K, Richter KS, Widra EA, McKeeby JL. Vitrified blastocyst transfer cycles with the use of only vaginal progesterone

replacement with Endometrin have inferior ongoing pregnancy rates: results from the planned interim analysis of a three-arm randomized controlled noninferiority trial. Fertil Steril. 2018;109(2):266–75.

Díaz-Gimeno P, Horcajadas JA, Martínez-Conejero JA, et al. A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature. Fertil Steril. 2011;95(1):50–60, e1–15.

Doyle N, Jahandideh S, Hill MJ, Widra EA, Levy M, Devine K. Effect of timing by endometrial receptivity testing vs standard timing of Frozen Embryo transfer on live birth in patients undergoing in vitro fertilization: a randomized clinical trial. Jama. 2022;328(21):2117–25.

Forman EJ, Hong KH, Ferry KM, et al. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. Fertil Steril. 2013;100(1):100–7.e1.

Glatthorn HN, Decherney A. The efficacy of add-ons: selected IVF "add-on" procedures and future directions. J Assist Reprod Genet. 2022;39(3):581–9.

Haouzi D, Entezami F, Torre A, et al. Customized frozen embryo transfer after identification of the receptivity window with a transcriptomic approach improves the implantation and live birth rates in patients with repeated implantation failure. Reprod Sci. 2021;28(1):69–78.

Haouzi D, Mahmoud K, Fourar M, et al. Identification of new biomarkers of human endometrial receptivity in the natural cycle. Hum Reprod. 2009;24(1):198–205.

Herlihy NS, Klimczak AM, Titus S, et al. The role of endometrial staining for CD138 as a marker of chronic endometritis in predicting live birth. J Assist Reprod Genet. 2022;39(2):473–9.

Horcajadas JA, Pellicer A, Simón C. Wide genomic analysis of human endometrial receptivity: new times, new opportunities. Hum Reprod Update. 2007;13(1):77–86.

Klimczak AM, Herlihy NS, Scott CS, et al. B-cell lymphoma 6 expression is not associated with live birth in a normal responder in vitro fertilization population. Fertil Steril. 2022;117(2):351–8.

Labarta E, Mariani G, Paolelli S, et al. Impact of low serum progesterone levels on the day of embryo transfer on pregnancy outcome: a prospective cohort study in artificial cycles with vaginal progesterone. Hum Reprod. 2021;36(3):683–92.

Lensen S, Shreeve N, Barnhart KT, Gibreel A, Ng EHY, Moffett A. In vitro fertilization add-ons for the endometrium: it doesn't add-up. Fertil Steril. 2019;112(6):987–93.

Lütjen PJ, Leeton JF, Findlay JK. Oocyte and embryo donation in IVF programmes. Clin Obstet Gynaecol. 1985;12(4):799–813.

Montoya-Botero P, Polyzos NP. The endometrium during and after ovarian hyperstimulation and the role of segmentation of infertility treatment. Best Pract Res Clin Endocrinol Metab. 2019;33(1):61–75.

Navot D, Anderson TL, Droesch K, Scott RT, Kreiner D, Rosenwaks Z. Hormonal manipulation of endometrial maturation. J Clin Endocrinol Metab. 1989;68(4):801–7.

Navot D, Laufer N, Kopolovic J, et al. Artificially induced endometrial cycles and establishment of pregnancies in the absence of ovaries. N Engl J Med. 1986;314(13):806–11.

Pakes C, Volovsky M, Rozen G, et al. Comparing pregnancy outcomes between natural cycles and artificial cycles following frozen-thaw embryo transfers. Aust N Z J Obstet Gynaecol. 2020;60(5):804–9.

Penzias AS. Luteal phase support. Fertil Steril. 2002;77(2):318–23.

Pirtea P, Cedars MI, Devine K, et al. Recurrent implantation failure: reality or a statistical mirage? Consensus statement from the July 1, 2022 Lugano Workshop on recurrent implantation failure. Fertil Steril. 2023;120(1):45–59.

Pirtea P, Cedars MI, Devine K, et al. Reply of the authors: recurrent implantation failure: reality or a statistical mirage? Fertil Steril. 2023;120(1):211.

Pirtea P, De Ziegler D, Tao X, et al. Rate of true recurrent implantation failure is low: results of three successive frozen euploid single embryo transfers. Fertil Steril. 2021;115(1):45–53.

Racca A, Alvarez M, Garcia Martinez S, et al. Assessment of progesterone levels on the day of pregnancy test determination: a novel concept toward individualized luteal phase support. Front Endocrinol (Lausanne). 2023;14:1090105.

Richter KS, Richter ML. Personalized embryo transfer reduces success rates because endometrial receptivity analysis fails to accurately identify the window of implantation. Hum Reprod. 2023;38(7):1239–44.

Roelens C, Santos-Ribeiro S, Becu L, et al. Frozen-warmed blastocyst transfer after 6 or 7 days of progesterone administration: impact on live birth rate in hormone replacement therapy cycles. Fertil Steril. 2020;114(1):125–32.

Rozen G, Rogers P, Teh WT, Stern CJ, Polyakov A. An algorithm to personalise the diagnosis of recurrent implantation failure based on theoretical cumulative implantation rate. Hum Reprod. 2021;36(6):1463–8.

Ruiz-Alonso M, Blesa D, Díaz-Gimeno P, et al. The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. Fertil Steril. 2013;100(3):818–24.

Sansone AM, Hisrich BV, Young RB, et al. Evaluation of BCL6 and SIRT1 as non-invasive diagnostic markers of endometriosis. Curr Issues Mol Biol. 2021;43(3):1350–60.

Scott RT, de Ziegler D, Pirtea P, Jalas C. Limits imposed by the experimental design of a large prospective non-inferiority study on PGT-A invalidate many of the conclusions. Hum Reprod. 2022;37(12):2735–42.

Somigliana E, Busnelli A, Kalafat E, Viganò P, Ata B. Recurrent implantation failure: a plea for a widely adopted rational definition. Reprod Biomed Online. 2022;45(2):183–5.

Tiegs AW, Tao X, Zhan Y, et al. A multicenter, prospective, blinded, nonselection study evaluating the predictive value of an aneuploid diagnosis using a targeted next-generation sequencing-based preimplantation genetic testing for aneuploidy assay and impact of biopsy. Fertil Steril. 2021;115(3):627–37.

Treff NR, Tao X, Ferry KM, Su J, Taylor D, Scott RT Jr. Development and validation of an accurate quantitative real-time polymerase chain reaction-based assay for human blastocyst comprehensive chromosomal aneuploidy screening. Fertil Steril. 2012;97(4):819–24.

van de Vijver A, Polyzos NP, Van Landuyt L, et al. What is the optimal duration of progesterone administration before transferring a vitrified-warmed cleavage stage embryo? A randomized controlled trial. Hum Reprod. 2016;31(5):1097–104.

Vitagliano A, Laganà AS, De Ziegler D, et al. Chronic endometritis in infertile women: impact of untreated disease, plasma cell count and antibiotic therapy on IVF outcome-a systematic review and meta-analysis. Diagnostics (Basel). 2022;12(9):2250.